

Growth hormone response to graded exercise intensities is attenuated and the gender difference abolished in older adults

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Abstract:

We investigated the joint impact of age, gender, and exercise intensity on growth hormone (GH) secretion. At a university center, nine young men, eight young women, seven older men, and six older women were each tested on six randomly ordered occasions [control (C) and 5 exercise conditions (Ex)]. Serum GH concentrations were measured by immunochemiluminometry [10-min samples: 0700–0900 (baseline); 0900–1300 (C or Ex + recovery)]. Integrated GH concentrations (IGHC) were calculated by trapezoidal reconstruction, and GH secretion was modeled by deconvolution analyses. Subjects exercised from 0900 to 0930 at graded intensities [standardized to individual lactate threshold (LT)] of 25 and 75% of the difference between rest and LT, LT, and 25 and 75% of the difference between LT and peak oxygen consumption. Data were analyzed via mixed-effects ANOVA for repeated measures with post hoc contrasts. We found that 1) Ex elevated IGHC above C in all four cohorts, 2) 1.75 LT Ex resulted in maximal IGHC, 3) IGHC differed by gender in young (women > men) but not older adults, 4) older adults secreted 50% less GH during graded exercise, 5) Ex selectively augmented the mass of GH secreted per burst, and 6) higher Ex + recovery IGHC in young women was due to higher baseline IGHC, rather than greater stimulated GH secretion. We conclude that young women manifest a greater absolute and incremental IGHC response to exercise than postmenopausal women and men of any age. Age diminishes the GH response to exercise and abolishes the young-adult gender difference. Attenuation of GH responses to all exercise intensities in older adults has implications for exercise prescription because higher exercise intensities may be required to stimulate GH release in older adults.

Keywords: aging | lactate threshold | human | somatotropic

Article:

Growth hormone (GH) is secreted by the anterior pituitary gland in a pulsatile fashion under the regulation of a final common trilogy of regulatory peptides: Growth hormone-releasing hormone (GHRH), somatostatin, and growth hormone-releasing peptide (GHRP)/ghrelin (10, 34). GHRH stimulates GH synthesis and secretion, somatostatin inhibits GH release, and GHRP/ghrelin may act synergistically with GHRH and/or stimulate GH release directly. All three peptidyl effectors and cognate signaling pathways are regulated by reversible autofeedback enforced by GH and IGF-I (10, 34). GH secretion changes throughout the life span with maximal GH secretion during the adolescent years. Postpubertal maturational and chronological age are strongly associated with a decline in the amount of GH released. In addition, multiple physiological factors modulate GH secretion, such as age, gender, pubertal status, nutrition, sleep, body composition, regional distribution of body fat, stress, gonadal steroids, insulin, and fitness (10).

Acute aerobic exercise is a potent stimulus to GH release (2–4, 9, 20, 21, 23, 27–30, 32, 45–48). Intensity and duration of exercise, fitness, gender, and age all influence the GH response to exercise. Although earlier research envisioned a required threshold of exercise intensity (3, 4, 9), recent data from our laboratory affirm that, in young men and women, GH secretion is related to exercise intensity in a graded fashion (28, 29).

Women maintain higher GH concentrations than men at all ages and manifest less orderly patterns of pulsatile GH release (8, 10, 13, 26, 35, 48). Exercise-induces significant GH release in both genders (2, 21), but responses in women differ in several specific features, viz., anticipatory GH release before exercise and more rapid attainment of peak GH concentrations during exercise (29, 47, 48). Time of day does not influence maximal GH responses to exercise at least in young men (18). Young women and men achieve comparable absolute GH concentrations during exercise (48), but the fractional increase over baseline is higher in young men due to lower prestimulus values (2, 47). Young women and men both manifest marked (although not complete) resistance of the exercise stimulus to GH autoinhibition (41).

Integrated concentrations and daily secretion rates of GH fall progressively after young adulthood (10, 40). Cross-sectional data suggest that beginning in young adulthood GH production declines by 50% approximately every 7 yr in men (17, 39). Gender comparisons indicate that GH output declines nearly twofold less rapidly in premenopausal women than comparably aged men (33, 45) and that GH release remains greater in women than men after age 50 yr (14). Many age-related physical adaptations resemble those recognized in GH-deficient adults, including reduced muscle mass and exercise capacity, increased body fat especially abdominal visceral fat, unfavorable lipid and lipoprotein profiles, reduction in bone mineral density, and cerebro- and cardiovascular disease (10). Thus strategies for maintaining adequate GH concentrations with aging, including exercise, may be important in healthy aging.

Although limited available data suggest that exercise may represent an adequate stimulus for GH release in older adults, other observations indicate the GH response to exercise may be blunted in aging (6, 11, 16, 25, 42, 50). None of the foregoing studies examined the effect of exercise intensity or the influence of gender on such responses in young and older cohorts. To address these issues, we investigated the tripartite impact of age, gender, and intensity of exercise on GH secretion in young and older healthy men and women. We hypothesized that 1) GH secretion would be related to exercise intensity in a graded fashion independently of age; 2) GH responses

to exercise would be blunted in older individuals even at higher exercise intensities; and 3) GH output during exercise would be higher in women than men of similar age.

METHODS

Subjects and preliminary screening procedures. Thirty healthy recreationally active young and older community-living men and women participated after providing voluntary written, informed consent, as approved by the Human Investigation Committee of the University of Virginia. Portions of the younger data have been presented previously (28, 29). Descriptive characteristics are presented in Table 1. Each subject underwent a detailed medical history and physical examination, and no subject had a history of hypothalamo-pituitary, renal, hepatic, hematological, or metabolic disease. The subjects were nonsmokers, did not abuse alcohol, and were not taking any systemic medications. Screening laboratory data revealed normal hematological, renal, hepatic, metabolic, and thyroid function. Subjects refrained from exercise for 24 h before each evaluation. To avoid confounding factors associated with a training effect, subjects agreed to maintain their exercise regimen for the duration of the study period. All older women were postmenopausal (for at least 7 yr) and were not on estrogen replacement therapy. None of the younger women were taking oral contraceptives.

Table 1. Descriptive characteristics of young and older men and women

Variable	Young Men (n = 9)	Young Women (n = 8)	Older Men (n = 7)	Older Women (n = 6)
Age, yr	27.2 (1.0)	24.3 (1.1)	64.1 (2.2)	66.0 (4.0)*
Height, cm	178.4 (1.7)	170.0 (2.8)	175.6 (1.1)	164.1 (3.2)†‡
Weight, kg	82.5 (2.9)	63.3 (2.2)	82.2 (3.4)	67.2 (6.7)‡
Percent fat	18.7 (2.1)	18.1 (2.2)	27.1 (1.5)	31.9 (2.4)*
$\dot{V}O_2$ LT, ml·kg ⁻¹ ·min ⁻¹	32.3 (2.9)	29.9 (2.5)	19.7 (1.4)	17.1 (1.8)†‡
$\dot{V}O_{2\text{ peak}}$, ml·kg ⁻¹ ·min ⁻¹	47.8 (2.3)	45.9 (2.1)	31.8 (1.4)	25.4 (2.3)†

Data are presented as means (SE). $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2\text{ peak}}$, peak $\dot{V}O_2$. *Older > Young, P < 0.05; †Young > Older, P < 0.05; ‡Men Women, P < 0.05.

Body composition analysis. Body density was determined by hydrostatic weighing (19). Each subject was weighed in air on an Accu-weigh beam scale accurate to ± 0.1 kg and subsequently weighed underwater on a Chatillon autopsy scale accurate to ± 0.01 kg. Residual lung volume was measured using an oxygen-dilution technique (49). The computational procedure of Brozek et al. (1) was used to estimate percentage body fat from body density measurements.

$\dot{V}O_{2\text{ peak}}$ and LT test. Peak oxygen uptake ($\dot{V}O_{2\text{ peak}}$) and lactate threshold (LT) were evaluated via a continuous treadmill (Quinton Q 65 treadmill) exercise protocol with increasing velocity until volitional fatigue. The initial velocity was set between 60 and 80 m/min, with increases in velocity of 10 m/min every 3 min. Open-circuit spirometry was used to collect metabolic data (SensorMedics model 2900Z metabolic measurement cart, Yorba Linda, CA). Heart rate was determined via a Marquette Max-1 electrocardiograph. An indwelling cannula was inserted into a forearm vein before testing and blood samples were taken at rest and during the last 15 s of each stage for the measurement of blood lactate concentration [Yellow Springs Instruments 2700 Select Biochemistry Analyzer, Yellow Springs, OH]. $\dot{V}O_{2\text{ peak}}$ was chosen as the highest O_2 consumption ($\dot{V}O_2$) attained. Heart rate, respiratory exchange ratio, and blood lactate values were monitored throughout, and values obtained at peak exercise were evaluated to ensure that volitional fatigue was associated with expected physiological responses.

Determination of LT and the constant-load treadmill velocities. The blood lactate-velocity relationship was determined by plotting blood lactate concentration against treadmill velocity. LT was chosen as the highest velocity obtained before the curvilinear increase in blood lactate concentration. An elevation in blood lactate concentration of at least 0.2 mM (the error associated with the lactate analyzer) above baseline was required for LT determination. $\dot{V}O_2$ associated with velocity LT was then determined (44).

Exercise admissions consisted of 30 min of constant-load exercise at a predetermined velocity. Treadmill velocity was set at 25 and 75% of the difference between the $\dot{V}O_2$ at LT and $\dot{V}O_2$ at rest (0.25 LT and 0.75 LT, respectively); at LT; and 25 and 75% of the difference between the $\dot{V}O_2$ at LT and $\dot{V}O_{2\text{ peak}}$ (1.25 LT and 1.75 LT, respectively), based on results obtained during the initial LT- $\dot{V}O_{2\text{ peak}}$ protocol.

GCRC admissions. After completion of the initial exercise test, each subject was studied at the General Clinical Research Center (GCRC) on a total of six separate occasions, five with exercise and one at rest. The order of study conditions was assigned in a randomized fashion. For the young women, admissions were scheduled in the early follicular phase of the menstrual cycle. No more than two admissions over a 2-mo time frame were allowed (to ensure that guidelines for blood withdrawal were not exceeded). Although ~6 mo were required for subjects to complete the study, the randomly assigned GCRC admissions and the selection of habitually active subjects who were asked to maintain their physical activity patterns likely minimized any changes in aerobic fitness, LT, and/or body composition that might have confounded the data.

Subjects were admitted to the GCRC on the evening before the exercise or control studies. Subjects were required to consume their evening meal at or before 1700 and then received a standardized snack (500 kcal) at 2000. The nutrient composition of the snack was 55% carbohydrate, 15% protein, and 30% fat. Subjects were allowed to consume water ad libitum. At 2100 an intravenous cannula was placed bilaterally in each forearm vein. Subjects remained at the GCRC after eating their snack and were asked to turn lights off by 2300. Beginning at 0700, blood samples were withdrawn every 10 min until 1300 for later measurement of serum GH concentrations. To avoid the confounding effects of meals on GH secretion, subjects fasted after ingesting their snack until the end of the admission (1300) (12).

Exercise admissions. After 2 h of baseline blood sampling, subjects began their exercise bout at the predetermined velocity. The exercise bout began at 0900 and continued until 0930. During the exercise bout, blood lactate was measured every 10 min, heart rate and ECG were monitored continuously, and metabolic data were measured minute by minute (by open-circuit spirometry SensorMedics 2900Z Metabolic Measurement Cart) during exercise and during the immediate 30 min postexercise while the subject sat quietly in the exercise laboratory. These assessments were made to ensure achievement of appropriate exercise intensity during the exercise admissions and for safety reasons. Thereafter, subjects resumed bed rest until 1300, when the test was terminated and vital signs were taken. Subjects were then fed and discharged.

Nonexercise admission. The above procedure was followed on the nonexercise days as well. However, at 0900, subjects remained in their rooms and rested quietly until 1300. At this time, the cannulas were removed and vital signs were taken. Subjects were fed and discharged.

GH assay. GH concentrations were measured in duplicate by modified ultrasensitive chemiluminescence assay (Nichols Institute Diagnostics, San Clemente, CA) with 22-kDa recombinant human GH (rhGH) used as standard (39). Cross-reactivity with 20-kDa GH was 30%. Assay sensitivity (defined as 3 SD above the zero-dose tube) was 0.005 $\mu\text{g/l}$. Median intra- and interassay coefficients of variation were 5.2 and 6.3%, respectively. All samples from a single subject were assayed together to eliminate interassay variability.

Data reduction. Assay data were analyzed by a model-free dose-dependent extrapolation of triplicate standards (31). Mean and integrated serum GH concentrations (IGHC) over 2 h (0700–0900, control) and 4 h [0900–1300, exercise + recovery] were calculated (38). The amount of GH secreted in bursts (nonbasal) was quantitated by modified biexponential deconvolution analysis (29, 36). As a time-limited measure of the effects of exercise on GH secretion, 90-min GH burst mass was calculated as the summed secretion during and after exercise (0900–1030).

Statistical analysis. With the exception of the 90-min GH burst mass data, the data for each of the deconvolution parameters were transformed to the natural logarithmic scale. This scale transformation was conducted as a remedial measure to produce symmetrical measurement distributions and to equalize measurement variability. Logarithmic measurements were analyzed via mixed-effects ANOVA for repeated measures (7). For each deconvolution variable, the ANOVA model specification included three classification factors to estimate the main effect of age (young, old), gender (female, male), and the level of the exercise intensity (control, 0.25 LT, 0.75 LT, 1.0 LT, 1.25 LT, and 1.75 LT). One-way, two-way, and three-way interactions were also estimated.

The ANOVA model parameters were estimated by way of residual maximum likelihood, and the variance-covariance matrix was modeled in the compound symmetry form (22). A priori comparisons were formulated by way of linear contrasts of the least squares means. Fisher's restricted least significant difference criterion was utilized to maintain an overall two-sided multiple comparisons type I error of 0.05. Confidence interval construction was similarly based on Fisher's least significant difference.

For the deconvolution parameters that were analyzed on the natural logarithmic scale, the within-group and between-group comparisons are expressed in terms of fold change in the value of the geometric mean. The geometric mean is a location parameter similar to the arithmetic and median. The value of the geometric mean identifies the central location of the measurement distribution and is calculated by taking the antilogarithm of the mean of the distribution of logarithmically transformed data (51). We compared geometric means instead of arithmetic means, because one of the critical statistical assumptions for ANOVA states that, to obtain valid statistical tests, residual variation should be approximately equal within all treatment groups. When the magnitude of the variance in the response increases as the mean of the response increases in value, the natural logarithmic transformation is generally used to stabilize the residual variance among two or more treatment groups.

The within-group and between-group comparisons for 90-min GH burst mass are presented as a difference between the non-log-transformed arithmetic means using the ANOVA models described above. The software of the PROC MIXED procedure of SAS version 8.2 was used to carry out statistical analyses (SAS Institute, Cary, NC). A Bonferroni multiplier with a prespecified experimental type I error rate of 0.05 was used to adjust probabilities and confidence limits to maintain a type I error rate of 0.05 for all comparisons of interest.

The effects of age and gender on the relationship between GH area under the curve and exercise intensity were examined by way of a random coefficient regression model and by way of a random coefficient piecewise regression model. The values for GH area under the curve were transformed to the natural logarithmic scale for these analyses. The same regression methods were utilized to examine the relationship between 90-min GH burst mass and exercise intensity.

RESULTS

As expected, young individuals had less percentage body fat and greater fitness than older individuals. Men were taller and heavier and had higher lactate threshold values than women (Table 1).

Basal secretion. Mean (SE) basal secretion of GH determined during the 2-h control period of each admission (0700–0900) was 0.005 (0.001) $\mu\text{g}\cdot\text{l}^{-1}\cdot\text{min}^{-1}$ in older men and 0.010 (0.005) $\mu\text{g}\cdot\text{l}^{-1}\cdot\text{min}^{-1}$ in older women ($P = 0.005$). Basal GH secretion averaged 0.006 (0.002) $\mu\text{g}\cdot\text{l}^{-1}\cdot\text{min}^{-1}$ in young men and 0.008 (0.005) $\mu\text{g}\cdot\text{l}^{-1}\cdot\text{min}^{-1}$ in young women ($P = \text{not significant}$).

Integrated GH concentration. Figure 1 presents the mean and SE values for 4-h integrated GH concentrations beginning at the onset of rest or exercise (0900–1300) for all six study conditions in young and older men and women. During the control condition, resting IGHC in young women exceeded that in the other three groups ($P < 0.03$). No other cohorts differed at baseline. For normalization, we compared the fold changes within groups among the five exercise conditions relative to cognate control. In young women, all exercise conditions induced a significant increase in IGHC over control (range = 1.5–2.5-fold). In young men, all exercise conditions except 0.25 LT elevated IGHC (1.6–3.6-fold), whereas in older women and older men only higher exercise intensities were effective (1.25 LT and 1.75 LT for older women, 1.7- and 2.4-fold increase; 1.75 LT for older men, 1.89-fold increase). Young women exhibited a greater fractional response than young men at 0.25 LT; than older women at 0.25 LT, 0.75 LT, and LT; and than older men at all exercise intensities. IGHC responses in young men and older women did not differ at any exercise intensity (with the exception of LT when the increase was 2.3-fold greater in young men). On the other hand, young men achieved greater increases in IGHC than older men at LT, 1.25 LT, and 1.75 LT. No differences were observed between older men and older women at any exercise intensity.

Regression analysis revealed a linear relationship between exercise intensity and IGHC within each group with no significant differences in slopes of the regression lines among young and older men and women. Significant differences in intercepts were observed with young women having higher intercept values than all other groups.

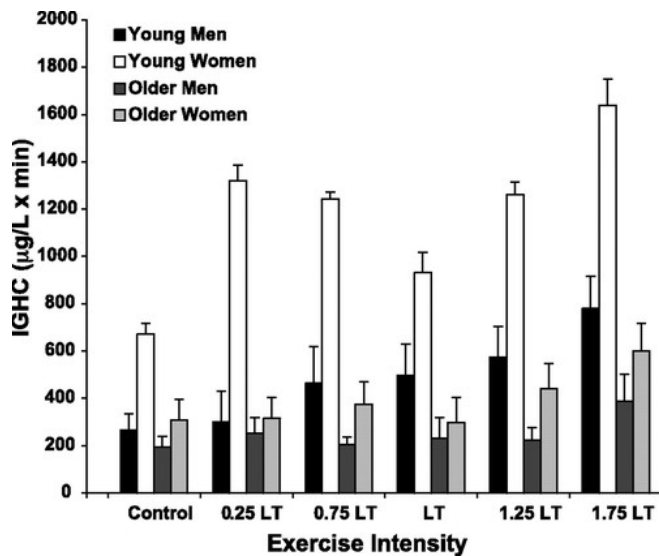


Fig. 1. Integrated growth hormone (GH) concentrations (0900–1300) across the 6 exercise conditions in young and older men and women. Data are means \pm SE. ANOVA revealed the following. Control: resting integrated GH concentrations (IGHC) in young women was greater than in all other groups ($P < 0.03$). Effects of exercise intensity within groups: Young men, all exercise conditions except 0.25 lactate threshold (LT) resulted in a significant increase in IGHC (1.6–3.6-fold). Young women, all exercise conditions resulted in a significant increase in IGHC over control (range 1.5–2.5-fold). Older men and women, only the higher exercise intensities (1.75 LT for older men, 1.89-fold increase; 1.25 LT and 1.75 LT for older women, 1.7 and 2.4-fold increase) resulted in a significant increase in IGHC. Among-group comparisons: Young men had a greater increase in IGHC than older men at LT, 1.25 LT, and 1.75 LT. Young women had a greater increase in IGHC over control than young men at 0.25 LT, than older women at 0.25 LT, 0.75 LT, and LT, and than older men at all exercise intensities. The increase in IGHC between young men and older women did not differ at any exercise intensity (with the exception of LT where the increase in young men was 2.3-fold greater). No differences were observed between older men and older women for IGHC above control at any exercise intensity.

GH secretory pulses. The number of GH secretory pulses (range = 5.3–6.1 over the 4-h time frame 0900–1330) did not differ among the four groups during the no-exercise control condition. Young men and young women manifested fewer GH secretory pulses relative to control in the 1.25 and 1.75 LT conditions. In older men, only 1.75 LT resulted in a decrease in the number of GH secretory pulses. Frequency remained constant in older women. Mean values did not vary significantly among the four cohorts when compared at any given exercise intensity.

GH secretory-pulse half duration. During the nonexercise control condition, GH secretory pulse half-duration ranged from 19 to 26 min (not significant). Exercise of varying intensity did not affect these values in young women or older men. Young men had abbreviated bursts during the LT, 1.25 LT, and 1.75 LT exercise intensities (viz., 18–19 min), as did older women at 1.75 LT (17 min). Group mean values were similar at each exercise intensity.

GH half-life. Apparent GH half-lives were consistent with differences within an absolute range of 0.4–7.2 min among interventions and age cohorts.

Mass of GH secreted per pulse. The mass of GH secreted per pulse during rest or exercise + recovery (0900–1300) was increased across exercise intensity within each group. In young men and women, all exercise intensities resulted in significant elevations in the mass of GH secreted

per pulse, with the exception of 0.25 LT in men (absolute range = 4.0–19.7 $\mu\text{g/l}$). In older men and women, only near-maximal exercise intensities (1.25 and 1.75 LT) resulted in a significant increase in GH mass secreted per pulse (range = 1.4–5.0 $\mu\text{g/l}$). Among-group comparisons revealed that younger men and women exhibited a higher mass of GH secreted per pulse than older men and women; young women had higher values than young men at lower exercise intensities (0.25 and 0.75 LT); and no differences emerged between older men and women at any exercise intensity.

GH production rate. The GH production rate ($\mu\text{g}\cdot\text{l}^{-1}\cdot\text{h}^{-1}$) followed a pattern similar to that observed for the mass of GH secreted per pulse (data not shown).

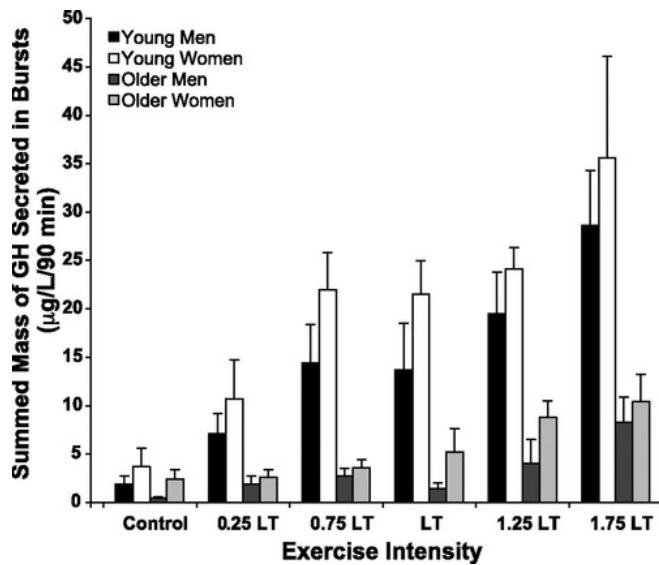


Fig. 2. Summed mass of GH secreted in bursts over the interval 0900 to 1030 (30 min of exercise + 1 h of recovery). ANOVA revealed the following. Control: no differences were observed for any comparison. Effects of exercise intensity within groups: Young men and women, a significant elevation in the 90-min summed mass of GH secreted per pulse at all exercise intensities (above control) with the exception of 0.25 LT. Older men and women, the mean change above control approached significance at 1.75 LT ($P = 0.07$ and 0.09 for older men and women, respectively). Among-group comparisons: the 90-min summed mass of GH secreted per pulse in young men compared with young women was not statistically different at any exercise intensity; the 90-min summed mass of GH secreted per pulse in young men was significantly greater than older men at 1.25 and 1.75 LT and approached statistical significance at 0.75 and 1.0 LT ($P = 0.08$), was significantly greater than older women at 1.75 LT, and approached significance at 0.75 and 1.25 LT ($P = 0.07$); young women had a greater 90-min summed mass of GH secreted per pulse than older men and older women at all exercise intensities, with the exception of 0.25 LT; and no differences were observed at any exercise intensity between older men and older women.

Ninety-minute summed mass of GH secreted in bursts. Because much of the GH response to exercise is completed within 90 min (28, 29) we examined the summed mass of GH secreted in bursts during the interval 0900 to 1030 (30 min of rest or exercise + 1 h of recovery) (Fig. 2). No differences in 90-min summed mass GH secreted in bursts were observed among the four cohorts at rest. Summed burst mass increased significantly in young men and women at all exercise intensities with the exception of 0.25 LT (in both genders). In older men and women, the mean change above control approached significance only at 1.75 LT ($P = 0.07$ and 0.09 , respectively). Comparisons among all conditions revealed that 1) absolute responses were similar in young men and women; 2) values in young women exceeded those in older men and older women at all

exercise intensities, with the exception of 0.25 LT (in both genders); 3) responses in young men were greater than those in older men at 1.25 and 1.75 LT [and approached significance at lower intensities ($P = 0.08$ for 0.75 and 1.0 LT)] and than those in older women at 1.75 LT only [but approached significance at 0.75 and 1.25 LT ($P = 0.07$)]; and 4) responses were comparable at all exercise intensities in older men and older women.

Regression analysis revealed a linear relationship between exercise intensity and 90-min summed mass of GH secreted in bursts within each group with no significant differences in the intercept of the regression lines among young and older men and women. Significant differences in the slopes of the regression lines were observed with young men and young women having higher slope values than both older men and women. No differences were observed for slopes between young men and women and between older men and women.

DISCUSSION

Tripartite comparisons of GH secretion by age, gender, and exercise intensity revealed several important interactions. In young adults 1) exercise at all intensities stimulated greater GH release than that observed at rest, 2) graded increases in exercise intensity augmented GH release, and 3) young women achieved higher IGHC at all exercise intensities than young men, but comparable pulsatile GH secretion, indicating that higher baseline IGHC in women accounts for the difference (28, 29, Fig. 1). In contrast, in older men and women 1) only the highest exercise intensities (1.25 and 1.75 LT) elevated GH output, and 2) the gender contrast observed in younger adults vanished (Fig. 1).

The present data support certain reports that the GH response to exercise is attenuated in middle-aged and older individuals (11, 15, 25, 50). Nonetheless, no earlier studies evaluated the impact of all three of age, gender, and exercise intensity. We show that the triad of factors strongly determines GH release. In the present study, young adults exhibited higher IGHC and greater GH secretion in bursts at almost all exercise intensities than older individuals of like gender. In addition, despite higher IGHC and GH secretory-burst values at rest, fractional increases in young men and women were greater than those in older individuals at several exercise intensities. Accordingly, age markedly damps GH responses to graded intensities of exercise in both genders and abrogates the young-adult gender contrast in IGHC.

The evident differences in GH responses to exercise intensity in young and older adults may help to explain some earlier conflicting data. For example, Zaccaria et al. (50) reported that the GH response to exercise was blunted in older compared with young men and that 4 mo of endurance training had no effect on GH release in older men. In contrast, Hagberg et al. (11) observed that, although the GH response to exercise was attenuated in older men, trained older men achieve greater GH responses to exercise than sedentary controls. More recently, Manetta et al. (24) in another cross-sectional analysis found that middle-aged endurance-trained cyclists evince a greater GH response to exercise than untrained subjects. Although one cannot discount the possibility that unequal duration of training affected the preceding differences (11, 24, 50), an alternative postulate is that the well-trained subjects recruited into the cross-sectional studies maintain greater fitness than those completing a 4-mo training study. The rationale for this new consideration is that only exercise intensities above LT stimulate GH release acutely in older

individuals. A corollary implication therefore is that the training intensity required to augment GH production may need to be higher in older than young adults.

Deconvolution analysis was used to distinguish burstlike GH secretion from concurrent basal hormone release. Statistical comparisons demonstrated that exercise intensity selectively determines the mass rather than the frequency of GH secretory bursts. Secretory-burst mass is important mechanistically, because pulsatile secretion constitutes most (>85%) of the total daily GH output (42). Moreover, aging primarily attenuates the size of GH pulses (17, 39, 40) and is associated with impaired GH autofeedback, which may contribute to attenuated renewal of high-amplitude GH pulses (37). Evaluation of immediate GH release (30 min of rest or exercise + 1 h of recovery) disclosed that higher postexercise IGHC in young women than young men is not due to greater incremental secretion of GH in pulses but rather to higher baseline IGHC in women. This distinction is important, because IGHC presumably represents the blood-borne GH stimulus to target tissues, whereas incremental GH secretory-burst mass reflects hypothalamo-pituitary responses to exercise. Only the former differed by gender (greater in young women). Higher IGHC in women is consistent with evidence of relatively impaired actions of GH in an estrogen-enriched milieu (10, 35).

Aging decreases GH responses to the majority of single secretagogues, with the exception of insulin-induced hypoglycemia (for a review, see Ref. 10). Several mechanisms could account for this contrast, with available data supporting excessive somatostatin release, diminished GHRH secretion, a deficiency of the putative ligand for GHRP, and/or a relative failure of feedback inhibition of pulsatile GH secretion independently of IGF-I concentrations in aging (10, 34, 37). In a rodent model, aging is associated with elevated hypothalamic somatostatin and pituitary somatostatin-receptor gene transcripts (10). Thus greater somatostatin outflow (release and action) might contribute to the attenuated GH response to graded exercise intensities observed here and to a single exercise intensity in some earlier studies in aging (6, 42). Aging lowers hypothalamic GHRH gene expression (rat) and blunts GH secretion induced by exogenous GHRH (rat and human) (6, 42). A prediction of the latter inference is that aging would reduce the supraadditive effect of exercise combined with GHRP-2 observed in young men and women (47), because GHRP synergizes with GHRH (6). This notion remains to be evaluated.

In addition to a decline in serum GH concentrations, aging is associated with declines in testosterone (in men) and estrogen (in women). These endocrine changes are thought to contribute to the increase in abdominal visceral fat (AVF) observed with age (43). Although AVF was not measured in the present study, we previously examined the relationship between age group (young or old), gender, body composition, AVF, gonadal steroids, fasting serum insulin, serum IGF-I, and fitness on 24-h GH release. In both young and older individuals AVF was a primary determinant (along with fasting insulin and IGF-I) of 24-h GH release (with higher AVF values older individuals) (5). In addition, we recently reported that in nonobese older subjects who were stratified by AVF content (high vs. low), elevated AVF was associated with a reduction in 24-h integrated GH concentration (by 40–50%), an unfavorable lipid and lipoprotein profile, and an elevation of nontraditional risk factors (fasting insulin, triglycerides, and apolipoprotein B), suggesting an increased risk of coronary artery disease (43). Although the mechanisms that account for the dominant relationship between AVF and GH release remain to be elucidated, two plausible hypotheses have been suggested: 1) increased plasma levels of

insulin, free IGF-I, and free fatty acids associated with greater AVF might result in negative feedback on GH secretion; or 2) reduced GH secretion associated with aging might allow for accumulation of AVF (as observed in adults with GH deficiency due to hypothalamic pituitary disease) (5). Therefore, interventional strategies designed to lower AVF, such as exercise training, may elevate GH release. In younger women, 1 yr of exercise training above (but not at or below) the LT resulted in amplification of pulsatile GH release (46). Whether a similar response occurs in older individuals cannot be addressed by the present data. However, the blunted pulsatile and IGHC response to exercise at all intensities in older individuals suggests that exercise training alone may not be sufficient to increase pulsatile GH.

Gender differences in IGHC before and after exercise are well articulated in younger individuals (2, 29, 47, 48). Age abrogated such differences at all five exercise intensities studied here. This outcome would support the more general hypothesis that the triad of age, gender, and sex-steroid concentrations determines the efficacy of various GH secretagogues, including exercise (40). Nonetheless, the precise mechanisms mediating gender differences in GH outflow are not known.

In summary, compared with young adults, healthy older men and women manifest attenuated GH responses to escalating exercise intensities extending from below to above the individual LT. In particular, aging damps the relationship between exercise intensity and GH secretion by >50% and abolishes gender differences in IGHC. According to these data, older individuals might achieve lesser GH elevations under even the most intense acute exercise prescription.

Notes

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