Immunoreactive and bioactive growth hormone responses to resistance exercise in men who are lean or obese

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1School of Nursing, Yale University, New Haven; 2Human Performance Laboratory, Department of Kinesiology, 3Department of Physiology and Neurobiology, University of Connecticut, Storrs, Connecticut; and 4Biochemistry and Molecular Biology, Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, Pennsylvania

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Thomas GA, Kraemer WJ, Kennett MJ, Comstock BA, Maresh CM, Denegar CR, Volek JS, Hymer WC. Immunoreactive and bioactive growth hormone responses to resistance exercise in men who are lean or obese. J Appl Physiol 111: 465–472, 2011. First published June 2, 2011; doi:10.1152/japplphysiol.00157.2011. It has been suggested that obese individuals have a blunted growth hormone (GH) response to spontaneous and stimulated GH secretion. The present study was designed to examine the effects of a high-volume, whole body acute resistance exercise (RE) protocol on immunoreactive GH (iGH), bioactive GH (bGH), and GH-binding protein (GHBP) in sedentary lean and obese men. Nine obese (mean ± SD: 20.8 ± 2.1 yr old, 177.0 ± 4.1 cm height, 108.7 ± 15.9 kg body mass, 37.6 ± 5.29% body fat) and nine lean (20.1 ± 2.1 yr old, 177.8 ± 8.7 cm height, 71.7 ± 5.8 kg body mass, 14.7 ± 3.54% body fat) men completed an acute RE protocol (6 exercises, 3 sets of 10 repetitions at 85–95% of 10 repetitions maximum with 120- and 90-s rest periods), and blood samples were collected before, at the midpoint, and immediately after exercise and during recovery (±50, ±70, and ±110). In contrast to prior studies, which examined acute responses to cardiovascular exercise protocols, groups did not differ in iGH response to the exercise stimulus. However, bGH concentrations overall were significantly lower in the obese than the lean participants (P < 0.001). Additionally, obese individuals had significantly higher GHBP concentrations (P < 0.001). Results suggest that obese and lean sedentary men performing a high-volume, whole body acute RE protocol demonstrate similar increases in iGH. Blunted bGH and elevated GHBP concentrations are indicative of altered GH activity associated with obesity. Prior research findings of blunted iGH response may be attributable to RE protocols not equated on relative intensity or volume. These results underscore the complexity of pituitary biology and its related mechanisms and may have implications for exercise prescription in the treatment of obesity.

GROWTH HORMONE (GH) is a family of polypeptide variants, with >100 forms known to exist in circulation that is released from the anterior pituitary in pulsatile manner (41). Heterogeneity of molecules in the GH family results from transcriptional and translational processing in the pituitary somatotroph, which, in turn, may lead to generation of GH isoforms in the circulation. Factors such as age, sex, body composition, sleep, nutritional status, and insulin-like growth factor I (IGF-I) can dramatically affect the pulsatility of GH secretion (6). In healthy, lean individuals, GH is released in three to six pulses throughout the day, with the most pronounced release occurring nocturnally (19, 47). This pulsatile release has multiple effects on peripheral tissue, with one of its key functions being regulation of body fat and lean tissue (30, 47). Recent work in humans has demonstrated that continuous GH administration primarily augments hepatic and muscle IGF-I, while only pulsatile GH administration augments adipose tissue lipolysis (47). One of the most potent stimulators of pulsatile GH release is exercise (48). Exercise has been shown to modify the activity and molecular character of GH variants in circulation (21). However, much remains unknown about the biological action of these GH variants.

Overall GH levels and those stimulated by cardiovascular exercise have been shown to be decreased in obese individuals. It is also well established that increased body fat and body mass index (BMI) suppress spontaneous and stimulated serum GH concentrations but that these pulsatile responses return to normal with reduction to normal levels of body weight (43, 46). Normal GH response to physiological stimuli such as sleep and cardiovascular exercise appears to be impaired in obese individuals (44). Lower cardiovascular exercise-induced GH secretions have been attributed to a reduction in the mass of GH secreted per pulse (26, 50). Alterations in the GH response to exercise may be related to severity of obesity (42) and the progression of obesity status from simple (excess adiposity) to physiological alterations in metabolic homeostasis. In obese individuals, reductions in spontaneous GH secretion (as much as 6% for each unit increase in BMI) and the half-life of circulating GH have been reported (decreases from 15 to 11 min) (46). Additionally, the biological effects of GH in obese humans may not be determined merely by the overall magnitude of GH output but, rather, by complex pulsatile patterns of GH presentation to peripheral tissues (47). GH has been used as a therapy to reduce total fat mass and abdominal fat mass, with the effect being more pronounced in males than in females (5). The dosages of GH administration have varied, but it seems that low dosages are effective in reducing fat mass and abdominal fat mass (47). GH administration has been successful in reducing abdominal/visceral fat deposits (28) and can prove to be beneficial at reducing obesity-related comorbidities that may be caused by the increased abdominal/visceral adipose tissue (6). A low-dose GH treatment in addition to calorie restriction has been shown to accelerate body fat loss and GH secretion (27). Kim et al. (27) and Johannsson et al. (25) demonstrated that low-dose GH administration and calorie restriction can favorably affect visceral fat levels and may be useful in reducing some of the metabolic complications associated with visceral obesity. GH
is stimulated by exercise, and exercise may offer an additional avenue for increasing GH in therapeutic approaches for weight loss.

Aerobic exercise and resistance exercise (RE) have demonstrated the ability to increase circulating GH in lean individuals. However, investigations examining responses to both modes of exercise within the same participants have shown that greater GH concentrations occur in response to a RE stimulus (7). In addition, in response to a cardiovascular exercise stimulus, it has been prolifically established that obese individuals' concentrations are blunted (17). However, only one prior study has examined immunoreactive GH (iGH; i.e., assays that use an antibody-based detection system) response to RE in obese individuals (43). It is important to point out that our understanding of the concentrations of GH variants stimulated by exercise has developed primarily through the use of immunoadsorbent enzyme immunoassay and RIA, which present an incomplete picture of the GH response to exercise (21). Previous investigations have thus established that RE can increase circulating iGH concentrations in lean individuals (8, 9), but whether bioactive GH (bGH) is also affected is less understood. McCullough et al. (37, 38) found an increase in bGH, but not iGH, in men after acute physical activity. Different assays signal different endor points of interaction; thus, divergence can exist for the magnitude and response of human GH to exercise or physiological stimuli (11, 15, 23, 30). Examining the bGH response to RE in obese relative to lean men may clarify the type of altered GH response in obese men.

GH assessment is further complicated by the fact that, in blood, GH is also bound to binding proteins. These GH-specific binding proteins (GHBP) (4) bind in a 1:1 ratio, which is increased in individuals who are GH-deficient, and GHBP concentrations can vary due to nutritional and metabolic status (13). Thus these binding proteins may play an important role in understanding the lower GH values observed in obese individuals (4). This notion is consistent with the observation that obesity is associated with high concentrations of GHBP (20). In normal-weight individuals, GHBP is positively correlated with body fat percentage and intra-abdominal visceral fat (14). While GHBP may help mediate the lower GH concentrations in obese individuals, no prior research has examined whether changes in GHBP concentrations differ in response to exercise in lean vs. obese men.

The purpose of this study was to examine whether a RE protocol equated on intensity and volume across groups with adequate familiarization would demonstrate differences in GH variables in lean and obese men. Chronic exercise has demonstrated bGH effects in women and in male astronauts (23, 32, 37, 38). Studies have also reported that GH in men after acute physical activity. Different assays signal different endor points of interaction; thus, divergence can exist for the magnitude and response of human GH to exercise or physiological stimuli (11, 15, 23, 30). Examining the bGH response to RE in obese relative to lean men may clarify the type of altered GH response in obese men.

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GH-stimulating acute protocol (29, 34). Therefore, during the acute RE protocol, the participants performed 3 sets of 10 repetitions at 85–95% of previously determined 10 RM for each exercise. Previous research indicates that loads that fall below this level would not adequately stimulate a GH response (31).

**Acute RE protocol.** At the acute RE protocol visit, the participants entered the laboratory after a 12-h overnight fast, and all exercise tests were performed between 0700 and 1100 (24-h clock). They had been instructed to abstain from drinking alcohol or ingesting high doses of caffeine (>2 cups per day) for 24 h prior to the testing protocol. Participants were required to consume 1 liter of water on the night prior to testing and 0.5 liter on the day of visit 6. Adequate hydration (urine specific gravity ≤1.020) was confirmed prior to venous catheterization via urine refractometry (2). Before the acute exercise protocol, an intravenous catheter was inserted into the antecubital vein. Blood samples were taken 15 min after initial placement of the catheter. Participants then engaged in the acute RE protocol. Blood samples were collected at six time points: preexercise, midexercise, immediately postexercise, and 50, 70, 110 min postexercise. Time points were chosen to correspond to differences identified in prior studies (43). The cannula was kept patent with a 10% heparin solution injection. Prior to blood draw, 3 ml of blood were extracted to avoid inadvertent saline dilution of the blood sample. Whole blood was collected by appropriate tubes with preservatives for processing for determination of the various hormones and metabolites and was centrifuged at 1,500g for 15 min at 4°C. After centrifugation, plasma and serum were immediately separated into aliquots and added to preservative-treated tubes, flash-frozen in liquid nitrogen, and stored at −80°C until later analysis.

**Biochemical analyses.** Serum samples were analyzed in duplicate for iGH and high-affinity GHBP (Diagnostic Systems Laboratory, Webster, TX) via commercially available ELISAs. Coefficients of variation for these assays were 6.9% and 4.5%, respectively. The human GHBP ELISA has a minimum detection limit of 1.69 pmol/l, whereas the human iGH ELISA has a minimum detection limit of 0.99 pmol/l. The assay precision was of the following forms: y = 0.5037x − 89.48 (r² = 0.998) for assay 1 and y = 0.4088x − 69.56 (r² = 0.999) for assay 2.

**RESULTS**

**Immunoreactive GH.**

A mixed ANOVA (group × time) was performed to examine changes in iGH. The interaction effect for group × time was not significant [F = 0.386, degrees of freedom (df) = 4, 64, P = 0.818, n² = 0.024; Fig. 1A]. The main effect of time was significant (F = 29.00, df = 4, 64, P < 0.001, n² = 0.610). The main effect of group was not significant (F = 0.414, df = 1, 16, P = 0.529, n² = 0.025). Serum iGH concentrations were not different at rest between lean and obese participants (Fig. 1A). iGH was significantly lower at preexercise than at midexercise and immediately postexercise. iGH was significantly lower at midexercise than immediately postexercise and greater than at 110 min postexercise. iGH immediately postexercise was significantly different from all other time points. Additionally, iGH at 50 min postexercise was different from 110 min postexercise. A one-way ANOVA examined differences between groups in iGH area under the curve (AUC). No significant differences were found between groups (F = 0.645, df = 1, 17, P = 0.434, n² = 0.042; Fig. 2A).

**Bioactive GH.**

A mixed ANOVA (group × time) was performed to examine changes in bGH. The interaction effect for group × time was not significant (F = 1.95, df = 4, 64, P = 0.113, n² = 0.109). The main effect of time was not significant (F = 0.527, df = 4, 64, P = 0.716, n² = 0.032). However, the main effect of group was significant (F = 27.24, df = 1, 16, P < 0.001, n² = 0.630). Lean participants had significantly greater bGH than obese participants at midexercise, immediately postexercise, and 50 min postexercise (Fig. 1B). A one-way ANOVA was used to test differences in bGH AUC. The between-groups effects indicate significant differences (F = 11.03, df = 1, 16, P = 0.004, n² = 0.408), consistent with the main effect from the mixed ANOVA. Lean participants had significantly greater bGH than obese participants. Mean differences are depicted in Fig. 2B.
**GH-Binding Protein**

A mixed ANOVA (group × time) was performed to examine changes in GHBP. The interaction effect for group × time was not significant ($F = 1.89$, df = 4.64, $P = 0.123$, $\eta^2 = 0.106$). The main effect of time was not significant ($F = 2.18$, df = 4.64, $P = 0.081$, $\eta^2 = 0.120$). However, the main effect of group was significant ($F = 46.11$, df = 1,16, $P < 0.001$, $\eta^2 = 0.742$). GHBP was significantly greater in obese than lean participants at all time points (Fig. 1C). A one-way ANOVA was used to test differences in GHBP AUC. The between-groups effects indicate significant differences ($F = 36.5$, df = 1,17, $P < 0.001$), consistent with the main effect from the mixed ANOVA. Obese participants had significantly greater GHBP AUC than lean participants. Mean differences are depicted in Fig. 2C.

Correlations between iGH, bGH, and GHBP AUCs were examined in lean and obese men. In lean men, iGH was significantly positively correlated with bGH ($r = 0.70$). Additionally, GHBP was significantly positively correlated with bGH ($r = 0.78$) and iGH ($r = 0.79$). However, in obese men GHBP was significantly negatively correlated with iGH ($r = -0.72$). Additional correlations examined GH variables across the acute exercise time points (preexercise, at midexercise, and immediately postexercise) for each group. Correlations between these variables for lean and obese men are presented in Table 2. bGH at preexercise is negatively associated with GHBP at midexercise for lean and obese men ($r = -0.63$ and $-0.70$, respectively). In lean men, GHBP at preexercise is positively associated with iGH at midexercise and immediately postexercise ($r = 0.71$ and 0.67, respectively); in the obese group, GHBP at preexercise is negatively associated with iGH at midexercise and immediately postexercise ($r = -0.65$ and $-0.66$, respectively).

Table 3 displays the correlations between GH variable AUCs and body composition in all participants. bGH is significantly negatively associated with BMI ($r = -0.63$), body fat percentage ($r = -0.56$), and android-to-gynoid ratio ($r = -0.50$). GHBP is significantly positively associated with the body composition variables BMI ($r = 0.76$), body fat percentage ($r = 0.81$), and android-to-gynoid ratio ($r = 0.70$).

**DISCUSSION**

The findings of this investigation indicate that whereas an acute RE protocol can stimulate iGH of the same magnitude in sedentary lean and obese men, the overall concentrations of bGH differ between obese and lean men. However, in contrast to iGH, an exercise-induced increase in bGH levels was not

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*Fig. 1. A: serum immunoreactive growth hormone (GH) concentrations before, during, and after resistance exercise (RE) in 9 lean and 9 obese sedentary men. *Significantly different from corresponding lean value ($P < 0.05$). †Significantly different from all other time points. ◇Significantly different from midexercise (Mid) and immediately postexercise (IP). ‡Significantly different from all other time points, except preceding time point. ††Significantly different from all but preexercise (Pre). B: bioactive GH concentrations before, during, and after RE in 9 lean and 9 obese sedentary men. *Significantly different from obese group ($P < 0.05$). There was no group × time interaction. C: serum GH-binding protein concentrations before, during, and after RE in 9 lean and 9 obese sedentary men. *Significant difference between lean and obese group ($P < 0.05$). There was no group × time interaction. Values are means ± SE.*
found. Additionally, this group difference was also reflected in overall concentrations of GHBP. Here, similar to previous studies, it was determined that GHBP concentrations were correlated to BMI, body fat, and body composition and higher intra-abdominal fat levels (12–14). GHBP concentrations were significantly greater in obese than lean men. No prior study has examined bGH and GHBP simultaneously or in obese vs. lean groups, although researchers have speculated that the currently unknown biological function of GHBP may be related to the regulation of GH bioactivity (45). Associations between GH system variables in lean men are positive and statistically significant. However, in obese men, there appears to be a disturbance of the associations between GH system variables. Therefore, our present findings are novel, in that they support assertions that GHBP concentrations and GH concentrations are inversely associated with one another in obese individuals. In addition, GHBP concentrations are positively and bGH concentrations are negatively associated with total fat mass. These associations may mediate the GH suppression in obese individuals that has been identified in prior research findings.

In contrast to our findings (Fig. 1), Ormsbee et al. (43) recently reported that lean, but not obese, men had higher serum levels of iGH after a bout of RE consisting of 2 sets of 10 repetitions and a third set to muscular exhaustion employing a load equaling 85% of the individual’s established 10 RM. Since neuromuscular recruitment during RE may be a factor influencing GH secretion (7) and since activation of even small muscle groups results in marked increases in GH release (29), we suggest that the exercise protocol used by Ormsbee et al. was not sufficient to cause a GH response in the obese participants. For this reason, our protocol utilized large (back squat) and small (bench press and shoulder press) muscle groups. Variables that influence GH secretion include 1) the amount of muscle mass recruited, which directly affects the metabolic and hormonal responses to RE (3), and 2) the total work performed, which affects GH release (1). Still other variables include intensity, volume, rest interval between sets, and magnitude of total work done.

Prior research has identified differences in GH system function between lean and obese individuals. Frystyk et al. (16) speculated that GHBP may regulate GH bioactivity via an unknown mechanism. Therefore, we examined correlations between bGH, iGH, and GHBP over the course of the exercise protocol to explore whether different feedback mechanisms may play a role in differences in GH secretion. We suggest that the inverse relationship between bGH and GHBP concentrations in obese, but not lean, men (Table 2) indicates suppression of release of a biologically active isoform of GH. Whether GHBP itself may control that GH release at the level of the pituitary gland is unknown. In addition, because of the prior findings of altered GH physiology associated with markers of obesity, we explored correlations between bGH, iGH, GHBP, and different time points in the RE protocol and between these variables and body composition variables. Others have suggested that visceral adiposity may account for lower iGH in the circulation (24), but prior findings are mixed on this point. One study found no association between 24-h circulating iGH concentrations and waist-to-hip ratio (49), while another reported associations between increased visceral fat and decreased pulsatile GH release (36). This is the first study, to our knowledge, to explore all three variables in the same sample. We found that, consistent with prior speculation on GHBP, adiposity, and iGH, GHBP was negatively associated with iGH AUC and iGH response at midexercise and immediately postexercise in obese men only. In lean men, preexercise GHBP was positively associated with the iGH response at
midexercise and immediately postexercise. These findings highlight the complexity of the associations between GH variables and the alterations associated with increased adiposity.

Increased circulating GH might be an effective way to reduce total and abdominal visceral fat mass in obese individuals and improve cardiometabolic risk (40). Administration of recombinant GH has been a form of therapy in obese adults, but it is not without associated risks (39). It has been linked to arthralgia, peripheral edema, and paresthesia, as well as increases in fasting plasma glucose and fasting insulinemia (10). Finding a method to stimulate GH in obese individuals that does not involve administration of recombinant GH and carries lower risk would, therefore, be very beneficial. The present findings suggest that bGH, not iGH, may be able to interactions of the GH assay with basal differences in GHBP. Findings of suppressed GH release in response to exercise in obese individuals in prior studies may be attributable to interactions of the GH assay with basal differences in GHBP and bGH between groups. GHBP has been shown to differentiate their possible roles in obese and lean individuals.

In summary, our results argue for the importance of measuring iGH, bGH, and GHBP levels to better understand the complexities of responses to any given stimulus such as exercise. Previous work from our laboratories has shown that an acute exercise bout in young women seems to elicit an increase in iGH, but not bGH, while chronic RE training increases bGH (23, 32, 33). On the basis of these results, we speculated that chronic RE increased the release of a spectrum of GH molecules that were necessary for full expression of the somatogenic and metabolic actions usually attributed to GH. We have argued that this response is physiologically important to the health and well-being of the individual. Utilizing a rat tibial line assay to assess bioactivity, McCullough et al. (37) demonstrated that an acute isometric plantar flexion exercise protocol using different maximal voluntary contractions increases biologically active GH. However, this has not been demonstrated within other acute RE protocols, and these results have led to the conclusion that the components for mediating the release of bGH include a metabolic component and a need for nerve stimulation to stimulate exercise-induced bGH release (21).

The present findings suggest that bGH, not iGH, may be relevant to understanding the altered functioning of the GH system in obese individuals that has been identified by prior research. The difference between obese and lean groups in circulating GH appears closely tied to concentrations of GHBP. Findings of suppressed GH release in response to exercise in obese individuals in prior studies may be attributable to interactions of the GH assay with basal differences in GHBP and bGH between groups. GHBP has been shown to interfere with many GH assays and is often not accounted for in GH investigations. Although a functional role for GHBP in the bioactivity of GH remains speculative, it is important to measure iGH, bGH, and GHBP to further understand and differentiate their possible roles in obese and lean individuals. Overall, these results integrate with prior research to suggest that bGH represents a chronic bioactivity adaptation potentially effective in reducing visceral fat mass and improving cardiometabolic risk in obese individuals.

Table 3. Correlations between GH variables and body composition variables

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<tr>
<th>BMI</th>
<th>%Body Fat</th>
<th>Android-to-Gynoid Ratio</th>
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<tbody>
<tr>
<td>bGH</td>
<td>−0.63*</td>
<td>−0.56*</td>
</tr>
<tr>
<td>iGH</td>
<td>−0.19∗</td>
<td>−0.20*</td>
</tr>
<tr>
<td>GHBP</td>
<td>0.76*</td>
<td>0.81*</td>
</tr>
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Values are Pearson’s product moment correlations (n = 18). *Significant correlation: P < 0.05.
related to alterations subsequent to increased adiposity. Our current findings of overall greater bGH in lean than obese sedentary men suggest that suppression of bGH is occurring in obese individuals even when equivalent iGH response to exercise has occurred. Our findings offer a basis for follow-up studies examining these variables in a chronic RE protocol. We would also argue that RE offers a mechanism whereby individuals who are obese are able to exercise at the same intensity as lean individuals and that further investigations of prolonged RE should be conducted to understand whether RE could be a intervention to alter GH systems related to increased adiposity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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