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Endogenous Growth Hormone Secretion and Clearance Rates in Normal Boys, as Determined by Deconvolution Analysis: Relationship to Age, Pubertal Status, and Body Mass*

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ABSTRACT. Mean plasma GH concentrations increase in normal boys during mid- to late-puberty. To investigate the nature of the pituitary secretory events and/or altered metabolic clearance responsible for these serum GH concentration changes, we performed multiple-parameter deconvolution analysis of 46 24-h serum GH concentration-time series obtained from normal boys at various stages of puberty and young adulthood. The subjects ranged in chronological age from 7–27 yr. The height and weight of each subject were between the 5th and 95th percentile for age.

The calculated daily mass of GH secreted was greatest ($P < 0.001$) in late pubertal boys (mean ± SE, 1810 ± 250 μg/24 h) and was triple the value in prepubertal boys (610 ± 65 μg/24 h). When the values were normalized and expressed as mass of GH secreted per unit (m^2) body surface area or per L distribution volume, GH secretion in late pubertal boys was still significantly greater than that in any other group ($P < 0.05$). These values for late pubertal boys were nearly double the corresponding values for prepubertal boys (1160 ± 160 *vs.* 600 ± 58 μg GH/m^2·24 h and 440 ± 63 *vs.* 270 ± 25 μg GH/L vol·24 h, respectively). When the effect of clearance mechanics on serum GH concentrations was removed mathematically, the primary change in predicted GH secretory burst parameters during pubertal development was an increase in GH mass released per burst resulting from an increase in the maximal rate of GH secretion attained within the bursts. These changes in the amplitude of GH release events were specific, in that they were largely independent of any accompanying alterations in duration or frequency of the GH secretory bursts or in serum GH half-life.

Correlation analysis revealed that the 24-h GH secretion rate varied inversely with the subjects' body mass index SD score ($r = -0.65$; $P < 0.01$), suggesting that differences in body mass, even within the normal range, contribute to the wide variability in daily GH secretion rates among normally growing children. The plasma insulin-like growth factor-I concentrations of all subjects correlated positively with the calculated 24-h GH secretion rate ($r = 0.51$; $P < 0.001$).

In summary, the primary neuroendocrine alteration responsible for the augmented serum GH concentrations characterizing mid- to late-puberty in boys is an increased mass of GH released per pituitary secretory episode resulting from an increased maximal rate of GH secretion within each burst. This process achieves a daily GH secretion rate during later puberty that is 2- to 3-fold the secretion rate during prepuberty. In addition, body composition, within the normal range, appears to be a physiological modulator of spontaneous GH secretion. These findings suggest that to emulate physiological changes and maximize growth during puberty in GH-deficient children, significant increases in daily GH replacement doses may be required in some individuals. (*J Clin Endocrinol Metab* **74:** 336–344, 1992)

IN RECENT years, techniques designed to assess the pattern of spontaneous fluctuations of serum GH concentrations in human subjects have extended our ability to investigate *in vivo* the function of the somatotropic axis. Existing data derived through application of such techniques indicate that these serum fluctuations, often referred to as GH pulses, are altered in a variety of physiological and pathophysiological states. Therefore, analysis of the GH pulse pattern may provide important information about the GH signal presented to the target tissues under specific conditions. Existing data indicate

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that normal puberty provides one example of such physiological alteration in the GH pulse pattern. Specifically, an augmentation in the size, but not the number, of GH pulses characterizes mid- to late-puberty, with a return to or a fall below prepubertal values occurring in early adulthood (1–3). Furthermore, significant alterations in serum GH pulses appear to be present during states of delayed or precocious pubertal development (4–6).

Although useful in defining the GH pattern encountered by peripheral tissues, standard analysis of serum hormone pulses provides limited information on the neuroendocrine secretory events and concurrent hormone clearance that together underlie and give rise to the serum pulse patterns. Newer techniques, generally termed deconvolution procedures, mathematically remove the impact of hormone clearance kinetics to uncover specific pituitary secretory parameters responsible for the circulating hormone concentration profile. The process of determining these underlying secretory (and clearance) parameters is referred to as deconvolution analysis. A detailed discussion of existing deconvolution methods has appeared recently (7).

In the present study we employed a multiple-parameter deconvolution method, which enables simultaneous resolution of endogenous hormone secretory rates and clearance kinetics (8), to characterize the GH secretory events subserving the changes in serum GH concentrations that occur during growth and development in normal boys.

Materials and Methods

Study subjects

The study group comprised 44 healthy boys and young men between the ages of 7–27 yr. The height and weight of each subject were between the 5th and 95th percentile for age (based on standards from the National Center for Health Statistics), and bone age was within 2 SD for age. Subjects whose epiphyses were fully fused were compared to adult norms. Two subjects returned at a later stage of puberty for a second study, bringing the total number of study periods to 46. A detailed description of the conventional GH pulse characteristics of the 24-h serum GH concentration profiles of these subjects was included in a previous report (1). The study was reviewed and approved by the Human Investigation Committee at the University of Virginia. The reason for the study as well as the potential risks were discussed with each child before participation. It was explained to each subject that conduct of the study itself would not provide direct benefit to him, although all data would be made available and explained upon request. All subjects under the age of 18 yr then gave assent, with consent obtained from a parent. Those over 18 yr gave their written consent. The studies were performed in the General Clinical Research Center at the University of Virginia. All subjects participated as paid volunteers. For a portion of the data analysis and for comparison with previously published results, the subjects were divided into 5 groups based on their degree of secondary sexual development, as described previously (1).

Hormone assays

All serum GH concentrations from any one subject were determined in the same assay using Nichols Institute immunoradiometric GH assay kits with horse serum diluent (San Juan Capistrano, CA). The lower limit of assay sensitivity was 0.5 μg/L. Intra- and interassay coefficients of variation (CVs) were 8% and 10% or less, respectively. The Nichols Institute double antibody RIA was used for assay of plasma insulin-like growth factor-I (IGF-I) levels. The IGF-I assay intra- and interassay CVs were less than 9% and less than 12%, respectively. Diagnostic Products Corp. (Los Angeles, CA) solid phase RIA kits were used to determine serum testosterone concentrations. The lower limit of sensitivity for the testosterone assay was 0.87 nmol/L (25 ng/dL), and the interassay CV was approximately 7% (6–9%) in the range of 15.7 nmol/L (438 ng/dL).

Experimental design

The experimental design was described previously (1). Briefly, 1.0–3.5 cc blood were withdrawn from an indwelling catheter every 20 min between 0800–0740 h the next morning for serum GH determinations. An additional blood sample was withdrawn at 0600 h on the second day for later measurements of serum testosterone and plasma IGF-I concentrations. The subjects were allowed only three standard meals at 0900, 1200, and 1700 h as well as a caffeine-free bedtime snack and water as desired. Normal activity was encouraged during the day, but subjects remained in bed with lights and television off between 2300–0600 h (with bathroom use as required).

Deconvolution modeling

The application of our deconvolution model for the estimation of endogenous GH secretory parameters has been described in detail (9, 10). Briefly, the goal of the model is the estimation of individual hormone secretion and clearance parameters based on serum hormone concentration-time series. The serum GH concentrations are assumed to arise from discrete GH secretory bursts with determinable durations, amplitudes, and temporal locations. Each molecule of secreted GH is then assumed to be acted upon by subject-specific clearance kinetics (8). For the present study, GH clearance was modeled as a one-compartment model, with a unique rate constant for each subject. A one-compartment model was chosen since the 20-min sampling paradigm did not provide sufficient information for assessment of the first phase distribution. The secretion and clearance functions were related by a convolution integral (8). The individual secretion and elimination functions were then estimated simultaneously by nonlinear least squares methods, as previously described (8).

Statistical analyses

Comparisons of group mean parameter estimates were made using analysis of variance, followed by Duncan's multiple range test. Secretory parameters were generally not distributed normally and were logarithmically transformed before analysis (9). Correlations between variables were assessed using linear regression analysis. Body mass index (BMI) was calculated using the formula: wt (kg)/ht (m^2) (Quetelet index). The values were then converted to the age-appropriate SD score (SDS) using previously reported standards (11). Results are expressed as the mean ± SEM. Statistical significance was accepted at $P < 0.05$, but individual P values are included to assist in the reader's own interpretation of the data.

Results

Illustrated in Fig. 1 are the measured serum GH concentrations (discrete data points in the *upper panels*), the computed pituitary GH secretion rates (*lower panel*), and the calculated reconvolution curves (continuous curves, *upper panels*) for three study subjects. The continuous calculated (deconvolution-predicted) curves depict the serum GH concentration profiles generated when GH secretory events occur as estimated in the *lower panels*. These fitted curves allow the investigator to directly visualize how well the model describes the actual measured hormone concentrations, thereby providing a check on the reasonableness of the estimated parameters. The predicted convolution curves very closely approximate the measured GH concentrations of the subjects. Similar close approximations were obtained for all 46 data sets in the present study. In addition, an objective measure of the fit is provided by the percentage ratio of the square root of the residual variance to the mean serum GH concentration. This coefficient of variation was less than 12% in the present analysis.

Based on this deconvolution technique, the GH concentration-time series of all subjects could be accounted for by 10.6 ± 0.5 (mean ± SEM) discrete pituitary secretory bursts/24 h (range, 3–18). Each deconvolution-estimated GH secretory burst had a mean half-duration (the duration at half-maximal amplitude) of 37 ± 1.5 min. (13–71 min). Predicted secretory bursts were separated by periods of 149 ± 6.8 min (67–260 min) during which little or no secretory activity occurred. The mass of GH released per burst averaged 29 ± 2.6 μg/L distribution volume. The estimated half-life of GH disappearance (first order model, see *Materials and Methods*) was

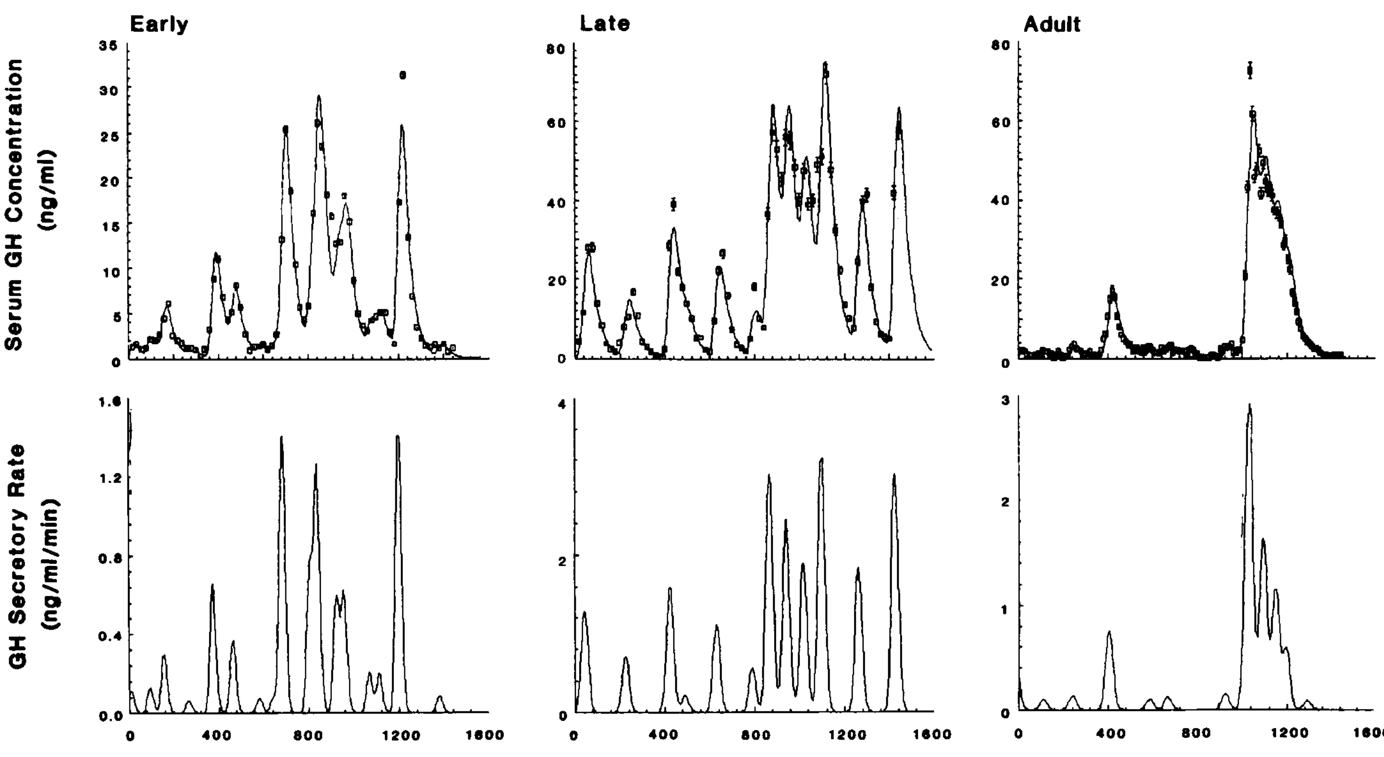

FIG. 1. Shown here are data from three study subjects, one in early puberty (two sets of axes to *left*), one in late puberty (two *center* sets of axes), and one young adult (two sets of axes to *right*). Note the differences in the range of the *vertical axes*. For each individual there are three plots of data. The discrete data points in the *upper panels* represent the measured serum immunoreactive GH concentrations obtained every 20 min over 24 h. Graphic representations of the underlying pituitary secretory events estimated by the deconvolution procedure appear in the *lower panels* (shown as GH secretory rates). Continuous reconvolution curves are shown in the *upper panels* to represent the hormone concentration profiles expected when the pituitary secretory events occur as predicted. The calculated (deconvolution-derived) curves very closely approximate the measured GH concentrations for each of the subjects. Similar close approximations were present for all 46 data sets.

23 ± 0.5 min and ranged from 16–33 min in the 54 profiles examined.

Endogenous GH secretion rate vs. age and pubertal status

The mass of GH secreted per 24-h period was calculated as the product of the daily secretion rate (micrograms per L vol/24 h) and an estimated distribution volume of 7.9% body weight (12). These values, arranged by the subjects' chronological ages, are illustrated in Fig. 2. Although there is a large degree of interindividual variability, the highest measured values clearly occur in boys of the midadolescent age range. To evaluate the effect of puberty on GH secretion characteristics, the data were grouped according to the subjects' degree of pubertal development, as described previously (1). As shown in Table 1, the total quantity of GH released per 24 h (column 2) was greater for later pubertal boys than for boys in any other pubertal group. The mean value for these later pubertal subjects (1810 ± 250 μg/24 h) was triple that for prepubertal boys (610 ± 65 μg/24 h).

To account for the increases in body size and total distribution volume that occur with age, GH secretion values were normalized for body surface area (Table 1, column 3) and unit of distribution volume (Table 1, column 4). The estimated quantity of GH release per m^2 in late pubertal boys was still greater than the value for any other pubertal group. The mean value of 1160 μg GH/m^2·24 h in late puberty was nearly double the next closest value (600 μg/m^2·24 h for prepubertal boys).

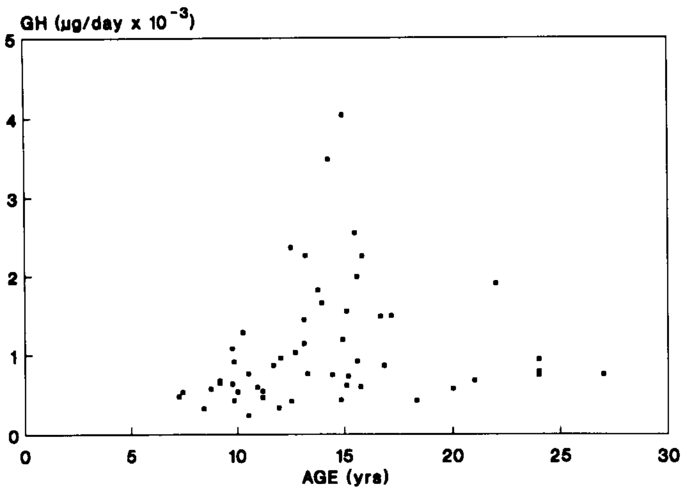

FIG. 2. The estimated quantity of GH secreted during each study period (n = 46) for the normal boys and young men is illustrated according to the subjects' chronological ages. The values were obtained by multiple parameter deconvolution analysis of GH concentration-time series based on blood samples obtained every 20 min for 24 h. The calculated GH secretion rate (micrograms per L distribution volume/24 h) was multiplied by an assumed distribution volume of 7.9% body weight (12) to obtain the illustrated estimates.

TABLE 1. Daily GH secretion values of normal boys and young men determined by deconvolution analysis

	n	Total GH secretion (μg/24 h)[a]	GH secretion/m^2 body surface (μg/m^2·day)	Daily GH secretion rate (μg/L·24 h)
Prepubertal	11	610 ± 65[b]	600 ± 58[b]	270 ± 25[b,c]
Early pubertal	12	740 ± 110[b]	570 ± 90[b]	230 ± 39[b,d]
Late pubertal	16	1810 ± 250[d]	1160 ± 160[d]	440 ± 63[c]
Postpubertal	7	900 ± 170[b]	490 ± 95[b]	160 ± 33[b,d]
Adult	8	910 ± 150[b]	500 ± 82[b]	170 ± 27[d]

The values were obtained by multiple parameter deconvolution analysis (8) of GH concentration-time series from GH concentrations in blood samples obtained every 20 min for 24 h. All values are the mean ± SEM. The subjects were divided into the five study groups by degree of pubertal development based on physical exam and skeletal maturity, as described previously in detail (1). Any two values within a column that are not followed by the same letter superscript differ significantly from one another ($P < 0.05$).

[a] Assuming a distribution volume of 7.9% body weight (12).

Similarly, the GH secretion rate (micrograms of GH per L vol/24 h) was higher in the late pubertal subjects than in the early pubertal, postpubertal, or adult groups, but was not statistically distinguishable from the mean prepubertal value. Since replacement doses of human GH are often calculated based on the subject's weight, we also estimated the quantity of daily GH secreted per kg BW. The values range from 5.1–71 μg/kg·24 h, with the mean (±SE) values for the pubertal groups as follows: prepubertal, 21 ± 2.0; early pubertal, 19 ± 3.1; late pubertal, 35 ± 5.0; postpubertal, 13 ± 2.6; and adult, 13 ± 2.1.

We next sought to identify the primary changes in secretory parameters giving rise to this pubertal increase in daily GH release. To address this, the relationships between deconvolution-derived GH secretory characteristics and chronological age were assessed using linear regression analysis for boys who were still growing and undergoing pubertal development (*e.g.* excluding subjects with fused epiphyses). As expected from the appearance of Fig. 2, the estimated total quantity of daily GH secretion and of GH secretion per unit (m^2) body surface increased significantly with age ($r = 0.58$, $P < 0.001$; and $r = 0.42$, $P = 0.007$, respectively) in growing boys. Among the assessed GH secretory parameters, only the mass of GH secreted per burst and maximal rate of GH secretion (burst amplitude) correlated directly with increasing age ($r = 0.37$, $P = 0.02$; and $r = 0.34$, $P = 0.03$, respectively). In contrast, there were no significant linear correlations between the subject's age and 24-h GH secretory burst frequency, the interval between consecutive secretory bursts, burst half-duration, or estimated serum GH half-life ($P > 0.05$ for all). The estimated GH secretory values for all subjects, divided into the same pubertal groups, are shown in Table 2.

GH secretory parameters of growing boys (not includ-

TABLE 2. Deconvolution analysis-derived pituitary GH secretory parameters underlying 24-h serum GH concentration-time series of normal boys and young men

	GH mass/burst (μg/L vol)	Secretory burst amplitude (μg/ L vol·min)	Burst half-duration (min)	Interburst interval (min)	24-h burst frequency (no./24 h)	Serum GH half-life (min)
Prepubertal	25 ± 2	0.71 ± 0.07	35 ± 2.5	137 ± 13	11.2 ± 1.3	21 ± 0.7
Early pubertal	24 ± 4	0.64 ± 0.08	34 ± 2.2	159 ± 15	10.1 ± 1.1	21 ± 0.8
Late pubertal	41 ± 5	0.99 ± 0.11	40 ± 3.1	145 ± 11	10.9 ± 0.7	24 ± 1.0
Postpubertal	28 ± 11	0.88 ± 0.40	31 ± 3.6	172 ± 19	8.3 ± 1.2	26 ± 1.9
Adult	17 ± 3	0.38 ± 0.09	45 ± 4.1	141 ± 23	11.8 ± 1.6	26 ± 0.7

The individual GH secretory parameters shown are the mean ± SE of values derived from application of multiple parameter deconvolution analysis (8) to 46 serum GH concentration-time series from normal boys and young men. Estimates of daily GH secretion among these subjects appear in Table 1.

ing subjects in whom growth had ceased) also varied with the serum testosterone concentration. Similar to the relationship with age, total daily GH secretion (r = 0.73) and GH secretion per unit (m^2) body surface (r = 0.61) both varied directly with the serum testosterone level ($P < 0.001$ for each comparison). Among the underlying GH secretory parameters, the strongest relationship to serum testosterone concentration existed for the mass of GH secreted per burst (r = 0.50; $P < 0.001$). Weaker, though statistically significant, positive correlations with testosterone concentration were also present for GH burst amplitude (r = 0.36; $P = 0.02$), burst half-duration (r = 0.37; $P = 0.02$), and estimated serum GH half-life (r = 0.35; $P = 0.03$). However, when values from the postpubertal and adult subjects were included in the analysis, the correlations between serum testosterone concentration and GH secretion per unit body surface, mass of GH secreted per burst, and GH burst amplitude were no longer statistically significant ($P > 0.05$). In contrast, statistically significant correlations were maintained between serum testosterone level and total daily GH secretion (r = 0.42; $P = 0.002$), GH secretory burst half-duration (r = 0.31; $P = 0.02$), and calculated serum GH half-life (r = 0.42; $P = 0.001$). The testosterone level did not correlate significantly ($P < 0.05$) with interburst interval or secretory burst frequency.

Relationship of BMI to GH production characteristics

The relationships between age-adjusted BMI SDS and 24-h GH secretion characteristics were also evaluated using linear regression analysis. These results appear in Table 3 and Fig. 3. As shown (Table 3), the BMI SDS correlated inversely with 24-h GH secretion per unit distribution volume (production rate), daily GH secretion per m^2 body surface, total quantity of daily GH secretion, GH mass per burst, and GH secretory burst amplitude (maximal rate of GH release achieved per pulse). The inverse relationship between the amount of GH secreted daily per kg BW and the subject's BMI SDS is shown in Fig. 3. Although the GH secretion values used to derive these correlations had been subjected to prior log transformation (see *Materials and Methods*), all statistically significant correlations listed in Table 3

TABLE 3. Results of linear regression analysis of the relationship between age-adjusted BMI (z-score) of normal boys and their endogenous 24-h GH secretion characteristics (GH secretion values were log-transformed before analysis)

Secretion characteristic	r	*P*
24-h GH secretion rate (μg/L vol·day)	−0.65	<0.001
24-h mass GH/m^2 body surface	−0.57	<0.001
Total 24-h GH secretion (μg/day)	−0.41	0.005
GH mass/secretory burst (μg/L vol)	−0.59	<0.001
Secretory burst amplitude (μg/L·min)	−0.55	0.005
24-h secretory burst frequency (no./day)	−0.15	0.309
Serum GH half-life (min)	−0.004	0.979

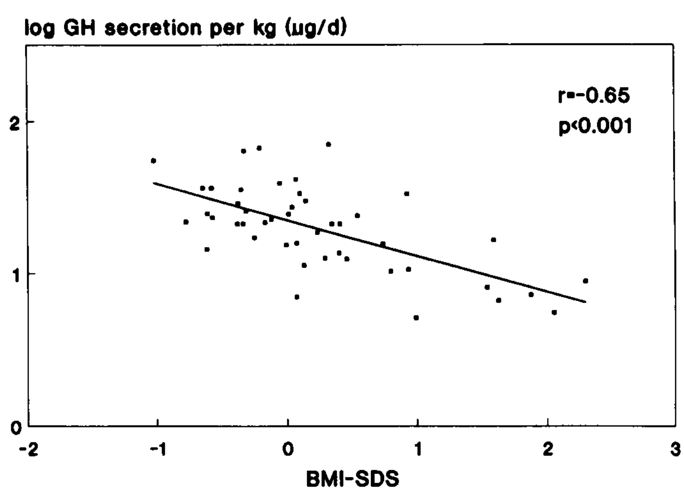

FIG. 3. The inverse linear relationship between the BMI SDS and the quantity of GH secreted per kg BW is illustrated for the normal boys (n = 46). The 24-h GH secretion values were determined for each subject by simultaneous multiple parameter deconvolution analysis of their 24-h serum GH concentration time series. Total estimated GH secretion values were then divided by the subject's body weight. The GH secretion values depicted here were log transformed (see *Materials and Methods*); however, the inverse relationship was also significant for the nontransormed values.

were also significant when nontransformed values were used. In contrast, there was no significant linear correlation between BMI SDS and either the number of GH secretory bursts per 24-h study or the serum GH half-life.

Relationship of IGF-I to GH secretion in normal subjects

There was a direct positive linear relationship between plasma IGF-I concentration and 24-h GH secretion rate among all subjects (Fig. 4). The IGF-I level also correlated directly with 24-h GH secretion per m^2 (r = 0.53; $P < 0.001$), total daily GH secretion (r = 0.52; $P < 0.001$), GH mass per secretory burst (r = 0.39; $P = 0.003$), and GH burst amplitude (r = 0.33; $P = 0.014$). However, similar to the finding for BMI SDS, the plasma IGF-I concentration did not correlate with the number of GH secretory bursts (r = 0.12; $P = 0.388$) or the serum GH half-life (r = 0.08; $P = 0.548$). In addition, there was no significant correlation between plasma IGF-I level and BMI-SDS regardless of whether IGF-I values were evaluated in absolute terms or as the z-score for age.

Discussion

The present study indicates that the quantity of pituitary GH secreted nearly triples in boys during mid- to late-puberty compared to prepubertal secretion. When differences in body size are accounted for, the mass of GH secreted per day (expressed either per unit distribution volume or per unit body surface area) still nearly doubles during the middle to later stages of puberty. The primary neuroendocrine alteration responsible for this enhanced GH secretion is an increased mass of GH released per secretory burst, resulting from an increase in the maximal rate of GH release during a burst. These changes are specific, in that they are largely unaccompanied by alterations in GH burst frequency, burst duration, or serum GH half-life. Our data also suggest that some of the variation in GH secretion among individuals of normal stature is related to differences in body composition, even when these differences are within the normal range.

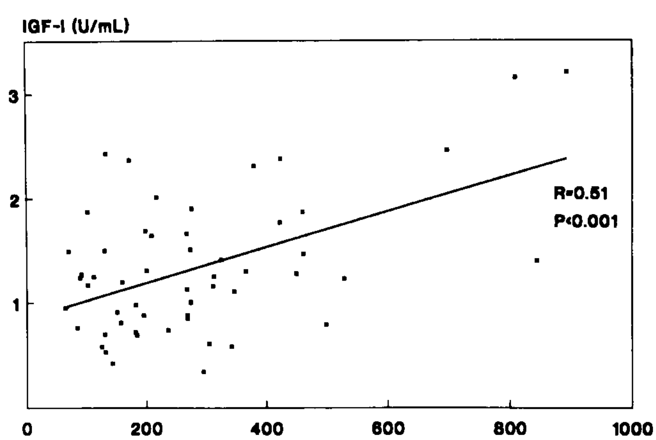

FIG. 4. Plasma IGF-I concentrations obtained at 0600 h during 24-h serum GH concentration studies (samples obtained every 20 min for 24 h) of the normal boys and young men are plotted according to the calculated GH secretion rates. As illustrated, there was a statistically significant positive linear relationship between plasma IGF-I and 24-h spontaneous GH production rate.

In a recent report, Hartman *et al.* (10) used the same deconvolution procedure employed here to evaluate spontaneous GH secretion in 12 normal men based on serum GH concentrations measured in blood collected at 5-min intervals over 24 h. By analyzing the parent 5-min data and constituent 10-, 15-, 20-, and 30-min data series, these investigators determined that estimates of the 24-h endogenous GH production rate and half-life of GH disappearance were statistically indistinguishable at all sampling frequencies. Therefore, the 20-min paradigm employed in the present study is reasonable for accurate and precise estimates of those parameters (24-h GH secretory rates and half-time of disappearance) and other calculations derived from them (such as GH secretion per m^2, *etc.*).

Very few data exist for GH secretion rates in normal pubertal children. However, the secretion rates calculated here for our young adults agree well with previous reports based on other techniques (13–15), where values range from 166–1510 μg/day. Rosenbaum and Gertner (16) recently estimated GH secretion rates in prepubertal children by multiplying the directly measured MCR by published ranges for mean 24-h serum GH concentrations. Their estimates of 260–565 μg/m^2 day also agree well with the values reported here. In another recent report (17), a different deconvolution technique which does not enable calculation of subject-specific clearance kinetics or the detection and identification of individual GH secretory bursts was used to estimate GH secretion rates in a large group of children. Since this method does not provide information on hormone clearance, the GH half-life values from five GH-deficient subjects were inserted into the calculation. Results of that analysis also indicated that the total quantity of GH secreted per 24 h increases 2- to 4-fold during mid- to late-puberty, a finding consistent with our results. Of note, because different immunoassay systems often produce quite different hormone concentration estimates (18), the absolute GH secretion rates estimated by deconvolution analysis are dependent on the specific immunoassay system employed. The GH assay used in the present study generally produces higher GH estimates than other commonly employed assays partly due to its ability to detect both 22- and 20-kDa molecular forms and also to a matrix effect (19).

GH secretion in the male rat is also characterized by augmented release during puberty (see Ref. 20 for review). Data from several studies strongly suggest that alterations in the androgen environment underlie in part this phenomenon. For instance, although serum GH concentrations in male adult rats are higher than those in females (20, 21), this difference depends upon the presence of functional androgen receptors, as demonstrated by absence of typical male pattern GH levels in androgen-resistant (testicular-feminized) male animals (22). *In vitro*, somatotropes from male rats release, on the average, more GH than cells from females in response to GH-releasing hormone, a characteristic not present in somatotropes from androgen-resistant littermates (23). Pituitary cells from male rats exhibit greater GHRH-stimulated GH secretory rates than cells from females (24, 25), a finding also dependent on functional androgen receptors (24). Such data from animal studies complement the recent report by Ulloa-Aguirre and colleagues (26) demonstrating that androgens, acting apart from conversion to estrogen, may be capable of augmenting daily GH production in boys by increasing both the mass of GH secreted per burst and the maximal rate of GH secretion within each burst. Such androgen-induced changes in GH secretion parallel those observed during puberty in our study subjects.

A novel finding in the present study is that several parameters of endogenous GH secretion in the normal boys varied significantly, albeit inversely, with BMI SDS. We used the SDS (or z-score), rather than the absolute BMI, since the normal range for BMI is strictly age dependent during childhood (11). Although it is known that obesity may depress serum GH concentrations and endogenous GH release (27–29), the finding of an inverse relationship between BMI and GH production in normal nonobese boys suggests that variations in body composition represent yet another physiological modulator contributing to the wide range of normal serum GH levels in children. A similar inverse relationship to BMI SDS has recently been described for spontaneously occurring serum GH concentrations in children with precocious puberty (30). The reason why healthy children with larger body mass require less GH production to maintain normal growth than children with comparatively lesser body mass is not yet clear. However, the recent demonstration of a strong positive correlation between BMI SDS and serum high affinity (receptor-related) GH-binding protein (GH-BP) in normal boys suggests one plausible underlying mechanism (31). This concept that alterations in the GH-BP/GH receptor system mediate in part the interrelationship between GH production and body mass is supported further by preliminary studies indicating that serum GH-BP and body mass exert predictable influences on the response to GH replacement therapy in GH-deficient children (32, 33).

The results of the present study also have potential implications with respect to currently employed hGH replacement practices in at least two ways. First, the data indicate that the quantity of GH produced per kg BW in normal boys is not constant, but varies inversely with body mass. That is, for a specific height, normal children who weigh relatively less appear to secrete more GH per kg BW than those who weigh more. This finding raises an obvious question about the basic assumptions underlying our current approach to GH "replacement" therapy. In most instances (at least in the United States), GH is administered as a standard constant dose per kg BW. Therefore, for a specific height, GH-deficient children with relatively greater body weights receive a larger total GH dose than those with less body mass. Rather than mimicking normal physiology, this appears to create a state quite distinct from that in normally growing children. As a result, this practice may be expected to produce variable growth responses among GH-deficient children. This is supported by our own preliminary observations that substantial variability in therapeutic response to GH can be predicted from variations in body mass index and may be mediated by parallel variations in serum GH-BP (32, 33).

A second possible therapeutic implication of these results concerns GH replacement therapy during puberty. Much attention has focused recently on strategies to maximize growth during this critical period. Toward this end, concurrent use of long-acting LHRH analogs to suppress gonadarche in these children has sometimes been advocated. Unfortunately, this approach carries the potential psychological and physiological risks of creating a second endocrinological abnormality during a critical period of psycho-social development (adolescence). Alternatively, it seems reasonable to focus efforts first on more closely recreating the normal endocrinological changes of puberty. In our subjects, the average daily GH secretion rate per kg during later puberty (35 μg/kg·day; 250 μg/kg·week) was nearly double the rate for early pubertal subjects (18 μg/kg·day; 130 μg/kg·week). Furthermore, individual late pubertal boys' values ranged as high as 71 μg/kg·day (497 μg/kg·week). While these endogenous GH secretion estimates fall in the general range of currently used replacement doses, there is an obvious difference, in that the endogenously produced hormone is presented to the target tissues in seven to nine major episodes per day (1) compared to therapeutic injections occurring at most once daily. Based on the results of the present study, we propose that an alternative approach to GH therapy during puberty deserves careful study. Since serum human GH levels return toward baseline 12 h after the sc injection of a typical GH replacement dose (34), addition of a second daily injection 12 h after the first would achieve the goal of doubling the quantity of GH presented to the target tissues (as occurs during normal puberty) while obviating the concern over GH receptor/GH-BP saturation that presumably would occur with further increases in the dose of a single daily injection. The temporary increase to twice daily injections in an attempt to maximize growth before skeletal epiphysial fusion might be as acceptable, if not more acceptable, to individual children (and their parents) as is the idea of arresting their pubertal development with an LHRH analog. Finally, addition of this second GH injection per day may pose less potential risk to children than pharmacological delay of an otherwise normal puberty, since such an increase in daily exposure of the tissues to circulating GH appears to be a condition, and perhaps a requirement, of normal adolescent development. Whereas pulsatile iv GH administration might closely emulate physiological delivery of somatotropic hormone and perhaps afford near-optimal tissue responses (35, 36), the practicability of this mode of endocrine therapy is currently limited in clinical practice.

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