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Multipathway Modulation of Exercise and Glucose Stress Effects upon GH Secretion in Healthy Men

Johannes D. Veldhuis, M.D.¹, Thomas P. Olson, Ph.D.², Paul Y. Takahashi, M.D.³, John M. Miles, M.D.¹, Michael J. Joyner, M.D.⁴, Rebecca J. Yang, R.N., B.S.N., B.A.¹, and Jean Wigham, R.N.¹

¹Endocrine Research Unit, Mayo Clinic College of Medicine, Center for Translational Science Activities, Mayo Clinic, Rochester, MN 55905

³Primary Care Internal Medicine, Mayo Clinic, Rochester, MN 55905

⁴Anesthesia Research, Mayo Clinic, Rochester, MN 55905

²Cardiovascular Research, Mayo Clinic, Rochester, MN 55905

Abstract

Objective—Exercise evokes pulsatile GH release followed by autonegative feedback, whereas glucose suppresses GH release followed by rebound-like GH release (feedforward escape). Here we test the hypothesis that age, sex steroids, insulin, body composition and physical power jointly determine these dynamic GH responses.

Methods—This was a prospectively randomized glucose-blinded study conducted in the Mayo Center for Advancing Translational Sciences in healthy men ages 19–77 yr (N = 23). Three conditions, fasting/rest/saline, fasting/exercise/saline and fasting/rest/iv glucose infusions, were used to drive GH dynamics during 10-min blood sampling for 6 hr. Linear correlation analysis was applied to relate peak/nadir GH dynamics to age, sex steroids, insulin, CT-estimated abdominal fat and physical power (work per unit time).

*Corresponding author: Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, USA, Tel: +011-507-255-0902, Fax: +011-507-255-0901, veldhuis.johannes@mayo.edu.

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Results—Compared with the fasting/rest/saline (control) day, fasting/exercise/saline infusion evoked peak GH within 1 h, followed by negative feedback 3–5 h later. The dynamic GH excursion was strongly ($R^2 = 0.634$) influenced by (i) insulin negatively ($P = 0.011$), (ii) power positively ($P = 0.0008$), and (iii) E_2 positively ($P = 0.001$). Dynamic glucose-modulated GH release was determined by insulin negatively ($P = 0.0039$) and power positively ($P = 0.0034$) [$R^2 = 0.454$]. Under rest/saline, power ($P = 0.031$) and total abdominal fat ($P = 0.012$) [$R^2 = 0.267$] were the dominant correlates of GH excursions.

Conclusion—In healthy men, dynamic GH perturbations induced by exercise and glucose are strongly related to physical power, insulin, estradiol, and body composition, thus suggesting a network of regulatory pathways.

Keywords

somatotropin; age; metabolic; body composition

Introduction

Aging reduces pulsatile GH secretion, including the amount of GH secreted over 24 h and per burst [1, 2]. Intercurrent acute illness, sex-steroid depletion, adiposity, sedentarism, hypothermia, hypothyroidism, type II diabetes mellitus and other chronic diseases often decrease GH secretion further [3, 4]. However, major unresolved mechanistic issues remain, including how daily negative and positive regulators coordinately control GH secretion.

The secretion of GH has been investigated extensively under highly standardized laboratory conditions over the last five decades [5, 6]. Typical interventions include insulin-induced hypoglycemia, administration of L-dopa, naloxone, clonidine, propranolol, L-arginine, GHRH and/or GHRP's, oral glucose, parenteral somatostatin, GH-receptor antagonists, GH itself to induce autofeedback, L-thyroxine, selected neuropharmacologic agents and calibrated exercise paradigms intended to probe, if possible, individual endocrine and neurotransmitter pathways [7–13]. Outcomes of such single-agent studies along with data in laboratory animals suggest the existence of more complex interactions, which comprise presumptively interlinked feedforward (stimulatory) and feedback (inhibitory) connections [5]. A theoretic projection is that aggregate (joint) interactions, rather than any single pathway, mediate day-to-day GH production [6]. A corollary postulate is that coordinated GH-axis interactions are secondarily modulated by various internal (*e.g.* body composition, age, sex steroids) and external (*e.g.* glucose exposure, exercise) factors.

GH production in healthy individuals is principally pulsatile, especially (>85%) overnight in the fasting state [14]. Pulsatile GH secretion preferentially induces anabolic and so-called male-pattern gene expression in liver, muscle and adipose tissue, most evidently in laboratory animals but also in the human [15]. Accordingly, impoverished GH pulsatility - - observed in obesity, the metabolic syndrome, hyperinsulinism, aging, cachexia, the overfed state and protracted critical illness - - could have important catabolic implications [16].

Understanding day-to-day factors that supervise GH pulsatility remains difficult, although interactions among such regulatory factors are likely to be particularly relevant to models of

chronic hyposomatotropism. A testable hypothesis is that components of an individual's day-to-day phenotype, *viz.* age, degree of adiposity, physical fitness, insulin and sex-steroid availability, interact with acute hour-by-hour regulators, such as the GH pulse-stimulating effect of exercise and the GH pulse-suppressing effect of glucose. The present investigation provides an initial test of this thesis.

Methods

Overall design

This study assessed GH secretion during fasting/rest/saline (FRS) infusion compared with that in response to a physical stressor (GH feedforward and feedback induced by submaximal exercise, defined as fasting/exercise/saline [FES]) and a common metabolic stressor (transient glucose elevation, fasting/rest/iv glucose [FRG]) in healthy men in a within-subject cross-over design single-blinded to glucose *vs* saline infusion. Each man served as his own control.

Subjects

Healthy community-dwelling volunteers provided written, witnessed informed consent approved by Mayo IRB. Participants were required to pass baseline wellness screening, which included medical history, physical exam, and blood chemistries to test hepatic, renal, metabolic, endocrine and hematologic function. Exercise screening comprised 12-lead ECG monitoring during maximal cycle ergometry at the Mayo Cardiovascular Health Center. Allowable ages were 18–80 yr.

Exclusion criteria

Individuals unable or unwilling to provide written voluntary consent for any reason including cognitive decline or mental illness were excluded. Volunteers with orthopedic limitations, hypertension, diabetes mellitus, cardiovascular disease, cancer, sleep apnea, pulmonary disease, weight loss (>2 kg in 6 wk), drug or alcohol abuse, psychiatric disability, hematological disorders, acute or chronic inflammatory conditions, renal insufficiency, hepatic disease, neoplasm, anemia, chronic infections, including viral hepatitis or HIV, and subjects receiving systemic medications were excluded. Allowable exposures were replacement thyroid hormone, laxatives, antacids, ophthalmic solutions, diuretics, or skin preparations. Hypogonadism (serum total T < 240 ng/dL, LH > 12 IU/L and/or FSH > 16 IU/L), glucocorticoid use, and transmeridian travel (over 3 time zones) in the 10 days prior were also disallowed.

Protocol

Eligible volunteers were admitted to the Mayo Center for Advancing Translational Sciences (CTSA) the evening before blood sampling. Beginning at 1900 h, subjects remained supine and fasting except for water, diet soda, and other non-caloric and non-caffeinated fluids. The next day, blood was sampled from an arm vein every 10 min from 0700 to 1300 h for GH and every 30 min for plasma glucose. This 6-h block permitted 1 h of baseline sampling before one of three interventions: fasting/rest/saline (FRS), fasting/exercise/saline (FES) or fasting/rest/iv glucose (FRG) during the interval 0800–0900 h, followed by 5 additional h of

sampling. FRS comprised 0800 h bolus iv saline injection (25 mL) over 3 min. FRG comprised 0800 h iv injection of 25 mL of dextrose 50% over 3 min. FES comprised sequential bouts of 7 min of bicycle ergometer at 65% peak work alternating with 2 min of bilateral arm curls. Curls began at 20 pounds and decreased to 15, 10 or 5 pounds as necessary to sustain one complete curl every 2 sec (1 sec for the upswing and 1 sec for the downswing using a metronome). This was followed by a 1-min rest and blood sample. The mixed-exercise sequence was conducted in the Energy Balance Core Laboratory of the CTSA with a physician in attendance.

Assays

Serum GH concentrations were determined in each subject (as one batch of 3 sets of 37 or 111 total samples) using a robotics-automated ultrasensitive chemiluminescence assay (DXI 800, Beckman Coulter Fullerton, CA), as described [17]. Estradiol (E₂) and testosterone (T) concentrations were measured by tandem mass spectrometry, and glucose using a glucose analyzer [18]. IGF-I and IGFBP-3 were assayed as described [19]. Fasting serum TSH, cortisol, LH, FSH and insulin were quantified in the Mayo Clinical Laboratories (website: <http://mayoweb.mayo.edu/dlmp/index.html>).

Computerized axial tomography (CT)

Relative obesity was appraised via single-slice CT of the abdomen at L3-L4 interface to estimate visceral (AVF) and total abdominal fat (TAF) as surrogates of body composition, as described [19].

Data analysis

The primary measurable endpoints were individual peak (maximum) and nadir (minimum) GH concentrations during each of 3 fasting interventions (FRS, FES, FRG) in each subject. The incremental GH peak (or nadir) was defined as the algebraic difference between the peak (or nadir) in the active intervention and the peak (or nadir) in the FRS session. The relation of effects of physical-metabolic phenotype to the incremental GH response to hyperglycemia and strenuous exercise was evaluated by univariate linear regression. The null hypothesis assumed that 95% confidence intervals of the slopes of the linear regressions overlap zero. Physical-metabolic phenotype variables were age, E₂, T, insulin, AVF, TAF or work power. Statistical power for detecting a 35% contribution of age to the slope variance if 23 men completed the study was >80% assuming a young to older adult decrement of 50% in GH concentrations at two-sided $P < 0.05$.

To visualize GH responses on a per-person basis, intervention-induced incremental GH responses were calculated in each subject by subtracting 10-min FRS GH concentrations from 10-min FES- and FRG-associated GH concentrations at each of the 37 time points. The result was termed the incremental GH time series. For treatment x time comparisons, incremental GH time series were assessed in sequential 1-h bins (means of 6 consecutive samples) by ANOVA followed by Tukey's multiple comparison test [20]. A secondary endpoint was the absolute GH concentration difference (maximum minus minimum) calculated individually within any given GH time series. This max-min difference, a surrogate for GH pulse-generating capacity, was termed the dynamic GH range [21].

Multivariate stepwise forward-selection regression was applied to this endpoint (Statistics Toolbox 6, MATLAB, The MathWorks, Natick, MA 01760). Data are given as the mean $\pm$ SEM. R was Pearson's correlation coefficient, and R^2 the coefficient of determination.

Results

Basic epidemiologic data for the 23 men comprised a range of ages (19–77 yr) and BMI's (20–36 kg/m²) by intent. Baseline (prestudy) endocrine data (including screening TSH, a.m. cortisol, IGF-I, IGFBP-3, insulin, GH, LH, FSH, E₂, T), along with CT estimates of abdominal visceral fat (AVF) and total abdominal fat (TAF) and maximal ergometer power (watts) [Table 1], as well as screening lab data were normal for age and sex according to Mayo Clinical Laboratories.

GH concentration time series were analyzed next in all 23 subjects, each studied 3 times by 10-min sampling over the 6-h interval 0700–1300 h. Corresponding plasma glucose measurements were obtained after 30-min sampling. Control (FRS) *GH*-concentration time series exhibited no significant drift over time, as verified by trend analysis ($P = 0.38$ by ANOVA). The same was true for FRS *glucose*-concentration time series trend analysis ($P = 0.41$) [Figure 1 (*top*)]. In contrast, FES consistently elevated GH secretion within 40–60 min, and also glucose levels to a small but consistently nonzero degree ($P < 0.01$) [Figure 1 (*bottom*)]. FRG inhibited and then stimulated GH secretion, while increasing and then decreasing plasma glucose concentrations.

Peak, nadir and incremental GH concentrations were quantified next for each of the 3 randomized interventions.

1. FRS (control)

Absolute peak and nadir fasting/rest/saline GH concentrations during FRS were 0.97 ± 0.11 and 0.12 ± 0.096 $\mu\text{g/L}$, respectively.

2. FES, and GH autofeedback

During FES, peak GH concentrations rose to 4.1 ± 0.9 $\mu\text{g/L}$ 40–60 min after the onset of exercise at 0800 h. Since sampling began at 0700 h, the peak occurred 1.9 h after the start of sampling. The subsequent minimum GH concentration was 0.15 ± 0.06 $\mu\text{g/L}$ at 5.5 h. The biphasic pattern was confirmed by ANOVA of incremental (rest/saline-corrected) hourly mean GH concentrations ($P < 0.001$) [Figure 2 (*top*)]. In particular, peak and nadir GH values were 3.9 ± 0.88 and -0.33 ± 0.16 $\mu\text{g/L}$ at 1.9 h and 5.7 h, respectively. The negative value was taken to reflect GH autofeedback.

3. FRG to evoke biphasic GH dynamics

Intravenous glucose infused after the first h of sampling during FRG lowered GH concentrations to an absolute minimum of 0.14 ± 0.12 $\mu\text{g/L}$ (at 3.1 h) and then triggered a rebound maximum of 1.2 ± 0.14 $\mu\text{g/L}$ at 5 h ($P = 0.007$). Hourly mean GH-concentration profiles behaved comparably ($P < 0.01$) [Figure 2, (*bottom*)]. Incremental (control-corrected) GH responses were a nadir -0.61 ± 0.33 and a peak of 0.87 ± 0.31 μg at 2.5 h and 4.5 h,

respectively. The maximum 30-min glucose value was 128 ± 2.5 mg/dL ($P < 0.001$ vs saline bolus of 95 ± 2.4 mg/dL, and $P < 0.01$ vs exercise 106 ± 3.2 mg/dL).

Regression analysis and dynamic range

In the cohort of 23 men, absolute FRS peak and nadir GH concentrations correlated negatively with CT-estimated TAF by univariate regression, wherein $P = 0.011$, $R = -0.519$ (peak) and $P = 0.047$, $R = -0.421$ (nadir) [Appendix Figure 1]. Peak GH values correlated positively with exercise power ($P = 0.031$, $R = 0.452$). The *dynamic* range of GH release was computed as the algebraic within-series peak-nadir (max-min) difference. For FRS, this averaged 2.1 ± 0.45 μ g/L, and correlated negatively with TAF ($P = 0.012$) and positively with power ($P = 0.031$) [joint coefficient of determination, $R^2 = 0.267$] [Figure 3].

On the FES day, GH *peak increments* over fasting/rest/saline peaks correlated negatively with TAF ($P = 0.029$, $R = -0.455$), and age ($P = 0.022$, $R = -0.476$), and positively with E_2 ($P = 0.047$, $R = 0.407$), and power ($P = 0.016$, $R = 0.499$) [Appendix Table 1]. Nadir GH increments correlated positively with power ($P < 0.05$, $R = 0.438$). The *dynamic* (max-min) GH concentration range during FES averaged 5.3 ± 0.87 μ g/L. By stepwise regression analysis, 3 factors together explained 63% ($R^2 = 0.634$) of the variance in FES-induced GH increments ($P < 0.001$); viz., physical power (positively, $P = 0.0008$), E_2 (positively, $P = 0.001$) and insulin (negatively, $P = 0.011$) [Figure 4].

After *iv* glucose infusion in FRG, nadir GH concentrations varied inversely with physical power ($P = 0.020$, $R = -0.481$), and directly with TAF ($P = 0.013$, $R = 0.508$). Incremental peak (rebound) GH concentrations after glucose suppression correlated positively with T concentrations ($P = 0.008$, $R = 0.538$), and negatively with AVF ($P = 0.021$, $R = -0.478$) and TAF ($P = 0.026$, $R = -0.464$) [Appendix Table 1; Appendix Figure 2]. The dynamic max-min GH-concentration difference during FRG averaged 2.4 ± 0.41 μ g/L. By multivariate assessment, insulin ($P = 0.039$) and power ($P = 0.0034$) jointly determined dynamic GH range [overall $P = 0.0024$, coefficient of determination $R^2 = 0.454$]: Figure 5.

Discussion

This work relates strength of GH pulse-amplitude generation to key metabolic-phenotypic variables during experimental perturbation of pulsatile GH outflow via exercise and glucose stress. Regression analyses showed that exercise-induced and post-glucose rebound-like GH pulse generation were both positively controlled by physical power, a surrogate measure of voluntary exertional capacity. Conversely, GH-pulse excursions after exercise and glucose were both negatively determined by insulin. An evident distinction between exercise and glucose rebound-induced GH pulses was the significantly positive correlation between exercise-driven GH increments and E_2 levels measured by mass spectrometry ($P = 0.001$), and the significantly positive correlation between post-glucose GH rebound and T concentrations measured similarly ($P = 0.008$). Additionally, exercise-stimulated and post-glucose rebound GH peaks were negatively associated with both AVF and TAF. Collectively, these outcomes identify exercise power, insulin, E_2 , T, AVF, and TAF as significant determinants of glucose-modified and/or exercise-evoked GH pulsatility in

healthy men. Whether these acute results also apply in women and in chronic regulation of GH pulsatility is not yet known.

The present 6-h fasting data in 23 men extend the importance of body-composition surrogates, AVF and TAF, in explaining intersubject variability in pulsatile GH secretion. In particular, AVF or TAF negatively predicted: (i) exercise-induced incremental GH secretion; (ii) the decrement in GH secretion imposed by iv glucose; and (iii) the rebound in GH secretion following transient glucose suppression. These insights complement earlier findings that AVF (or TAF) explains significant effects of age and gender on fasting/rest GH output in healthy subjects [22–25] and in patients with HIV lipodystrophy [26]. Whereas the precise bases for these negative effects of AVF are not known, obesity-associated factors like insulin and free fatty acids putatively suppress GH secretion, adiponectin and ghrelin amplify GH secretion, and leptin inhibits fasting-induced GH elevations [27, 28]. Whatever the final mechanisms, significant loss of AVF in obese individuals only partially reinstates suppressed GH secretion [29, 30]. Our results suggest a framework in which acute day-to-day fluctuations in glucose levels (here from 95 ± 2.4 to 128 ± 2.5 mg/dL) and physical exertion (here 65% of individual power) influence pulsatile GH secretion via interactions with the longer-term stable variables, AVF and TAF. Although total body fat is a stronger inverse correlate than AVF of overnight pulsatile GH secretion in pubertal children [31], AVF and intramyocellular fat are dominant predictors of low GH in fasting adults studied at rest [6, 32].

The impact of graded (dose-dependent) exercise intensity on GH secretion has been studied extensively [33]. Whereas BMI is a consistent negative correlate of exercise-induced GH responses, there are significant effects also of age, gender and neuropharmacological interventions [34]. A major new finding in the present work is that exercise power (a measure of voluntary work/unit time), E_2 concentrations, and insulin concentrations together explain more than 63% of variance in interindividual dynamic (max-min) GH excursions driven by exercise. The negative effect of insulin on GH responses to exercise ($P = 0.011$) may reflect either direct hypothalamo-pituitary inhibition by insulin, as suggested by *in vivo* and *in vitro* studies in animals, and/or indirect effects of insulin, such as to reduce IGFBP-1 levels and thereby elevate free IGF-I feedback [5, 6, 35]. Thus, the multifactorial complexity of exercise-induced GH pulsatility arises in part from inferable interactions among insulin, estrogen and fitness. Whether such interactions are strictly linear, as might be implied by our linear correlation analysis, is not known.

GH concentrations peaked about 40–60 min after the exercise stimulus, and then decreased to a nadir approximately 4 h later. If the sequential rise and fall in GH secretion is a paradigm of autonegative GH feedback [36], then the exercise-evoked GH peak and nadir (max-min GH) difference would provide a surrogate measure of dynamic GH feedback. This concept is important, since GH autofeedback putatively mediates recurrent GH pulses [37], wherein escape of GH secretion from autofeedback initiates the next GH pulse.

An iv pulse of glucose (12.5 g) was used to simulate an acute stress-like increase in hepatic glucose output, *e.g.* as initiated by glycogenolysis in acute illness, or other stresses [38]. The protocol used here achieved a modest (35%) increase in plasma glucose levels still within

the normal range, which effectively suppressed GH concentrations. By regression analysis, higher physical power and lower TAF were related to larger absolute decrements in GH under glucose suppression. The initial GH decrement was followed by marked (8.6-fold incremental) escape of GH secretion. By univariate regression, incremental GH rebound after iv glucose was positively related to T concentrations and exercise power, and negatively related to AVF and TAF. In an earlier study using oral glucose, adiponectin (positively) and AVF (negatively) predicted rebound GH release in healthy men [39]. In the present paradigm, more than 45% of the variance in the amplitude of dynamic glucose-triggered GH excursions could be explained by physical power (positively) and insulin (negatively). Exactly how these prominent factors interact at the cellular level will require further evaluation.

Caveats in this study include the relatively small number of men studied (23 individuals each sampled every 10 min for 6 h on 3 occasions); the ultimate desirability of exploring additional adipokines or cytokines, evaluating wider doses of iv glucose, and examining men 80 yr of age as well as women of all ages. Thus, further investigations will be necessary to explore the generality of these results in additional cohorts. Even so, the present data elucidate new facets of hour-by-hour regulation of GH pulse generation by typical daily activities and metabolic stresses.

In summary, dynamic GH-pulse excursions after exercise and glucose stress are suppressed by greater insulinemia and abdominal (visceral) adiposity, and potentiated by higher E_2 and T concentrations and physical power. Together, such findings indicate a multifactorial basis for dynamic GH regulation under expected daily stressors. Pathophysiological implications are that chronic reductions in GH concentrations - - with attendant risks of sarcopenia, osteopenia, visceral adiposity, insulin resistance, and increased cardiovascular diseases - - reflect the composite effects of interconnected GH-regulating pathways. This integrative concept could explain in part the longstanding investigative difficulties in identifying any single regulatory deficit in the hyposomatotropism of aging, obesity, prediabetes, the metabolic syndrome and/or frailty.

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Abbreviations

GH	growth hormone
CT	computed tomography

E₂	estradiol
GHRH	growth hormone releasing hormone
GHRP	growth hormone releasing peptide
Mayo IRB	Mayo Institutional Review Board
ECG	electrocardiography
T	testosterone
LH	luteinizing hormone
FSH	follicle stimulating hormone
Mayo CTSA	Mayo Center for Advancing Translational Sciences
IGF-I	Insulin-like growth factor 1
IGFBP-3	insulin-like growth factor-binding protein 3
TSH	thyroid stimulating hormone
AVF	abdominal visceral fat
TAF	total abdominal fat
ANOVA	analysis of variance
SEM	standard error of mean
BMI	body mass index
IGBP-1	insulin-like growth factor-binding protein 1

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GH Response to IV Glucose, Exercise, Saline/Rest

Glucose Response to IV Glucose, Exercise, Saline/Rest

Figure 1.

Top. Time course of serum GH concentrations (mean $\pm$ SEM) sampled every 10 min for 6 h beginning at 0700 h fasting (time zero on abscissa). The 3 curves reflect placebo (FRS) session in red [closed boxes], exercise (FES, applied at 1 h) in blue [closed circles], and iv glucose (FRG, infused at 1 h) in green [open triangles]. The post-glucose nadir and rebound GH regions are marked. *Bottom.* Matching time course of plasma glucose concentrations sampled every 30 min during the 3 interventions. Data are from 23 men.

Incremental Effects of Exercise and IV Glucose on GH

Figure 2.

Hourly GH-concentration increments before (time 0–1 h, plotted at 1 h) and after (times 1–2, 2–3, 3–4, 4–5, 5–6 h, plotted at 2–6 h) exercise [top] and glucose [bottom] interventions. The increment was the algebraic difference in GH concentrations between the active interventions (FES, FRG) and FRS session. Data are the average of six 10-min samples each h ($\pm$ SEM) for $N = 23$ subjects. P values were obtained by ANOVA. Means with distinct (unshared) alphabetic superscripts are significantly different by Tukey's *post hoc* multiple-comparison test.

Fasting/Rest/Saline: Net GH Excursion

Figure 3.

Combined correlates of dynamic GH excursions during FRS (N = 23 subjects). The dynamic GH excursion (z axis) was defined in each GH time series as the peak-minus-nadir (max-min) concentration difference. Overall joint P was 0.012 and coefficient of determination (R^2) was 0.267. Individual P values for exercise power and TAF are given on the corresponding x and y axes.

Fasting/Saline with Exercise: Net GH Excursion

Figure 4.

Physical power (P = 0.0008), insulin (P = 0.011) and estradiol (E₂, P = 0.001) together (P < 0.001) determine 63.4% of the interindividual variance in dynamic, FES-stimulated GH excursions (max-min, z axis) in 23 men. The corresponding pairwise relationships (x and y axes) are shown in each of the 3-dimensional subplots.

Fasting/Rest with IV Glucose: Net GH Excursion

Figure 5.

Joint two-variable determination of 45.4% of the intraindividual variance in dynamic post-glucose GH excursions during FRG (max-min) in 23 men. The overall P value was 0.0024, $R^2 = 0.454$; and, the individual P values were 0.0034 for exercise power (positive effect), and 0.039 for insulin (negative effect).

Fasting/Rest/Saline Peak and Nadir GH: relation to TAF **Appendix Figure 1.**

Negative impact of TAF on fasting peak (*top*) and nadir (*bottom*) GH concentrations in 23 fasting men at rest receiving iv saline (FRS). Pearson's R (correlation coefficient) and P values are shown for each linear regression.

Glucose-Induced Rebound GH Concentration is Related to Testosterone **Appendix Figure 2.**

Glucose-induced rebound GH concentration during FRG is related to total serum testosterone concentration. P and R are given, as in Appendix Figure 1.

Table 1

Baseline Subject Characteristics (N = 23)

	<u>Mean ± SEM</u>	<u>Median</u>	<u>Range</u>	<u>NL</u>
<u>A. Physical Data</u>				
Age (yr)	48 ± 3.9	50	19–77	_____
BMI (kg/m ²)	27 ± 0.82	26	20–36	_____
Albumin (g/dL)	4.4 ± 0.59	4.4	4.0–5.0	3.8–5.2
<u>B. Endocrine Data</u>				
TSH (mU/L)	2.8 ± 0.41	2.2	0.5–6.0	(0.05–6.0)
Cortisol (µg/dL)	12 ± 0.60	13	11–20	(10–22)
IGF-I (µg/L)	144 ± 13	134	72–338	(65–350)
IGFBP-3 (mg/L)	3.5 ± 1.5	3.4	2.5–5.5	(2–6)
Insulin (µU/mL)	2.6 ± 0.33	1.9	0.9–6.9	(0.3–20)
GH (µg/L)	0.41 ± 0.33	0.44	0.01–20	(0.01–24)
LH (U/L)	4.5 ± 0.51	3.5	1.5–9.1	(2–12)
FSH (U/L)	7.0 ± 0.95	6.0	2.8–15	(2–16)
E ₂ (pg/mL)	24 ± 1.5	24	12–47	(8–50)
T (ng/dL)	532 ± 37	252	252–1000	(240–1050)
<u>C. Body Composition</u>				
Abdominal visceral fat (cm ²)	139 ± 15	140	34–352	_____
Total abdominal fat (cm ²)	325 ± 30	323	100–715	_____
<u>D. Power (watts), maximal</u>	240 ± 15	233	147–345	_____

NL denotes normal limits in Mayo Clinical Laboratory.

Data are from 23 men.

Appendix Table 1

Univariate correlation coefficients with incremental GH responses, defined by the algebraic difference between data in the interventional (FES, FRG) and the control (FRS) GH time series.

Dependent Variable	Independent Variable						
	Age	E ₂	T	Insulin	AVF	TAF	Power
<u>Exercise GH[‡]</u>							
Max	-0.476 [*]	+0.407 [*]	NS	NS	NS	-0.455 [*]	+0.498 [*]
Min	NS	NS	NS	NS	NS	NS	+0.438 [*]
<u>Glucose GH[‡]</u>							
Max	NS	NS	+0.538 [‡]	NS	-0.478 [*]	-0.464 [*]	+0.522 [*]
Min	NS	NS	NS	NS	NS	+0.508 [*]	-0.481 [*]

^{*} P<0.05

[‡] P<0.01

NS denotes P>0.05

[‡] Dependent variable was GH-concentration difference with saline (intervention minus saline GH).