Androgens May Mediate a Relative Preservation of IGF-1 Levels in Overweight and Obese Women Despite Reduced Growth Hormone Secretion*

A Utz¹, A Yamamoto¹, P Sluss², J Breu³ and KK Miller¹.

¹Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, 02114; ²Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, 02114 and ³MIT Clinical Research Center, Massachusetts Institute of Technology, Cambridge, MA, United States, 02139.

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Corresponding Author:
Karen K. Miller
Neuroendocrine Unit
Bulfinch 457B
Massachusetts General Hospital
Boston, MA 02114
KKMiller@Partners.org
Tel: 617-726-3870
Fax: 617-726-5072

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Abstract

Context: Obesity is characterized by reduced GH secretion, but data regarding IGF-1 levels and their determinants are conflicting.

Objective: To determine whether IGF-1 levels are reduced and to investigate determinants of GH and IGF-1 in healthy overweight and obese women

Design: Cross-sectional

Setting: General Clinical Research Center

Study Participants: 34 healthy women without pituitary/hypothalamic disease: 11 lean (BMI < 25 kg/m²), 12 overweight (BMI ≥25 kg/m² and < 30 kg/m²) and 11 obese (≥ 30 kg/m²) women of comparable age (overall mean 30.7±7.8 y).

Intervention: None

Main Outcome Measures: 24-h q 10 minute frequent sampling for GH, peak GH after GHRH-arginine stimulation, IGF-1, IGFBP-3, estrone, estradiol, testosterone, free testosterone, SHBG, HOMA-IR and abdominal fat.
**Results:** Mean 24-hour GH and peak stimulated GH were lower in overweight than lean and lowest in obese women. Mean IGF-1 levels trended lower in obese, but not overweight, compared with lean, women. Free testosterone was positively associated with IGF-1 (R=0.36, \( p=0.04 \)) but not with GH measures. Visceral fat was the only determinant of mean 24-hour GH (\( R^2=0.66, \ p<0.0001 \)) and of peak stimulated GH (\( R^2=0.63, \ p<0.0001 \)), and mean 24-hour GH accounted for 39% of the variability of IGF-1 (\( p=0.0002 \)), with an additional 28% (\( p<0.0001 \)) attributable to free testosterone levels.

**Conclusions:** Despite a linear decrease in GH secretion and peak stimulated GH levels with increasing BMI in healthy overweight and obese women, IGF-1 levels were not commensurately reduced. Androgens may contribute to this relative preservation of IGF-1 secretion in overweight and obese women despite reduced GH secretion.
Introduction

Although it is established that obesity is characterized by reduced growth hormone (GH) secretion, data regarding IGF-1 levels and their determinants in obesity are conflicting. Although some studies have demonstrated a degree of reduction in IGF-1 levels commensurate with the known reduction in endogenous GH secretion (1-6), others report only slightly low IGF-1 levels despite marked reductions in GH secretion (7). Still other studies report normal (8, 9), or high IGF-1 levels (10, 11). Studies investigating the effects of body composition on suppression of GH levels in obese men and women have established that visceral adipose tissue mass is a strong determinant of GH (12-14) and is also a predictor of IGF-1 levels (4, 15). We therefore measured GH (mean 24-hour, as measured by every ten-minute sampling and peak after stimulation with GHRH and arginine) and IGF-1 levels in overweight and obese women and compared them with those of lean female controls to determine whether IGF-1 levels are reduced in such women.

Because GH receptor activation is the primary determinant of IGF-1 levels, the underlying mechanisms for the dissociation between GH and IGF-1 levels in this group of women are not clear, and we therefore investigated whether body composition, estrogens, androgens or elevated IGFBP-3 levels predict GH or IGF-1 levels. There are few published studies that have investigated gonadal steroids, either estrogens or androgens, as potential determinants of GH and
IGF-1. In addition, although androgens are known to stimulate the GH-IGF-1 axis in men (16-23), little is known about their effects in women with low GH secretion, either hypopituitary or obese. Relative hyperestrogenemia or hyperandrogenemia in overweight and obese women might be expected to stimulate GH secretion and are therefore unlikely to be primary determinants of the reduced growth hormone secretion observed in this group of women. However, when we found that endogenous IGF-1 secretion was relatively preserved compared with GH secretion in our group of obese and overweight women, we hypothesized that because testosterone augments the GH-dependent stimulatory effect on IGF-1 production (24), relative hyperandrogenemia might stimulate liver IGF-1 production in opposition to diminished GH action in overweight and obese women. This is in contrast to the known effects of estrogens to cause GH resistance in the liver, resulting in a relative reduction of IGF-1 production per unit of GH secretion (25-28). We therefore investigated putative determinants of GH and IGF-1 levels in order to characterize the effects of androgens in comparison to other known determinants, including estrogens and body composition parameters, on GH and IGF-1 secretion in healthy young overweight and obese women.
Subjects and Methods

Subjects

We studied 34 healthy volunteers recruited from the community through advertisements. In order to participate in the study, volunteers were required to be eumenorrheic and with serum testosterone levels in the normal female range. Exclusion criteria included hypothalamic or pituitary disorders, diabetes mellitus or other chronic illnesses, estrogen or glucocorticoid use and weight greater than 280 pounds (due to the limitations of the DXA and CT scanners).

Materials and Methods

The study was approved by the Partners Healthcare Inc. Institutional Review Board, and written informed consent was obtained from each study participant. Each participant was admitted to the General Clinical Research Center at the Massachusetts General Hospital, where serum was collected every 10 minutes for 24 hours starting at 0800h during the follicular phase of the menstrual cycle. During this admission to the General Clinical Research Center, vigorous activity, including exercise, was prohibited. Fasting blood was obtained for IGF-1, IGFBP-3, estrone, estradiol, testosterone and SHBG. A fasting GHRH-arginine stimulation test was performed as follows. GHRH 1 mcg/kg plus arginine 0.5 g/kg (maximum 30 gm) IV were administered and GH levels drawn at baseline and every 30 minutes for two hours. This test has been validated in comparison
to the gold standard insulin tolerance test, with proposed cut-offs for the
diagnosis of GH deficiency of 4.1 to 9 ng/ml (29, 30). Baseline clinical
characteristics, GHRH-arginine stimulation test results, IGF-1, waist
circumference and fasting insulin and glucose levels in these study subjects were
included in a previously published manuscript (31).

**Body Composition Measures**

Fat and fat-free mass were measured by dual-energy x-ray absorptiometry
(DXA) using a Hologic QDR-4500 densitometer (Hologic Inc., Waltham,
Massachusetts), with an accuracy error for body fat mass of 1.7% and for fat-free
mass of 2.4 % (32). Total, subcutaneous fat, and visceral abdominal fat
compartments were measured in duplicate using single-slice quantitative CT
scans at the level of L4 with 10-mm thick axial images (General Electric RP High
Speed Helical CT Scanner, Milwaukee, WI) and graphical analysis software
(General Electric Advantage Windows Work Station Version 2.0, General
Electric). Technical factors for the scanning were 80 kVp, 70mA, and 2-second
scan time. Mid-waist circumference was measured as the midpoint between the
iliac crest and the lowest rib measured in a horizontal plane parallel to the floor.

**Biochemical Analyses**

Serum samples were collected and stored at -80˚C. Serum GH was measured
using an immunoradiometric assay (IRMA) kit [Diagnostic Systems Laboratories
(DSL), Inc., Webster, TX], with a minimum detection limit of 0.01 ng/ml, an intra-
assay coefficient of variation (cv) of 3.1-5.4% and an inter-assay cv of 5.9-11.5%. Serum IGF-1 levels were measured using an Immulite 2000 automated immunoanalyzer (Diagnostic Products Corporation, Inc., Los Angeles, CA), by a solid-phase enzyme-labeled chemiluminescent immunometric assay, with an inter-assay cv of 3.7-4.2%. IGFBP-3 was measured by IRMA kit (DSL, Inc.) with a minimum detection limit of 0.5 ng/ml, an intra-assay cv of 1.8-3.9% and an inter-assay cv of 0.5-1.9%. Estrone was measured by radioimmunoassay (RIA) kit (DSL, Inc.), with a minimum detection limit of 1.2 pg/ml, an intra-assay cv of 4.4-9.4% and inter-assay cv of 6.0 to 11.1%. Estradiol was measured by ultra-sensitive RIA kit (DSL, Inc.) with a minimum detection limit of 2.2 pg/ml, intra-assay cv of 6.5-8.9% and inter-assay cv of 7.5-12.2%. Serum testosterone was measured by RIA kit (DPC, Inc.) with a minimum detection limit of 2 ng/dL, an intra-assay cv of 4.1-10.5% and an inter-assay cv of 5.9-12%. Sex hormone binding globulin (SHBG) was measured by IRMA (DPC, Inc.), with a minimum detection limit of 0.5 nmoles/L, an intra-assay coefficient of variation (cv) of 2.8 – 5.3%, and an inter-assay cv of 7.9-8.5%. Free testosterone was calculated from total testosterone and SHBG by the laws of mass action, which has been validated in comparison to free testosterone by equilibrium dialysis (33). Insulin was measured using a radioimmunoassay (RIA) kit (Linco, Research, Inc., St. Charles, MI), with a sensitivity of 2 µU/ml, an intra-assay cv of 2.2-4.4% and an inter-assay cv of 2.9-6.0%. The homeostasis model assessment of insulin resistance (HOMA-IR) has been validated as an accurate measurement of insulin resistance and was calculated as \[\text{[insulin(µIU/mL) \times glucose(mmol/L)]/22.5}\] (34).
Statistical Analysis

JMP Statistical Discoveries (version 4.0.2, SAS Institute, Inc., Cary, NC) was used for statistical analyses. All variables were tested for normality using the Shapiro-Wilk test. Means were compared with analysis of variance (ANOVA) for variables with normal distributions and with the Wilcoxon test for those with non-normal distributions. Corrections for multiple comparisons were made by Tukey-Kramer. Univariate regression models were constructed, and Spearman coefficients are reported. Forward stepwise regression models, with 0.250 for probability to enter and 0.100 for probability to leave, were constructed to determine predictors of 24-hour mean GH, peak stimulated GH, and IGF-1 levels. The variables entered into the models are delineated in the Results section and were log-transformed before entry into the models if not normally distributed. Linear regressions were controlled for BMI by constructing multivariate least-squares regression models and entering BMI as a covariate into the models. All variables that were not normally distributed were log-transformed before being entered into these regression analyses. Statistical significance was defined as a 2-tailed p value < 0.05. Results are expressed as mean ± SEM.
Results

Clinical Characteristics of Study Subjects

Clinical characteristics, body composition and endocrine data are shown in Table 1. Study subjects were categorized as lean (n=11) if < 25 kg/m², overweight (n=12) if ≥ 25 but < 30 kg/m² or obese (n=11) if ≥ 30 kg/m², based on WHO definitions (35). The mean age of the three groups was similar. Study participants ranged in age range from 19-45 years, and in BMI from 19.2 to 40.6 kg/m². Mean 24-hour GH and mean peak stimulated GH were lower in overweight than lean women and lowest in obese women (Figure 1). Mean IGF-1 was lower in obese than overweight women, and there was a trend toward a lower mean IGF-1 level in obese compared with lean women. However, the mean IGF-1 level was not reduced in overweight (Figure 1). Mean free testosterone levels were higher in overweight and obese than lean women (Table 1). Mean levels of other gonadal steroids and IGFBP-3 were similar among the groups (Table 1).

Determinants of 24-hour Mean GH, Peak Stimulated GH and IGF-1 Levels

Linear regression models investigating potential body composition and endocrine determinants of 24-hour mean GH, peak GH after stimulation with GHRH and arginine, and IGF-1 were constructed in the group as a whole (n=34), and results (correlation coefficients and “p” values) are shown in Table 2. BMI and all
measures of fat mass were strong inverse predictors of mean 24-hour GH and peak GH after stimulation. BMI, total fat mass, and visceral adipose tissue were also negative predictors of IGF-1 levels. Free testosterone (R=0.36, \(p=0.04\)) was positively associated with IGF-1 (Figure 2A), and there was a trend toward an association between total testosterone and IGF-1 levels (R=0.30, \(p=0.08\)). After controlling for BMI, the association of total testosterone and IGF-1 became significant. \(p=0.006\). After controlling for BMI, the statistical significance of the association between free testosterone and IGF-1 increased \(p=0.002\). Free testosterone was inversely associated with peak stimulated GH (R= -0.37, \(p=0.04\)) (Figure 2B), but this relationship was no longer significant after controlling for BMI. There was trend toward an inverse association of estrone (R= -0.31, \(p=0.09\)), but not estradiol, with IGF-1 levels; the association was no longer evident after controlling for BMI using multivariate regression modeling. Although neither estrone nor estradiol levels correlated with IGF-1 levels, after controlling for BMI a positive association between estrone, but not estradiol, and IGF-1 became evident (R=0.33, \(p=0.03\)).

Visceral fat, free testosterone, HOMA-IR and estrone were entered into stepwise regression models for peak stimulated GH and 24-hour mean GH. Visceral fat was the only significant determinant of peak GH, determining 66% of the variability \(R^2=0.63, p<0.0001\) and of 24-hour mean GH \(R^2=0.66, p<0.0001\), determining 66% of the variability. Mean 24-hour GH, visceral fat, free testosterone, HOMA-IR and estrone levels were entered in the stepwise
A regression model constructed to investigate the determinants of IGF-1 levels. 24-hour mean GH accounted for 39% of the variability of IGF-1 levels ($R^2=0.39$, $p=0.0002$), with an additional 28% (cumulative $R^2=0.67$, $p<0.0001$) attributable to free testosterone levels. When age also was entered into the model, age accounted for 41% of the variability ($p=0.0001$), mean 24-hour GH accounted for an additional 10% of the variability (cumulative $R^2=0.51$, $p=0.021$) and an additional 14% of the variability in IGF-1 levels was attributable to free testosterone levels (cumulative $R^2=0.65$, $p=0.003$).

*Predictors of Gonadal Steroid and Binding Protein Levels*

Predictors of gonadal steroid levels are shown in Table 3. Estrone was positively associated with BMI ($R=0.35$, $p=0.04$), total abdominal fat ($R=0.38$, $p=0.03$) and subcutaneous abdominal fat ($R=0.41$, $p=0.02$). Free testosterone was positively associated with BMI ($R=0.36$, $p=0.04$), as well as with total abdominal fat ($R=0.38$, $p=0.03$), visceral adipose tissue ($R=0.36$, $p=0.04$), subcutaneous abdominal fat ($R=0.36$, $p=0.04$) and fat-free mass ($R=0.35$, $p=0.04$). Neither estradiol, total testosterone nor IGFBP-3 levels were associated with BMI or any body composition measures.

**Discussion**

Our data demonstrate that despite a linear decrease in GH secretion and peak stimulated GH levels with increasing BMI, IGF-1 levels are not reduced in
overweight women and are not reduced to the same degree as GH secretion in obese eumenorrheic women. We also demonstrate that androgens may contribute to the relative preservation of IGF-1 secretion in viscerally obese women despite reduced GH secretion. Consistent with data from other groups, we also show that visceral adiposity is a strong determinant of decreased GH secretion in obese women and a significant, though less important, determinant of IGF-1 levels.

IGF-1 levels have been variably shown to be low (1-6), normal (8, 9) or even high (10, 11) in overweight and obese women. Although IGF-1 has been shown in one study to increase in concert with GH secretion after gastric bypass (36), in two other studies, mean IGF-1 levels failed to increase despite increases in mean stimulated GH after a significant reduction in BMI (37, 38). In addition, data from two studies suggest that the relationship between BMI and IGF-1 levels may be non-linear, following an inverse “U” shape, with a peak at a BMI of about 25 kg/m² (9, 39). Our data suggest that although IGF-1 levels may be modestly reduced in women with obesity, they are normal in overweight women. Because GH stimulation is thought to be the primary determinant of IGF-1 levels, the underlying mechanisms for the dissociation between GH and IGF-1 levels in this group of women are not clear, and we therefore investigated whether body composition, estrogens, androgens, measures of insulin resistance or elevated IGFBP-3 levels predict GH or IGF-1 levels.
The effects of androgens on GH secretion and IGF-1 levels have been studied in men but little is known about the relationship between androgens and the GH-IGF-1 axis in women. In men, evidence from studies using several different physiologic models demonstrates that testosterone stimulates GH release, thereby contributing to an increase in IGF-1 levels. In hypogonadal men, GH levels are decreased, and restoration of testosterone levels, with androgen replacement or pulsatile GnRH therapy, results in normalization of GH (16-19); testosterone replacement also increases IGF-1 secretion in hypogonadal men (16, 18, 19). Similarly, administration of testosterone to prepubertal and peripubertal boys (20-22), as well as elderly men (23), increases endogenous GH and IGF-1 secretion. In addition, and of note, there is evidence of a direct, independent effect of testosterone to stimulate IGF-1 levels in men, as shown by Gibney et al., who investigated the effects on IGF-1 of testosterone administration alone, GH alone or the combination to 12 hypopituitary men. Although testosterone administration alone did not increase IGF-1, the combination of GH plus testosterone increased IGF-1 more than GH alone, suggesting that testosterone exerts an independent effect to increase IGF-1 in the presence, but not absence, of GH, in men (24). As expected, free testosterone levels in our study negatively correlated with stimulated GH levels, the latter increasing and the former decreasing with weight. Also, as predicted, after controlling for BMI, no independent association of GH, either 24-hour or peak stimulated, could be detected. However, an interesting finding was that free testosterone levels positively predicted IGF-1 levels and that the level of
significance of this relationship increased after controlling for the effects of BMI. In addition, in stepwise regression models that included HOMA-IR, a validated measure of insulin resistance, free testosterone was chosen by the model over HOMA-IR as a significant predictor of IGF-1 levels. These data suggest a direct stimulatory effect of testosterone on IGF-1 production. Although the degree of hyperandrogenemia was similar in overweight and obese women, GH levels (both mean 24-hour and peak stimulated) were lower in obese than overweight women. This combination of effects may at least partially explain our finding of normal mean IGF-1 levels in overweight women, and a lower mean IGF-1 level in obese women, but one that was relatively higher than would be predicted from decreased GH stimulation alone.

To our knowledge, we are the first to report evidence of a possible dissociation of the effects of testosterone on hypothalamic versus pituitary function in the GH-IGF-1 axis in women. Data exploring the relationship between GH and androgens in obese women has not been published. In contrast, there is a small literature on androgens as determinants of IGF-1 levels in women without organic hypothalamic or pituitary disease. Our data investigating determinants of IGF-1 are consistent with three reports of associations of androgen and androgen precursors with IGF-1 levels, including DHEAS (7, 40, 41), testosterone and androstenedione (7) in healthy women. Androstenedione is the most prevalent, though not most potent, circulating androgen in women, and a precursor to both testosterone and estrone. Further investigation into the role of
androstenedione as a moderator of the GH-IGF-1 axis is merited. Moreover, additional studies investigating the effects of androgens on hepatic IGF-1 production in women are warranted to determine whether our data suggesting that relative hyperandrogenemia in overweight and obese women may be one mechanism underlying a relative preservation of endogenous IGF-1 despite reduced GH secretion in this population.

In contrast to our data suggesting that androgen levels may influence IGF-1 levels in overweight and obese women, our data do not suggest an important role for estrogens as determinants of GH or IGF-1 secretion in healthy obese and overweight women. Our data are consistent with data from Maccario et al. of 234 healthy women in which androgens were positively associated with IGF-1 levels in contrast to estradiol levels, which were not; estrone levels were not assessed, nor was GH secretion (7). Studies in healthy women have suggested a stimulatory role for endogenous estradiol on GH secretion as supported by periovulatory increases in GH secretion associated with the rise in estradiol and higher GH levels in pre- than post-menopausal women (42, 43). Oral estrogens induce a state of GH resistance at the level of the liver, resulting in decreased IGF-1 levels despite increased GH secretion (43-45). In addition, it has been demonstrated that women have lower levels of IGF-1 for comparable endogenous GH levels than their male counterparts, or a relative GH resistance state compared to men. This has been shown in healthy women as well as women with growth hormone deficiency and those with acromegaly, and it has
been attributed to the effects of estrogens (25-27). In contrast, our data do not support an important role for estrogens in the determination of GH or IGF-1 levels in overweight or obese otherwise healthy women of reproductive age.

Similarly, our data do not support dysregulation of IGFBP-3 levels as a mechanism underlying the relatively high IGF-1 levels in overweight and obese women. If IGFBP-3, the most ubiquitous IGF-1 binding protein (46-48), were elevated in overweight and obese women, a relative preservation of total IGF-1 levels could belie depressed free IGF-1 levels. Our data do not suggest this to be the case, as IGFBP-3 levels were not increased in overweight or obese women and were not positively associated with BMI, consistent with published data from other groups (9, 11). Our data reporting normal IGFBP-3 levels in overweight and obese women suggest that the relative sparing of IGF-1 levels likely reflects biological activity. However, measurement of IGF-1 action using a bioassay would be an important next step to investigate this hypothesis further.

In addition, Roelen et al. have demonstrated a strong positive correlation between visceral adipose tissue and growth hormone-binding protein, such that, in general, those men and women with more visceral adiposity had higher levels of circulating growth hormone binding protein levels (49). Therefore, a reduction in growth hormone-binding protein is not a likely cause of low total GH levels. Instead, low total GH levels in obesity likely do reflect low free GH levels, and the reasons for the lack of a commensurate decrease in IGF-1 levels are not evident.
Our data confirm reports from other groups of the importance of body fat, particularly visceral stores of abdominal fat, as determinants of GH (50-52) and, less so, IGF-1 (15) levels in obese healthy women. We also have demonstrated truncal fat to be an important determinant of GH levels in healthy overweight women (53), and a number of studies have demonstrated visceral adipose tissue to be an important determinant of GH secretion in healthy lean men and women (12-14). Therefore, our data are consistent with these studies in that they demonstrate body fat, particularly visceral fat mass, to be strong predictors of GH, and predictors, though less important ones, of IGF-1 secretion in healthy women.

In summary, our data suggest that despite a linear decrease in GH secretion with increasing BMI in young women of reproductive age, IGF-1 levels are relatively preserved. Our data also suggest that relative hyperandrogenemia in such women may be one mechanism underlying the maintenance of relatively higher IGF-1 levels than would be expected based solely on the degree of GH stimulation. Estrogen levels were not important determinants of GH or IGF-1 levels in the group of women studied. Our data are also consistent with published results that have established that body fat, particularly visceral adipose stores, are important inverse determinants of GH levels in young women, and significant, though weaker, predictors of IGF-1 levels. Further studies are warranted to investigate the effects of androgens on the GH-IGF-1 axis in women.
Acknowledgements

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References


18. **Liu L, Merriam GR, Sherins RJ** 1987 Chronic sex steroid exposure increases mean plasma growth hormone concentration and pulse amplitude in men with isolated hypogonadotropic hypogonadism. J Clin Endocrinol Metab 64:651-656


secretion in young males with hypogonadotropic hypogonadism pharmacologically exposed to progressive increments in serum testosterone. J Clin Endocrinol Metab 82:1210-1219


27. **Span JP, Pieters GF, Sweep CG, Hermus AR, Smals AG** 2000 Gender difference in insulin-like growth factor I response to growth hormone (GH)


31. Utz A, Yamamoto A, Hemphill L, Miller KK 2008 Growth hormone deficiency by GHRH/arginine testing criteria predicts increased cardiovascular risk markers in normal young overweight and obese women J Clin Endocrinol Metab


from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412-419


42. Ovesen P, Vahl N, Fisker S, Veldhuis JD, Christiansen JS, Jorgensen JO 1998 Increased pulsatile, but not basal, growth hormone secretion rates and plasma insulin-like growth factor I levels during the periovulatory interval in normal women. J Clin Endocrinol Metab 83:1662-1667


Figure Legends

Figure 1. Mean 24-hour GH (panel A) and peak stimulated GH (panel B) were lower in overweight than lean women and lowest in obese women. Mean IGF-1 levels (panel C) were lower in obese than overweight women, and there was a trend toward a lower mean IGF-1 level in obese than lean women. There was no difference in mean IGF-1 level in the lean and overweight groups. *, $p<0.05$.

Figure 2. Free testosterone levels positively predicted IGF-1 levels ($R=0.36$, $p=0.04$) (panel A) and inversely predicted peak stimulated GH levels ($R=-0.37$, $p=0.04$) (panel B). After controlling for BMI using standard least squares multivariate regression modeling, the positive association between free testosterone and IGF-1 achieved greater statistical significance ($p=0.002$), and the association of free testosterone with peak stimulated GH levels was no longer evident. Spearman coefficients are reported. Lines were fitted to the data, which were log-transformed if not normally distributed.
Table 1. Clinical Characteristics, Body Composition and Endocrine Data

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Lean BMI &lt; 25 kg/m²</th>
<th>Overweight BMI ≥ 25 ≤ 30 kg/m²</th>
<th>Obese BMI ≥ 30 kg/m²</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>30.7 ± 1.3</td>
<td>30.5 ± 2.3</td>
<td>28.1 ± 2.5</td>
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<td>Weight (kg)</td>
<td>77.1 ± 2.9</td>
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<td>72.8 ± 1.3</td>
<td>90.2 ± 4.7**</td>
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<td>BMI (kg/m²)</td>
<td>28.4 ± 1.0</td>
<td>22.3 ± 0.6</td>
<td>27.6 ± 0.4</td>
<td>35.4 ± 0.8**</td>
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<td>Mid-waist circumference (cm)</td>
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<td>77.4 ± 1.5</td>
<td>88.5 ± 1.6</td>
<td>104.9 ± 3.6**</td>
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<tr>
<td>Mean 24-hour GH (ng/ml)</td>
<td>0.87 ± 0.13</td>
<td>1.57 ± 0.17</td>
<td>0.81 ± 0.18</td>
<td>0.22 ± 0.05**</td>
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<tr>
<td>GH stimulation peak (ng/ml)</td>
<td>17.7 ± 2.1</td>
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<td>15.2 ± 2.6</td>
<td>6.1 ± 1.1**</td>
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<td>IGF-1 (ng/ml)</td>
<td>201 ± 14</td>
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<td>IGFBP-3 (µg/mL)</td>
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<td>Total fat mass (kg)</td>
<td>29.0 ± 2.0</td>
<td>17.8 ± 1.3</td>
<td>28.7 ± 1.0</td>
<td>42.8 ± 2.2**</td>
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<td>Non-trunk fat mass (kg)</td>
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<td>Fat-free mass (kg)</td>
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<td>Abdominal fat cross-sectional area (mm²)</td>
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<td>47789 ± 4236</td>
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<td>Visceral fat cross-sectional area (mm²)</td>
<td>7195 ± 831</td>
<td>3484 ± 556</td>
<td>6787 ± 747</td>
<td>11351 ± 1718**</td>
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<td>Subcutaneous fat cross sectional area (mm²)</td>
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<td>19231 ± 2047</td>
<td>20522 ± 1489</td>
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<td>Estradiol (pg/mL)</td>
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<td>Estrone (pg/mL)</td>
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<td>50.9 ± 5.1</td>
<td>68.3 ± 10.2</td>
<td>71.5 ± 10.0</td>
</tr>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>28.8 ± 2.7</td>
<td>21.4 ± 2.8</td>
<td>31.5 ± 4.8</td>
<td>33.3 ± 5.6</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>44.3 ± 3.7</td>
<td>55.1 ± 6.7</td>
<td>43.3 ± 6.9</td>
<td>34.4 ± 4.0*</td>
</tr>
<tr>
<td>Free testosterone (ng/dL)</td>
<td>0.48 ± 0.05</td>
<td>0.30 ± 0.05</td>
<td>0.52 ± 0.07</td>
<td>0.63 ± 0.12*</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>83.0 ± 1.8</td>
<td>80.5 ± 4.1</td>
<td>81.8 ± 1.9</td>
<td>87.1 ± 2.9</td>
</tr>
<tr>
<td>Fasting insulin (µIU/mL)</td>
<td>10.1 ± 1.2</td>
<td>6.2 ± 0.7</td>
<td>10.9 ± 1.8</td>
<td>13.2 ± 2.8*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.1 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>2.2 ± 0.4</td>
<td>3.0 ± 0.9*</td>
</tr>
</tbody>
</table>

* p < 0.05, compared to lean group (Control: BMI < 25 kg/m²); † p < 0.05, compared to overweight group (25 ≤ BMI < 30 kg/m²)
Table 2. Predictors of GH and IGF-1 Secretion: Univariate Analyses

<table>
<thead>
<tr>
<th>Predictor</th>
<th>24-hour Mean GH</th>
<th></th>
<th>Peak Stimulated GH</th>
<th></th>
<th>IGF-1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.76</td>
<td>&lt;0.0001</td>
<td>-0.81</td>
<td>&lt;0.0001</td>
<td>-0.36</td>
<td>0.04</td>
</tr>
<tr>
<td>Mid-waist circumference (cm)</td>
<td>-0.73</td>
<td>&lt;0.0001</td>
<td>-0.76</td>
<td>&lt;0.0001</td>
<td>-0.25</td>
<td>0.16</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>-0.80</td>
<td>&lt;0.0001</td>
<td>-0.80</td>
<td>&lt;0.0001</td>
<td>-0.38</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-trunk fat mass (kg)</td>
<td>-0.75</td>
<td>&lt;0.0001</td>
<td>-0.72</td>
<td>&lt;0.0001</td>
<td>-0.39</td>
<td>0.02</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>-0.18</td>
<td>0.30</td>
<td>-0.37</td>
<td>0.04</td>
<td>0.03</td>
<td>0.87</td>
</tr>
<tr>
<td>Abdominal fat cross-sectional area (mm²)</td>
<td>-0.70</td>
<td>&lt;0.0001</td>
<td>-0.76</td>
<td>&lt;0.0001</td>
<td>-0.29</td>
<td>0.10</td>
</tr>
<tr>
<td>Visceral adipose tissue (mm²)</td>
<td>-0.84</td>
<td>&lt;0.0001</td>
<td>-0.75</td>
<td>&lt;0.0001</td>
<td>-0.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Subcutaneous abdominal fat (mm²)</td>
<td>-0.72</td>
<td>&lt;0.0001</td>
<td>-0.72</td>
<td>&lt;0.0001</td>
<td>0.24</td>
<td>0.16</td>
</tr>
<tr>
<td>IGFBP-3 (µg/mL)</td>
<td>0.22</td>
<td>0.20</td>
<td>0.17</td>
<td>0.34</td>
<td>0.50</td>
<td>0.002</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>0.16</td>
<td>0.40</td>
<td>-0.13</td>
<td>0.49</td>
<td>0.11</td>
<td>0.65</td>
</tr>
<tr>
<td>Estrone (pg/mL)</td>
<td>-0.11</td>
<td>0.52</td>
<td>-0.31</td>
<td>0.09</td>
<td>0.16</td>
<td>0.31</td>
</tr>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>-0.06</td>
<td>0.73</td>
<td>-0.22</td>
<td>0.24</td>
<td>0.30</td>
<td>0.08</td>
</tr>
<tr>
<td>Free testosterone (ng/dL)</td>
<td>-0.21</td>
<td>0.23</td>
<td>-0.37</td>
<td>0.04</td>
<td>0.36</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>-0.24</td>
<td>0.19</td>
<td>-0.19</td>
<td>0.31</td>
<td>-0.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Fasting insulin (µIU/mL)</td>
<td>-0.39</td>
<td>0.03</td>
<td>-0.52</td>
<td>0.003</td>
<td>-0.03</td>
<td>0.85</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.39</td>
<td>0.03</td>
<td>-0.52</td>
<td>0.004</td>
<td>-0.05</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Table 3. Predictors of Gonadal Steroid Levels: Univariate Analyses

<table>
<thead>
<tr>
<th></th>
<th>Estradiol R</th>
<th>Estradiol p</th>
<th>Estrone R</th>
<th>Estrone p</th>
<th>Total Testosterone R</th>
<th>Total Testosterone p</th>
<th>Free Testosterone R</th>
<th>Free Testosterone p</th>
<th>IGFBP-3 R</th>
<th>IGFBP-3 p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>0.09</td>
<td>0.61</td>
<td>0.35</td>
<td>0.04</td>
<td>0.25</td>
<td>0.16</td>
<td>0.36</td>
<td>0.04</td>
<td>-0.02</td>
<td>0.92</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>0.08</td>
<td>0.66</td>
<td>0.31</td>
<td>0.07</td>
<td>0.20</td>
<td>0.25</td>
<td>0.31</td>
<td>0.08</td>
<td>-0.03</td>
<td>0.67</td>
</tr>
<tr>
<td>Abdominal fat cross-sectional area (mm²)</td>
<td>0.14</td>
<td>0.44</td>
<td>0.38</td>
<td>0.03</td>
<td>0.29</td>
<td>0.11</td>
<td>0.38</td>
<td>0.03</td>
<td>-0.05</td>
<td>0.78</td>
</tr>
<tr>
<td>Visceral adipose tissue (mm²)</td>
<td>-0.04</td>
<td>0.83</td>
<td>0.27</td>
<td>0.11</td>
<td>0.25</td>
<td>0.15</td>
<td>0.36</td>
<td>0.04</td>
<td>-0.06</td>
<td>0.74</td>
</tr>
<tr>
<td>Subcutaneous abdominal fat (mm²)</td>
<td>0.14</td>
<td>0.42</td>
<td>0.41</td>
<td>0.02</td>
<td>0.20</td>
<td>0.25</td>
<td>0.36</td>
<td>0.04</td>
<td>-0.05</td>
<td>0.77</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>0.24</td>
<td>0.18</td>
<td>0.22</td>
<td>0.21</td>
<td>0.18</td>
<td>0.32</td>
<td>0.36</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.15</td>
<td>0.42</td>
<td>0.30</td>
<td>0.10</td>
<td>0.40</td>
<td>0.02</td>
<td>0.55</td>
<td>0.001</td>
<td>0.18</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Figure 1

A. Mean 24-hr GH (ng/mL)

B. Peak Stimulated GH (ng/mL)

C. IGF-1 (ng/mL)

* indicates a significant difference, p < 0.05.
Figure 2

A. 

IGF-1 (ng/mL) vs Free testosterone (ng/dL) 

R = 0.36
p = 0.04

B. 

Peak Stimulated GH (ng/mL) vs Free testosterone (ng/dL) 

R = -0.37
p = 0.04