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A Sexually Dimorphic Pattern of Growth Hormone Secretion in the Elderly

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ABSTRACT

In rodents, the sexually dimorphic pattern of pulsatile GH secretion is an important determinant of growth, liver enzyme function and insulin-like growth factor I (IGF-I) expression. Whether this difference is present in humans at different ages is unclear. We studied GH secretory patterns in the elderly by constructing 24-h serum GH profiles in 45 male and 38 female (age, 59.4–73.0 yr) volunteers and related patterns to IGF-I, IGF-binding protein-3 (IGFBP-3), and GH-binding protein levels; body mass index; and waist/hip ratio.

Serum GH concentrations were measured in samples drawn at 20-min intervals and analyzed using a sensitive chemiluminescent assay (Nichols Institute Diagnostics: sensitivity, 0.036 mU/L). The 24-h serum GH profiles were analyzed using a concentration distribution method to determine GH peak and trough levels, spectral analysis, and assessment of serial irregularity by approximate entropy (ApEn).

There was a highly significant difference in mean 24-h serum GH concentrations in females compared to males (males, 0.88 mU/L; females, 1.31 mU/L; $P = 0.009$) as a result of significantly higher trough GH levels (males, 0.04 mU/L; females, 0.16 mU/L; $P < 0.001$). Peak values were not significantly different. Serum IGF-I levels were significantly higher in males (males, 162.4 ng/mL; females, 87.8 ng/mL; $P < 0.001$). Peak GH values were related to serum IGF-I levels (males: r = 0.39; $P = 0.009$; females: r = 0.5; $P = 0.002$), whereas trough GH levels were not. IGFBP-3 levels were similar and related to GH peaks only in males (r = 0.32; $P = 0.03$). GH was secreted with a dominant periodicity of 200 min in males and 280 min in females ($P < 0.025$). The proportion of time taken up by regular oscillatory activity was less in females (females, 11.1%; males, 14.7%; $P = 0.01$). GH secretion assessed by ApEn was more disordered in females (males, 0.60; females, 0.81; $P < 0.001$), and increasing disorder was associated with lower IGF-I levels. Body mass index was negatively related to GH in both sexes. In males, trough values were the major determinant (r = −0.31; $P = 0.04$), whereas in females, the peak value was the major determinant (r = −0.35; $P = 0.04$). Trough GH levels were inversely related in both sexes to waist/hip ratio (males: r = −0.40; $P = 0.006$; females: r = −0.44; $P = 0.006$) and to increasing secretory disorder (ApEn; r = −0.46; $P < 0.001$). These data demonstrate a sexually dimorphic pattern of GH secretion in the elderly. (*J Clin Endocrinol Metab* **84:** 2679–2685, 1999)

IN THE MAJORITY of animal species studied, GH is secreted in a pulsatile manner (1). There is a sexually dimorphic pattern of GH secretion in rodents, which is an important determinant of the sexually dimorphic pattern of growth, liver enzyme function, circulating GH-binding protein (GHBP) concentration, and hepatic GH receptor levels (2–4). There is increasing evidence that intracellular pathways responsible for GH signaling (STAT 5b) respond differently to continuous or intermittent exposure to GH (5). Adult male rats display a discrete high amplitude, pulsatile pattern of GH secretion, with a peak periodicity of 3 h, whereas pulsatile secretion in the female is of low amplitude with irregular periodicity. Recent studies have underscored the importance of GH pulsatility and GH pulse amplitude rather than total GH dose for growth stimulation in the rat. If baseline GH levels are increased without a concomitant increase in peak concentrations, the growth rate is stimulated relatively poorly. Conversely, low trough concentrations between pulses in male rats are not absolutely required for growth stimulation, provided that high amplitude pulses are present (6).

There is increasing evidence to suggest that a sexually dimorphic pattern of GH secretion is present in the human. The majority of work has centered on identifying significantly higher mean 24-h serum GH concentrations in females compared to males (7–10). In a small number of young men and women, Pincus *et al.* (11) have confirmed these observations and noted that females exhibited greater statistical irregularity in their GH time series than males. Beside these observations, little is known about the contribution made by components of the GH signal to the mean value derived or whether these differences can be observed at different ages.

Alterations in the pattern of the GH signal in man could have effects on target organ functions similar to those seen in rodents. There is circumstantial evidence from studies of GH replacement that this may be the case (12, 13), and we have recently demonstrated that peak and trough GH concentrations have different associations with the insulin-like growth factor (IGF) axis, body composition and metabolic parameters in adult males, 59–70 yr of age (14). We now report an extension of this study to include adult postmenopausal females using a technique for determining the trough component of GH profiles (15), spectral analysis (16), and

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assessment of serial irregularity employing approximate entropy (ApEn) (17, 18).

Subjects and Methods

Subjects

Forty-five men and 38 postmenopausal women, between 59.4–73.0 yr of age, were studied. The cohort was drawn from a larger population study of risk factors for cardiovascular disease comprising 3000 individuals. Anthropometric and social profiles did not differ between the 83 individuals and the UK population. No subject was receiving medications known to influence GH secretion, and none of the women were receiving hormone replacement therapy. Standard anthropometric measures of height, weight, and waist and hip circumference were obtained. Body mass index (BMI) was calculated using the formula: weight (kilograms)/height^2 (meters). Waist and hip measurements were expressed as the waist/hip ratio (WHR).

Subjects were admitted to the Clinical Investigation Area of the Middlesex Hospital on the day before the construction of the 24-h GH profile to acclimatize them to the hospital environment. Standard meals were provided at 0800, 1230, and 1730 h, and exercise was permitted within the confines of the hospital. Smoking was not permitted. On the study day blood samples were drawn from an indwelling iv cannula for the measurement of serum GH concentrations from 0730 h and at 20-min intervals for 24 h. At 0600 h, an additional sample was drawn for the measurement of serum concentrations of IGF-I, IGF-binding protein-3 (IGFBP-3), T_4, LH, FSH, PRL, testosterone, estradiol, and GHBP. The studies were approved by the ethics committee of University College London Hospitals, and written informed consent was obtained.

Hormone assays

GH. GH concentrations were measured using the Nichols Chemiluminescent assay for human GH (Nichols Institute Diagnostics, San Juan Capistrano, CA). The assay was modified as described in our previous report (14), and an additional standard of 0.014 mU/L was included to define the working range more adequately. The sensitivity of the assay [mean of zero tubes (n = 10) + 3SD] was 0.036 mU/L (1 μg/L = 2.6 mU/L), and a limit of detection of 0.04 mU/L was used throughout. Eight of the 45 males had GH values below the detection limit, but none of the females had values as low as this. The between-assay coefficients of variation (CVs) at serum GH concentrations of 3.3, 6.3, and 18.0 mU/L were 12.1%, 12.3%, and 9.0% respectively. Within-assay CVs at GH concentrations of 0.4, 10.0, 18.6, and 23.3 mU/L were 5.5%, 6.8%, 10.5%, and 10.8%, respectively. The assay standards were calibrated against the First International Standard (80/505).

IGF-I. Serum IGF-I was measured using an in-house polyclonal RIA with acid/alcohol extraction. The sensitivity of the assay was 13.6 ng/mL. The within-assay CVs were 11.3%, 6.5%, and 4.7% at serum concentrations of 44.6, 238.6, and 684.8 ng/mL, respectively. Between-assay CVs were 10.5%, 12.1%, and 5.1% at concentrations of 73.7, 192.1, and 684.8 ng/mL, respectively.

IGFBP-3. Serum IGFBP-3 was measured using a RIA kit (Diagnostics Systems Laboratories, Inc., Webster, TX). Samples were analyzed at a 1:100 dilution. The within-assay CVs were 3.9%, 3.2%, and 1.8% at serum concentrations of 7.4, 27.5, and 7.8 μg/L, respectively, and the between-assay CVs were 7.6% and 4.2% at serum concentrations of 5.4 and 27.2 μg/L, respectively. The standards were calibrated against recombinant IGFBP-3, originally quantified by amino acid analysis. The minimum detection limit of the assay was 0.5 μg/L.

Other measurements. GHBP concentrations were measured using a ligand-mediated immunofunctional assay (19). The concentrations of testosterone, estradiol, and T_4 were measured using standard commercial RIA kits. Gonadotropin levels were measured using immunoradiometric assay systems.

Analysis of hormone pulsatility

Peak and trough assessments. A distribution method for analysis of 24-h GH profiles was used (15). For each 24-h serum GH concentration profile, the cumulative frequency distribution was calculated, and from the probability-serum GH concentration distribution plot, discrete probabilities (linear probits) were derived. The threshold concentration at or below which the 24-h profile spent 5% trough or 95% peak of the time could then be estimated from the regression equation. These values are termed the observed concentration (OC) at which the profile spends 5% (OC5) or 95% (OC95) of the time. For the sake of clarity, these derivations will be known as peak, meaning OC95, and trough, meaning OC5.

Fourier spectral analysis. As a means of quantifying the degree of periodicity in the data series, spectral analysis was performed (16, 20). The strength of each signal (*i.e.* its contribution to the overall function) is displayed as a histogram relating the power of the signal to any particular frequency or period. When variability is random, the spectrum would be approximately flat. Results can be expressed as a percentage of the constant power of the signal and are referred to as relative power. This gives a measure of oscillatory activity within the data array. Absolute FT depicts oscillations without respect to the mean concentration, in effect the amplitude component of the signal. Formal testing of the differences between spectra was made using the technique of Bridges *et al.* (21).

ApEn analysis. To quantify sequential irregularity, we used ApEn, a model- and scale-independent statistic whose mathematical description and statistics have been described previously (17, 18, 22). ApEn is complementary to pulse detection algorithms, and it evaluates both dominant and subordinant patterns in data. It will detect changes in underlying episodic behavior that do not reflect peak occurrences or amplitudes. ApEn assigns a nonnegative number to a time series with larger values corresponding to greater apparent process randomness and smaller values to more recognizable patterns or features. The value is derived from the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on the next incremental comparison. Profiles were analyzed with m = 1 and r = 20% of the SD of the individual subject time series (23). These values produce good statistical reproducibility in theoretical practice (17) and endocrine practice (11).

Statistics

Nonnormally distributed data were natural log transformed before analysis. Univariate and multiple linear regression were used to explore relationships between various parameters. The differences between regression slopes and the differences in line positions of the IGF-I-GH and WHR-GH relationships were evaluated using techniques for regression in groups and analysis of covariance (24). Where appropriate, Student's *t* test was used to compare two groups.

Results

General (Table 1)

The mean ages of the male and female subjects were similar. Mean heights and weights showed the differences expected between the sexes. BMI was similar in both sexes, but WHR was significantly lower in the females. Gonadotropin concentrations were significantly different between the sexes because of the postmenopausal state in the women, which was supported by undetectable plasma estradiol levels in the majority. In the males, only one individual had elevated gonadotropin and low testosterone concentrations. Serum PRL and T_4 concentrations were within the normal ranges.

GH secretory patterns

Peaks and troughs. Figure 1 illustrates the pulsatile patterns observed in two representative subjects. Mean 24-h serum GH concentrations were significantly higher in the females [females, 1.31 (SD, 0.87) mU/L; males, 0.88 (SD, 0.42) mU/L; $P = 0.009$]. This difference arose as a result of significantly lower trough GH concentrations in the males compared to

TABLE 1. Anthropometric and endocrine characteristics of the male and female subjects

	Males (n = 45)	Females (n = 38)	*P* value
Age (yr)	64.2 (59.4–69.9)	64.6 (61.2–73.0)	NS
Ht (cm)	172.5 (155.2–186.3)	160.3 (150.4–169.7)	<0.001
Wt (kg)	79.5 (62.0–100.0)	71.0 (45.5–104.5)	0.001
Waist/hip ratio (%)	93.1 (81.1–105.0)	78.8 (65.0–92.0)	<0.001
Body mass index (kg/m^2)	26.7 (21.9–36.5)	27.6 (18.3–38.6)	NS
Peak GH (mU/L)	4.0 (0.9–10.6)	4.6 (0.9–15.8)	NS
Trough GH (mU/L)	0.04 (0.001–0.34)	0.16 (0.001–1.24)	<0.001
IGF-I (ng/mL)	162.4 (75.2–255.4)	87.8 (51.0–182.5)	<0.001
IGFBP-3 (μg/L)	2.45 (1.59–3.31)	2.42 (1.59–3.92)	NS
GHBP	309.3 (81.7–1028)	250.3 (75.9–1000)	NS
LH (U/L)	6.1 (1.7–33.5)	22.1 (11.6–40.9)	<0.001
FSH (U/L)	7.6 (3.2–28.0)	44.6 (22.3–82.3)	<0.001
Testosterone (nmol/L)	16.2 (2.7–33.2)	1.3 (0.5–3.0)	<0.001
Estradiol (pmol/L)	74.5 (8.2–146.0)	71.8 (10.5–104.0)	NS

Data shown are means, with ranges in *parentheses*.

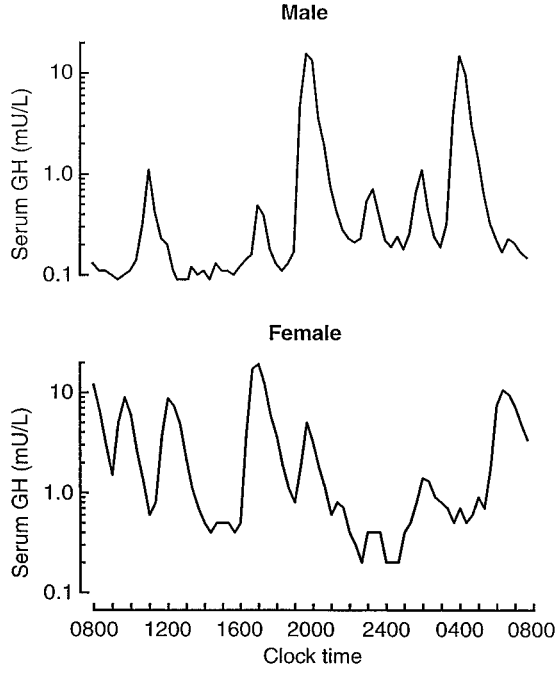

FIG. 1. Representative male (*upper panel*) and female (*lower panel*) 24-h serum GH concentration profiles. Note the logarithmic scale on the GH axis.

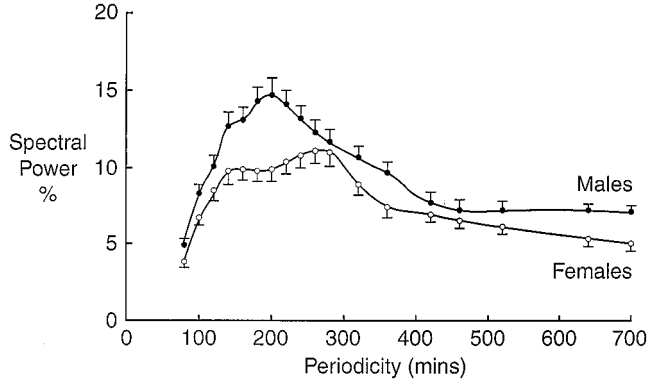

FIG. 2. Relative Fourier transforms of 24-h serum GH concentration profiles in men (*closed circles*) and women (*open circles*). Data are shown as the mean ± SEM. Where bars fail to overlap, a significant difference in spectral power exists at the $P < 0.025$ level. Males pulse with a dominant periodicity of 200 min, with 14.7% oscillatory activity, whereas females had a less well defined periodicity between 180–280 min, with a lower oscillatory activity (11.1%).

the females. Peak values were similar between the sexes (Table 1). Mean plasma estradiol concentrations were similar between the sexes. Neither peak, trough, nor mean GH levels appeared to be related to sex steroid levels. None of the GH parameters was related significantly to the age of the subject.

Fourier spectral analysis. Aggregated Fourier transform spectral estimates for male and female subjects are shown in Fig. 2. The male subjects had a sharply defined dominant periodicity of 200 min, with a spectral power of 14.7% (SEM, 1.1). In contrast, female subjects had a less well defined dominant periodicity range (180–280 min), with the more dominant peak occurring at 280 min. This represented a significant shift toward slower frequency oscillations in the females ($P < 0.025$), which was also associated with a significant reduction in oscillatory activity [females, 11.1% (SEM, 0.8); males, 14.7% (SEM, 1.1); $P = 0.01$]. The amplitudes of the GH profiles, as derived from the absolute Fourier transform, were similar between the sexes (females, 14.4% (SEM, 2.0); males, 14.4% (SEM, 1.8); P = NS].

ApEn analysis. Figure 3 depicts a scatterplot of ApEn values between the sexes. ApEn was significantly higher, that is GH secretion more irregular, in females [mean for females, 0.81 (SD, 0.23); mean for males, 0.60 (SD, 0.20); $P < 0.001$]. Both highest and lowest ApEn values were reasonably associated with appropriate gender match. For example, for ApEn > 0.75 there were 21 females who exceeded this value, in contrast to 6 males.

GH and the IGF axis

IGF-I and IGFBP-3. Peak GH concentrations were significantly related to serum IGF-I levels in both sexes (males: r = 0.39; $P = 0.009$; females: r = 0.5; $P = 0.001$). The slopes of the regressions were similar (males: 24.8; SE, 8.8; females: 21.6; SE, 6.3), but the regression line was set higher in the males, so that for any given peak serum GH value, males had greater serum IGF-I levels than females (regression constant for males, 134.9; females, 58.8; by analysis of covariance, $P <$

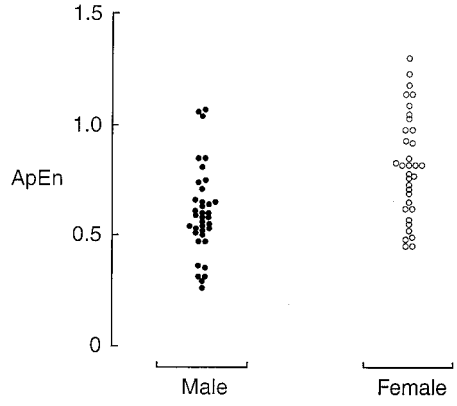

FIG. 3. Scatterplot of individual subject ApEn values for men (*left panel*) and women (*right panel*). High ApEn values imply greater irregularity.

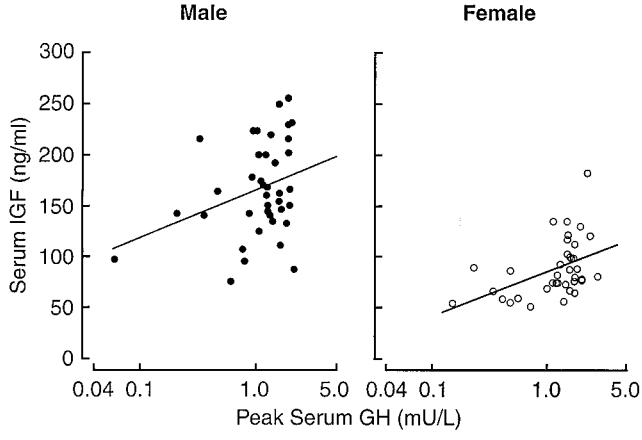

FIG. 4. The relationship between peak serum GH concentrations and serum IGF-I levels in men (a; *left panel*; $r^2 = 0.15$; $P = 0.009$) and women (b; *right panel*; $r^2 = 0.25$; $P = 0.001$). The slopes of the regression lines are similar, but the lines were set higher in males than females ($P < 0.001$).

0.001; Fig. 4). There was no relationship between trough GH concentrations and IGF-I levels. However, ApEn was negatively correlated to IGF-I levels ($r = -0.45$; $P < 0.001$).

There was a positive relationship between peak GH values and serum IGFBP-3 concentrations in males ($r = 0.32$; $P = 0.03$; slope gradient), but this was not observed in the females ($r = 0.05$; $P =$ NS). This was despite similar serum IGFBP-3 concentrations in males and females (Table 1). Trough values did not influence IGFBP-3 levels, and only in males was there an independent effect of plasma estradiol concentration on IGFBP-3 ($r = 0.33$; $P = 0.04$). ApEn values were not related to IGFBP-3 ($r = -0.06$; $P =$ NS).

GH and GHBP. Serum GHBP concentrations were slightly, but not significantly, lower in females compared to males (Table 1). In both sexes the serum GHBP concentration was strongly related to current weight and BMI ($r = 0.35$; $P = 0.002$ for both), but not to WHR or current height. Although trough GH concentrations were negatively related to serum GHBP levels in both sexes, this effect disappeared in multiple regression analysis with BMI.

GH and body composition

BMI. Peak serum GH values tracked significantly and inversely with BMI in females ($r = -0.35$; $P = 0.04$), whereas trough GH values were related more to BMI in males ($r = -0.31$; $P = 0.04$).

WHR. Trough GH concentrations were significantly related to WHR in both sexes (males: $r = -0.40$; $P = 0.006$; females: $r = -0.44$; $P = 0.006$). The slopes of the regressions were similar (males: $r = -1.7$; SE, 0.03; females: $r = -1.8$; SE, 0.04), but the regression line was set higher in the males, so that for any given peak serum GH value, males had a greater WHR than females (males, constant 87.3; females, 74.2; by analysis of covariance, $P < 0.001$; Fig. 5). There was no significant relationship between peak GH concentrations and WHR.

Discussion

These data demonstrate a clear difference in the serum GH concentration profiles between elderly male and female subjects. Mean 24-h serum GH concentrations were greater in the females than in males, confirming observations made in other populations (9, 11, 25). The major difference between the two sexes at this age lies less in the peak GH levels achieved and more in an elevation of trough concentrations, with a 4-fold increase in trough GH concentrations in the female compared to that in the male. In addition, the pattern of GH secretion differed significantly between the sexes, with females secreting GH in a more disordered manner (as assessed by ApEn) than males, confirming observations in a younger cohort (11). This was verified independently by a reduced spectral peak in the females compared to the males, indicating a reduced period of time during which regular GH oscillatory events took place. Further, there was a significant difference in the periodicity of these regular events between the sexes, with a slower pulse pattern observed in the females.

In most respects the pattern of GH concentration profiles observed in this study were similar to those observed in rodents. In the adult male rat, there are discrete high am-

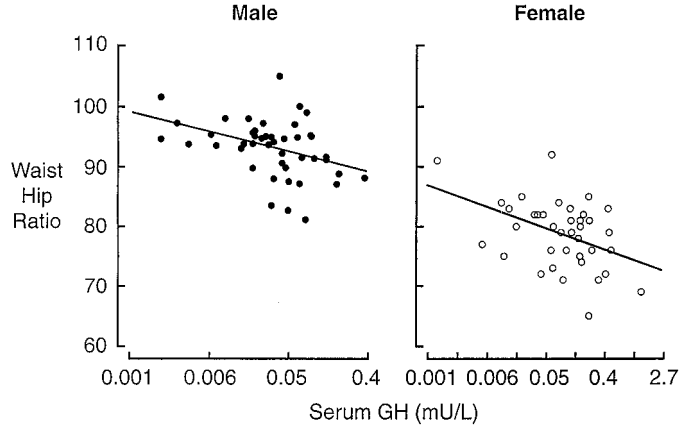

FIG. 5. The relationship between trough serum GH concentrations and WHR in men (a; *left panel*; $r^2 = 0.16$; $P = 0.006$) and women (b; *right panel*; $r^2 = 0.19$; $P = 0.006$). The slopes of the regression lines are similar, but the lines were set higher in males than females ($P < 0.001$).

plitude, pulsatile patterns of GH secretion, with a peak periodicity of approximately 3 h, whereas in the adult female rat, the pulsatile secretion is set at a lower amplitude, with an irregular periodicity (1, 2). The primary difference between the species is that female rats secrete GH at a faster pulse frequency than males and with lower pulse amplitudes, the opposite of what was found in this human study, although female rats are estrogen replete. This may relate either to the difference in sex steroid concentrations in this population [testosterone levels are inversely related to GH pulse frequency (26)] or to the use of a more sophisticated method for the analysis of regularity within a time series.

The pattern of hormone pulsatility observed in rodents largely depends on the close interplay between GHRH and somatostatin. In the male rat and *in vitro* studies, it has been postulated that GHRH and somatostatin cycle out of phase by 180° with each other, such that a GH pulse is engendered by a rise in hypothalamo-portal GHRH concentrations concomitant with a fall in somatostatin (27, 28). These findings, although applicable to the rodent, are more difficult to replicate in other species, although there is evidence to support the suggestion that a similar situation pertains in the generation of a GH pulse in man (29). In the female rat it is proposed that there is less regularity in the secretion of these hypothalamic peptides, leading to the more disordered secretion observed.

Other hormones that might influence the pulsatile pattern are sex steroids. In this elderly population, plasma estradiol concentrations were low in both sexes, with the expected difference in serum testosterone concentrations. It would appear unlikely that estradiol levels were the main determinant of the difference in the pulsatile pattern, as the actual differences between male and female levels were quite small. In addition, the major difference between the sexes lay in trough concentrations and not in peak values. Data obtained in younger populations have suggested that the main effect of estradiol in the human is to augment the pulse amplitude of the GH secretory pattern without any obvious effect on trough values (30–32). That peak values were similar between the sexes in this elderly population suggests that the difference between the sexes in this attribute would be greater in a younger population.

It is unlikely that the difference is explained by the difference in testosterone concentrations between the sexes. The majority of the testosterone effect on pulsatile GH secretion appears to be mediated by aromatization of testosterone to estradiol (33–35). As the peripheral concentrations of estradiol were similar between the sexes, this would be a less likely explanation, although the possibility that hypothalamo-pituitary aromatization of testosterone to estradiol leads to higher concentrations of estradiol in those structures cannot be excluded. Evidence certainly exists in animals to suggest that part of the sexual dimorphic pattern of GH secretion is due to a reduction in the inhibitory effect of somatostatin in females, which may be estrogen mediated (36). In humans, a similar situation may pertain, with different feedback inhibition of GH release by IGF-I (10) and glucose (37) in males compared to females. Even if the difference were attributable to estradiol, the preservation of the sexually dimorphic pattern of GH secretion after the menopause would raise the intriguing possibility that the pattern once defined remains fixed. Whether this represents early neonatal programming, as in the rodent (2), or follows from sex steroid exposure during puberty is unclear (38).

We have previously demonstrated that peak and trough GH concentrations have different associations with IGF axis, body composition, and metabolic parameters in adult males, aged 59–70 yr (14). The data in this study, which extend our previous observations by including a female population, largely confirm the observations made in the male population. Serum IGF-I concentrations in both males and females were significantly related only to peak concentrations. The slopes of the regression lines were similar, implying that GH sensitivity was similar in both sexes. As the constant of the regression equation was significantly lower in the female population, it would appear that the system is set at a lower operation value in the females. Whether this reflects the contributions of differences in trough concentrations needs to be tested more formally. There was no relationship between the trough GH concentration and IGF-I levels, but regularity appeared to be an important factor. These observations extend our findings in the elderly male population and confirm other reports of the importance of the peak GH value in determining the level of IGF-I (32, 39). That trough concentrations might modify the amount of IGF-I that can be generated is suggested largely by the observations of differences in the serum IGF-I levels between adult male and female rats. Recent studies have underscored the importance of GH pulsatility and GH pulse amplitude (rather than total GH dose) for growth stimulation in the rat (6). A similar situation appears to pertain in short children; those who have the slowest growth rate and generate the least IGF-I in response to GH tend to have the highest trough concentrations (40). These observations coupled with evidence of the altered IGF-I feedback (10) serve to heighten the difference between the sexes.

Although serum IGFBP-3 concentrations were similar between the sexes, it was only in the males that a relationship with circulating GH levels could be established. A similar situation has been observed in young and old postmenopausal women, in whom a reduction with age in circulating GH and IGF-I, but not IGFBP-3, was noted (41).

Peak and trough GH levels have differing relationships with BMI in this population. In males, trough GH concentrations appeared to relate (inversely) to BMI, whereas both peak and trough concentrations appeared to be related (inversely) with BMI in the female. These observations confirm previous studies that have found a greater correlation between GH secretory status and BMI in females than in males (42). It is difficult to explain precisely why there is a lack of peak GH effect on BMI in males, but this may relate in part to the heterogeneous populations that have been studied in previous reports, particularly in studies where a wide range in age of the population has been analyzed and where there is perhaps greater variance in BMI values than in this more focussed study population. An alternative explanation is that the overall measure that BMI represents does not adequately represent the components of body composition between the sexes (38). Support for this suggestion comes from analysis of the relationship between trough GH and WHR in this and

other populations (38). Trough GH concentrations were significantly related to WHR in both sexes. The slopes of the regression lines were similar, whereas the regression line was set at a higher level in the male so that at any given trough serum GH value males had a higher WHR than females. There was no relationship between peak GH and WHR. These observations suggest that trough GH concentrations may be one of the mechanisms by which WHR values differ between the sexes.

In conclusion, we have demonstrated a sexually dimorphic pattern of GH secretion in the elderly. These findings confirm a number of studies that show GH concentrations during oral glucose loading to be higher in the female population (37), mean concentrations of GH to be slightly higher in females than males (9, 11, 25), and the dose of GH required to produce effects in GH-deficient adults higher in females than males (43). All of these observations serve to highlight the possibility that in females there is a degree of GH insensitivity and raise the question of whether this relates to the trough/more constant exposure component of the GH secretory profile. The major difference in the pattern of GH secretion appeared to reside in the trough concentration parameter, which was 4 times higher in females than males, whereas peak serum GH values were similar. GH was secreted in a more disorderly manner in females and at a slower and less well defined pulse periodicity. The differences in trough concentrations influenced a number of measures of body composition, particularly WHR. Peak GH concentrations largely determined serum IGF-I levels, with the relationship set at a lower value in females. These GH observations might explain the differences in body composition seen in the elderly. From a practical standpoint, these gender differences suggest that in the context of GH replacement in adults, the same level of GH might be expected to influence body composition and IGF-I levels in different ways in the sexes. In terms of GH administration or the use of other agents to enhance GH secretion (*e.g.* GHRH or GH-releasing substances), consideration needs to be given in devising dosing schedules relevant to the levels and pattern of GH achieved.

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