Serum Insulin But Not Leptin Is Associated With Spontaneous and Growth Hormone (GH)-Releasing Hormone–Stimulated GH Secretion in Normal Volunteers With and Without Weight Loss

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Weight loss in humans is associated with elevated hypothalamic-pituitary growth hormone (GH) secretion. This study evaluates the effects of weight loss on the hypothalamic-pituitary (GH-releasing hormone [GHRH]-GH) axis in 14 normal-weight (body mass index [BMI], 25 ± 1 Kg/m^2) subjects, of whom half had undergone a diet-induced weight loss of 14% ± 2% (mean ± SEM). Insulin-like growth factor-1 (IGF-1), insulin, oral glucose tolerance, leptin, and GH pulse patterns were determined in both groups after weight maintenance for 1 week. Of note, we tested the effects of recent weight loss (3 months) and not a recent dietary intake, since both groups ingested a normal calorie diet for 2 days in the Clinical Research Center (CRC) prestudy. Serum insulin (3.8 ± 0.7 *v* 9.0 ± 0.9 μU/mL, $P < .01$) and C-peptide (0.44 ± 0.06 *v* 0.59 ± 0.04 ng/mL, $P < .05$) were significantly lower in the weight loss group. Serum leptin was not different. Endogenous GH pulse height (11.9 ± 4.8 *v* 1.3 ± 0.1 μg/L, $P < .05$), area per GH pulse ([AUC] 57 ± 28 *v* 6 ± 1 μg/L, $P < .05$), and mean GH (3.91 ± 0.76 *v* 0.85 ± 0.16 μg/L, $P < .01$) were increased in the weight loss group. The serum insulin level was inversely associated with the mean GH concentration ($r = -.678$, $P < .01$) and GH pulse height ($r = -.733$, $P < .01$). In addition to spontaneous GH secretion, the GHRH-stimulated GH pulse height (41.8 ± 18.1 *v* 7.1 ± 1.6 μg/L, $P < .05$) and AUC (161 ± 35 *v* 46 ± 13 μg/L/min, $P < .05$) were also increased in the weight loss group. The insulin concentration was also inversely correlated with the GHRH-stimulated GH pulse height ($r = -.718$, $P < .01$). The leptin concentration was correlated with the BMI ($r = .554$, $P < .05$) and body fat ($r = .744$, $P < .01$), but not with GH secretion. In summary, even though these patients were on a normal calorie diet, a history of recent weight loss in young men and women of normal weight and health can be associated with a significant increase in spontaneous GH pulse height and GHRH-stimulated pulse height. Weight loss was also associated with a reduced serum insulin level. The observed increase in GH secretion may be secondary to the reduction in insulin or alterations of other factors acting at the site of the pituitary.

A SMALL WEIGHT LOSS in individuals of normal weight reduces the serum insulin concentration and increases growth hormone (GH) secretion patterns.[1,2] Similar amounts of weight loss in obese individuals do not reduce the serum insulin or reverse the hyposomatotropism.[1,2] However, a large weight loss (±30 kg) in obese individuals reduces serum insulin and increases the GH pulse height, mean GH concentration, GH area under the curve (AUC), and GH response to GH-releasing hormone (GHRH).[3] The specific factors responsible for the recovery of GH secretion patterns with weight loss are not known.

Insulin levels are frequently elevated in obesity[1-3] and may play an inhibitory role in GH secretion. Insulin is known to inhibit GH translation in the rat pituitary.[4] The inhibitory effect of insulin administration on GH synthesis in rats begins rapidly and is maximal at 4 hours. Insulin infusion in humans (1.0 and 10.0 mU/kg/min) during a euglycemic clamp study decreases the GH concentration within 40 minutes.[5] Rats with diet-induced obesity have increased serum insulin and a reduction in GH secretion without a change in either pituitary GH content, pituitary GH mRNA, hypothalamic GHRH mRNA, or somatostatin mRNA concentrations.[6] The hyposomatotropism associated with obesity in these rats also could not be explained by their normal free insulin-like growth factor-1 (IGF-1) concentration.[6] The investigators suggest that some peripheral factor such as serum insulin or glucose may have contributed to the reduction in GH secretion.[6] Both the in vitro[4,6] and in vivo[1,2,3,5] studies suggest that insulin may play a role in the inhibition of GH secretion.

The purpose of the present study is to identify whether a history of recent weight loss, despite a normal caloric intake, influences GHRH-stimulated and spontaneous GH secretion. We studied GH secretion in 14 subjects, half with diet-induced weight loss. All were on a normal diet for 7 days. It is well known that weight loss decreases the fasting insulin concentration, but the effects of weight loss on leptin concentrations have not been studied. Leptin is known to act centrally, but its relationship to spontaneous GH secretion and GHRH-stimulated GH secretion is not known. Our hypothesis is that a history of recent weight loss would be associated with a reduced serum insulin concentration (<7 μU/mL), which would reduce insulin's inhibition of pituitary GH secretion.

SUBJECTS AND METHODS

Subjects

Fourteen subjects (11 men and three women) participated in the study after providing informed consent. Seven subjects consumed a balanced, caloric-deficit diet and were studied after 3 months. They had lost a minimum of 5% body weight. The mean weight loss was 14% ± 2%. One of the weight-losing men did not complete the GH sampling period on day 3 of the study. All subjects were weight-steady for 1 week before admission to the Clinical Research Center (CRC). None were physically active (exercise once per week, jogging, etc.). None had a family history of diabetes, fasting blood glucose greater than 7 mmol/L, overt diabetes mellitus, clinical evidence of cirrhotic liver disease, renal disease, or

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recent infectious illness. Subjects were admitted to the CRC and consumed a 300-g carbohydrate diet. The mean 24-hour dietary food intake was similar for subjects with and without weight loss (2,578 ± 254 *v* 2,257 ± 322 cal/d, respectively). Carbohydrate intake (336 ± 36 *v* 307 ± 44 g/d) and protein intake (80 ± 12 *v* 91 ± 9 g/d) were also similar for both groups before sampling.

Methods

The CRC dietitian performed the dietary analysis and standardized anthropometry by measuring the triceps skinfold and midarm muscle circumference of the left arm. Bioelectrical impedance analysis was performed for determination of body water as previously described.[7] Lean body mass was estimated by the measurement of body water, and the fat mass was the difference between lean body mass and total body weight. Grip strength was determined as an index of muscle mass/function for both the right and left hand (Danymar).

On the morning of day 2, a fasting 75-g oral glucose tolerance test (OGTT) was performed. Glucose, insulin, C-peptide, and glucagon levels were measured every 30 minutes and the GH level was measured every 10 minutes over a 5-hour period. This test evaluated whether the recent weight loss altered GH secretion during an OGTT.

After an overnight fast, on the morning of day 3, blood samples were obtained every 10 minutes for 8 hours for GH determination (6 AM to 2 PM). Fasting blood samples were obtained for thyroid function tests (thyrotropin, thyroxine [T_4], triiodothyronine [T_3], free T_4 [fT_4], fT_3), IGF-binding protein 3 (IGF-BP3), and free fatty acid concentrations. GHRH (GEREF; Serono, Norwood, MA) was administered as 1 μg/kg body weight immediately after the 240-minute blood sample by intravenous bolus. Fasting blood samples were also taken at baseline and every 30 minutes from 180 to 480 minutes for insulin, C-peptide, IGF-1, cortisol, glucagon, epinephrine, and norepinephrine.

Assays

Blood levels of insulin, C-peptide, GH, cortisol, glucagon, epinephrine, norepinephrine, and thyroid hormones (T_4, fT_4, T_3, and fT_3) were measured using established methods.[8] The sensitivity of the GH assay was 0.3 μg/L. The intraassay coefficient of variation (CV) for GH was 14.0% for the low pool and 9.8% for the high pool. The sensitivity of the insulin assay was 1.0 μU/mL, and the interassay CV was 8.7% for the low pool. Leptin was assayed by radioimmunoassay (RIA) (Linco, St. Charles, MO). The interassay CV for leptin was 3.7% for the low pool and 2.7% for the high pool. The IGF-1 level was measured as acid ethanol–extracted IGF-1 as previously described.[9] The intraassay CV for IGF-1 was 4.1% for the low pool and 5.4% for the high pool. The IGF-BP3 level was measured by RIA.[10] The intraassay CV for IGF-BP3 was 1.8% for the low pool and 3.9% for the high pool. Free fatty acid levels were measured as previously described.[11] Serum transferrin was determined by nephelometry at the hospital laboratory. Glucose levels were measured with an Abbott ABA-100 analyzer (South Pasadena, CA) by the glucose oxidase method.

Data Analysis

GH pulse characteristics were analyzed by the computer program Detect.[12] The program provides the AUC for each peak detection with a sampling interval of 10 minutes. A *P* value of .01 was used as the threshold for detection of a peak. The AUC for GHRH stimulation was determined by the program. The mean peak duration was 110 ± 22 minutes (mean ± SEM). Peak detection was based on analysis of the first derivatives with the assumption that peaks have exponential decays. A curve-fitting approach differentiates between upstrokes, exponential decays, and flat baselines. GH samples were assayed in triplicate due to the requirements of the Detect model. GH sensitivity by RIA was 0.3 μg/L, with values less than the detection limit set at a value of 0.3 μg/L. Because of the sensitivity of the assay, small peaks were not detected and total peak frequency was not reported. Data analysis was performed using the BMDP biostatistical package (Los Angeles, CA). The groups with weight loss and without were compared by Student's nonpaired *t* test. Simple linear regression analyses were performed by the method of least squares. Significance was defined as a *P* value not greater than .05.

RESULTS

Subject Characteristics

Seven subjects who were weight-stable and seven with recent weight loss were enrolled into the study. There were 11 men and three women who were postmenopausal and not on estrogen treatment. One woman was in the weight loss group and two were in the group without weight loss. The mean weight loss was 14% ± 2% (mean ± SEM; range, 6% to 20%) in the weight loss group (83.7 ± 5.7 to 72.1 ± 4.3 kg). The BMI decreased from 27.1 ± 1.4 to 23.3 ± 1.3 kg/m^2 ($P < .05$). Weight loss occurred over the preceding 3 months due to a reduced dietary intake. Weight-losing and weight-stable groups had similar weights at the time of study (72.1 ± 4.3 *v* 73.8 ± 1.7 kg). The BMI was slightly but not significantly less in the weight loss group (23.3 ± 1.3 *v* 26.3 ± 0.7). Fat mass was significantly smaller in the weight loss group (12.6 ± 1.3 *v* 19.4 ± 1.9 kg, $P < .05$). Lean body mass was slightly but not significantly greater in the weight loss group (59.5 ± 4.0 *v* 54.4 ± 2.0 kg, $P = .15$). Midarm muscle circumference (27.1 ± 1.7 *v* 27.3 ± 1.0 cm) and grip strength (70 ± 11 *v* 70 ± 8 lbs) were similar. The weight loss group had a similar dietary intake for 2 days in the CRC compared with the weight-stable group (2,578 ± 254 *v* 2,257 ± 322 cal/d, respectively).

Effects of Recent Weight Loss on Fasting Hormone Concentrations

The weight loss group had a lower fasting serum insulin (3.8 ± 0.7 *v* 9.0 ± 0.9 μU/mL, $P < .01$, weight loss *v* normal weight, respectively) and C-peptide (0.44 ± 0.06 *v* 0.59 ± 0.04 ng/mL, $P < .05$). Neither leptin (3.0 ± 0.6 *v* 10.8 ± 5.0 ng/mL), IGF-1 (177 ± 34 *v* 171 ± 25 ng/mL), IGF-BP3 (2.6 ± 0.2 *v* 2.4 ± 0.3 μg/mL), nor free fatty acid (0.47 ± 0.07 *v* 0.54 ± 0.14 mEq/L) levels were reduced in the weight loss group. The serum transferrin concentration, a marker of protein malnutrition, was reduced in the weight loss group (294 ± 17 *v* 345 ± 17 mg/dL, $P < .05$). Fasting glucose, glucagon, cortisol, epinephrine, norepinephrine, and thyroid function tests were normal in both groups (data not shown). The leptin concentration was correlated with the BMI ($r = .554$, $P < .05$) and body fat ($r = .744$, $P < .01$), but not with GH secretion.

Effects of Weight Loss on Endogenous GH Secretion

Subjects with weight loss had a significant increase in GH pulse height (11.9 ± 4.8 *v* 1.3 ± 0.1 μg/L, $P < .05$), AUC (57 ± 28 *v* 6 ± 1 μg/L/min, $P < .05$; Fig 1), and mean GH (3.91 ± 0.76 *v* 0.85 ± 0.16 μg/L, $P < .01$). The one woman in the weight loss group had similar results as the men in the weight loss group (10.1 μg/L, 51 μg/L/min, and 4.26 μg/L, respectively). The GH concentration was inversely correlated with the serum insulin concentration for the weight loss group ($r = -.669$, $P < .05$), but not significantly for the non–weight loss group ($r = -.491$, $P = .12$). For the entire group, the mean GH concentration was inversely correlated with the insulin concentration ($r = -.678$, $P < .01$; Fig 2). Logarithmic transformation of the GH data improved the correlation between the mean GH and insulin concentrations ($r = -.726$, $P < .01$). The mean GH level was inversely correlated with the C-peptide concentration ($r = -.509$, $P < .05$). Mean GH pulse height was inversely associated with both serum insulin ($r = -.733$, $P < .05$); and C-peptide ($r = -.578$, $P < .05$) concentrations. Mean GH pulse height was also inversely associated with fat mass ($r = -.457$, $P < .05$). GH pulse height was not associated with the BMI or free fatty acid concentration.

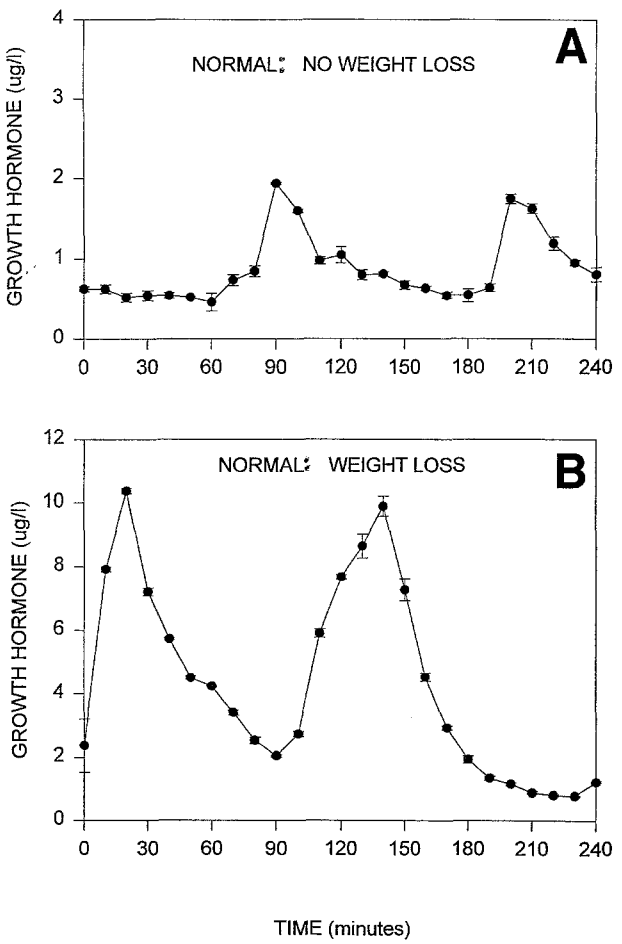

Fig 1. Endogenous GH secretion over a 4-hour period for a single normal male subject without recent weight loss (A) and a single male subjects in the weight loss group (B). Data are the mean ± SEM for a single subject.

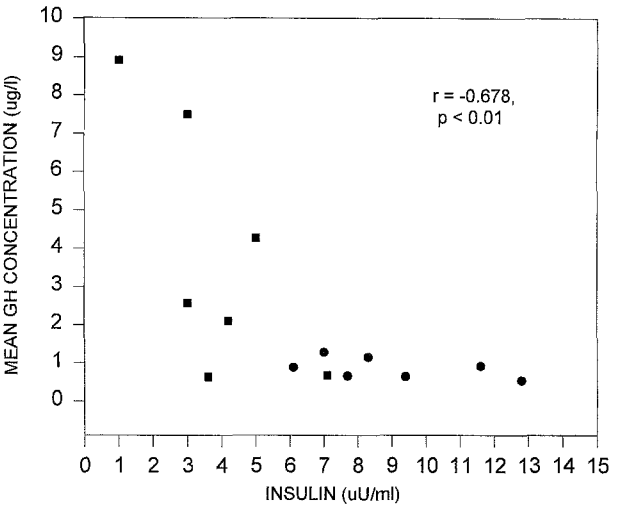

Fig 2. Mean GH concentration inversely correlated ($r = -.678$, $P < .01$) with fasting serum insulin concentration for the entire subject population. The relationship improves with the natural logarithm of the mean GH concentration ($r = -.726$, $P < .01$). (■) Weight loss, (●) without weight loss. The relationship appears to have the greatest effect with an insulin concentration <7 μU/mL. C-peptide concentrations were also inversely correlated ($r = -.509$, $P < .05$) with the mean GH concentration. Insulin was also significantly associated with mean GH in the weight loss group ($r = -.699$, $P < .05$). This failed to reach significance in the group without weight loss ($r = -.491$, $P = .12$).

The maximum height of the GH pulse after GHRH administration (41.8 ± 18.1 *v* 7.1 ± 1.6 μg/L, $P < .05$), mean pulse height (Fig 3), and mean AUC (161 ± 35 *v* 46 ± 13 μg/L/min, $P < .05$) were all increased in the weight loss group. The maximum height of the GH pulse after GHRH was also inversely correlated with insulin ($r = -.718$, $P < .01$) and C-peptide ($r = -.538$, $P < .05$) concentrations. These inverse correlations between insulin and the GH pulse height were similar to the correlations between insulin and spontaneous GH secretion mentioned earlier. Maximum GH pulse height post-GHRH was not associated with the fat mass, BMI, or leptin or free fatty acid concentrations.

The plasma IGF-1 level was weakly correlated with the mean GH concentration ($r = .590$, $P < .05$; Fig 4). IGF-1 was also directly associated with GH pulse height ($r = .610$, $P < .05$) and AUC ($r = .540$, $P < .05$).

OGTT

The OGTT was normal in both groups (data not shown). GH was suppressed to a value less than 1.2 μg/L in all subjects. Both groups had nadir glucose levels during the end of the OGTT that were similar (66 ± 3 *v* 68 ± 4 mg/dL). Plasma glucagon concentrations were suppressed to the same degree during the OGTT (data not shown). The weight-losing subjects had a greater maximum GH-secretion (10.6 ± 2.6 *v* 3.8 ± 1.8 μg/L, $P < .05$) over the last 2 hours of the OGTT. Serum insulin ($r = -.718$, $P < .05$) and C-peptide ($r = -.466$, $P < .05$) were inversely associated with the maximum height of the GH

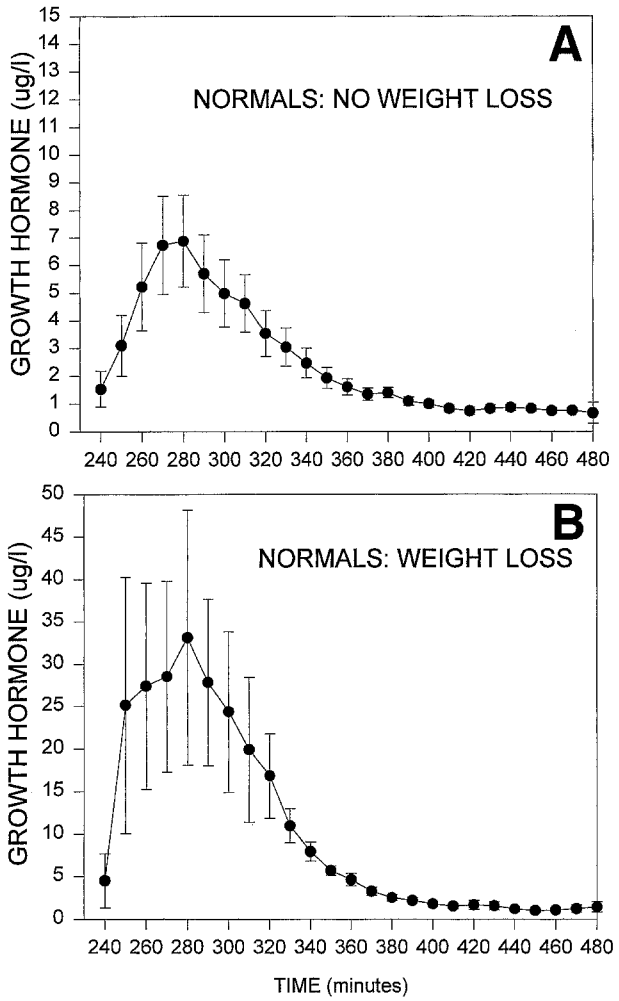

Fig 3. Mean GH response to intravenous GHRH (1 μg/kg) for normal subjects with weight loss *v* without weight loss. (A) Mean response for subjects without recent weight loss, (B) with weight loss. Note the different y-axis scale for GH concentration. Subjects with weight loss had a significant increase in the mean GH pulse height after GHRH ($P < .05$). The peak GH height occurred 30 to 60 minutes after GHRH administration. As expected the AUC was also greater ($P < .05$) in the weight loss group. In addition, the mean of the maximum height of each individual was also significantly increased for subjects with weight loss (41.8 ± 18.1 *v* 7.1 ± 1.6 μg/L, $P < .05$). Data are the mean± SEM.

pulse after the initial suppression. Body fat mass was weakly inversely associated with GH secretion ($r = -.525$, $P < .05$).

DISCUSSION

Serum Insulin and GH Pulse Height

Obesity is associated with suppression of the normal GH pulse height in humans[1,3,13] and rats.[6] The exact mechanism responsible for the reduced GH pulse height is unclear. Recent studies of normal and obese subjects who have lost weight demonstrate an important relationship between serum insulin and the mean GH pulse height.[2,3,13] While this association was not universally reported in the studies, the mean value for fasting insulin was inversely correlated with the mean GH pulse height ($r = -.927$, n = 4, Rasmussen et al[3]; $r = -.847$, n = 4, Riedel et al[2]; $r = -.912$, n = 6, Rasmussen et al[13]). This observation, while very strong, may have been due to the limited number of groups in each study (ie, n = 2 is a straight line). Two additional studies also support this observation and our hypothesis that insulin inhibits GH pulse height. Acipimox administration inhibits lipolysis, reduces free fatty acid and insulin concentrations, and increases the mean spontaneous GH height[14] and GHRH-stimulated GH pulse height.[15] Insulin concentrations in the former study[14] were inversely correlated with GH pulse height ($r = -.939$, n = 4). Insulin concentrations in the later study[15] were also inversely correlated with GH pulse height ($r = -.605$, n = 6). Combining all mean insulin and GH pulse height values, there exists a significant negative correlation between insulin and GH pulse height ($r = -.610$, $P < .05$). These observations do not prove causality. However, these data support the hypothesis that systemic insulin or factors associated with insulin may influence GH secretion.

The data in Fig 2 suggest that insulin has an inhibitory role in normal GH secretion. Insulin was inversely correlated with the spontaneous GH height, GHRH-stimulated GH height, and GH height at the end of an OGTT. The relationship between insulin and GH pulse height may not be linear, since the effect of insulin may be greatest in the lower physiological range (3 to 10 μU/mL; Fig 2). The best fit was for logarithmic transformation of the mean GH concentrations, which improved the correlation ($r = -.726$, $P < .01$). We have retrospectively evaluated this association by examining an earlier study.[8] In that study, GH height was also inversely correlated with fasting insulin ($r = -.522$; Fig 5). Logarithmic transformation of the prior data improves the regression analysis ($r = -.600$). However, both of these data sets may be better described by a segmental regression analysis which implies that there are two relationships over the range of insulin concentrations.[16] Our current data and previous data[8] suggest that there may be an insulin

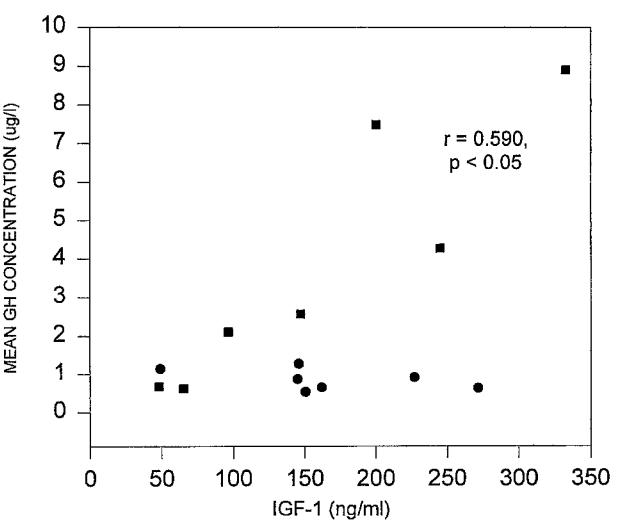

Fig 4. IGF-1 concentration weakly correlated ($r = .590$, $P < .05$) with mean GH concentration over a 4-hour period of observation. (■) Weight loss, (●) without weight loss. GH was sampled every 10 minutes, and the program Detect was used to determine GH pulse height and mean concentration. The number of pulses was not reported due to the short sampling period and the sensitivity of only 0.3 μg/L for the GH assay.

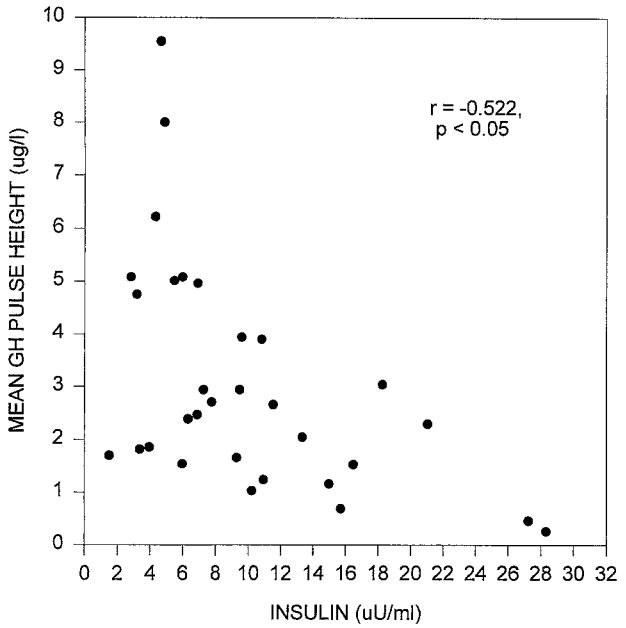

Fig 5. GH pulse height and fasting insulin data from a prior study.[8] The relationship between serum insulin and GH pulse height was not reported.[8] These data may be better described by either a logarithmically transformed relationship or a segmental regression analysis which implies that there are 2 relationships over the range of insulin concentrations. Of note is the apparent threshold that occurs at an insulin concentration < 7 μU/mL.

threshold of 7 μU/mL. Concentrations less than 7 μU/mL are associated with a disinhibition of insulin's effect on GH secretion (Fig 2).

Intravenous insulin administration during a euglycemic clamp condition acutely inhibits GH secretion,[5] which suggests that it has an inhibitory role in GH pulse secretion. Clearly, pituitary concentrations of somatostatin and GHRH are the major regulatory agents responsible for GH secretion, but insulin and other factors such as testosterone, estrogens, or free fatty acids may play an important role.[14,15,17] In the latter study,[17] none of the men had impotence and none of the postmenopausal women were on oral estrogen therapy. While women have been shown to have higher GH secretion, the GH secretion patterns of women in our study were similar to those of their male counterparts.[17] Free fatty acids have been recently demonstrated to be inversely correlated with the GH AUC for normal-weight, elderly, and obese subjects.[15] Free fatty acids may act at the site of the pituitary or hypothalamus to inhibit GH secretion.[15] These researchers propose that there exists a threshold free fatty acid concentration under which the GH response to GHRH becomes maximal. Free fatty acid concentrations in our weight loss group were not below this threshold. If free fatty acids were lower in the weight loss group, then the GH secretion pattern may have been further increased.[15]

Body Composition and GH Secretion

Obesity is associated with a blunted GH secretion.[1-3] On the other hand, cachexia is associated with an increased GH secretion. Body fat was inversely associated with spontaneous GH pulse height. This association is not new, and has been demonstrated in many studies.[2,3,8,15,17,18] Alterations in GH secretion patterns may actually be a type of adipostat for states of abundant fuel reserve (adipose tissue). GH secretion patterns may be secondary to adipose content, for which insulin may have been a better marker than our method to estimate body fat. Prospective testing of the insulin hypothesis is required since the data presented here are correlative and do not prove causality.

Weight Loss and GH Secretion Patterns

Due to the limitation of our GH assay (0.3 μU/mL), we underestimated the number of GH peaks that occurred. This would have overestimated the mean peak area by a modest amount but only underestimated the peak height by 0.3 μg/L. More importantly, the peak height appears to be most influenced by recent weight loss. Spontaneous GH height was nine times higher in weight loss subjects versus those who had no recent history of weight loss. This is true despite the fact that both groups had a similar caloric intake before study in the CRC. Even though weight loss can increase the number of GH pulses in horses,[19] dogs,[20] and man,[21,22] the major effect of weight loss is to increase GH pulse height.[2,3,18-22] The weight loss group had a significant increase in the mean GH concentration, mean GH pulse height, and GH AUC (Fig 1). This was also true for the maximum GH pulse height, mean GH pulse height (Fig 3), and mean GH concentration after GHRH administration. Furthermore, GH pulse height was also significantly greater in the weight loss group at the end of the OGTT. Fasting for a few days results in a small weight loss and an increase in GH pulse height and GH pulse frequency in normal-weight subjects.[21,22] This is not true for obese subjects[2] until the weight loss becomes more pronounced and serum insulin decreases.[3] Adipose content also decreases, but the in vitro data[4] suggest that insulin may have an inhibitory effect on GH secretion.

Patients with severe malnutrition, such as those with anorexia nervosa, have a reduced CSF somatostatin concentration. This is the likely explanation for their increased GH secretion.[23] Obese individuals also have a reduced CSF somatostatin concentration, but their GH secretion is not increased—it is paradoxically reduced.[24] GHRH concentrations in the CSF are normal in obesity.[24] The lower CSF somatostatin concentration should result in an increased GH secretion such as that observed in anorexia nervosa. The etiology for the hyposomatotropism in obesity is not known, but systemic factors such as free fatty acids[15] or insulin[4,6] may be responsible. Obese rats also have reduced GH secretion, yet they have normal hypothalamic somatostatin mRNA, normal GHRH mRNA, normal pituitary GH mRNA, and normal free serum IGF-1 concentrations.[6] These researchers postulate that the reduced GH secretion was due to elevated peripheral factors such as insulin and glucose.[6] We also postulated that leptin may inhibit GH secretion. While we did not find any evidence for leptin's role in GH secretion, the data on insulin's relationship with GH pulse height suggest that insulin may have an influence at the site of the pituitary via insulin receptors.[4]

GH Secretion and IGF-1 Concentration

GH was only weakly correlated with IGF-1 whether represented as the mean GH concentration ($r = .590$; Fig 4), mean

GH pulse height ($r = .610$), or GH AUC ($r = .540$). A direct correlation between IGF-1 and GH height has been previously demonstrated in normal subjects.[25] GH secretion and dietary intake are both important modulators of the IGF-1 concentration in the weight loss group probably reflects their normal recent dietary intake. Unfortunately, blood samples were not obtained at the end of the weight loss period, which most likely would have demonstrated a reduced IGF-1 concentration, consistent with the significantly reduced transferrin concentration (longer half-life, 7 days) observed in this study (description follows).

Weight Loss and IGF-1 Concentrations

A reduced protein intake decreases IGF-1, and refeeding abruptly increases IGF-1.[26] However, the short half-life of IGF-1 (12 to 16 hours) and the normal dietary intake before GH sampling in both groups may explain the normal IGF-1 concentration in the weight loss group. If the weight loss group had IGF-1 and IGF-BP3 determined at the end of the weight loss period, both would have been reduced. The effect of 1 week of a normal diet most likely would have normalized both values. Serum transferrin (half-life, 7 days) was still significantly reduced in the weight loss group, which may have been due to its longer half-life compared with IGF-1. The calorie counts on the 3-day inpatient diet confirm that the weight loss group was eating well. In addition, the normal total T_3 and fT_3concentrations in the weight loss group would support the fact that dietary carbohydrate and caloric intakes were adequate over the previous week. While T_3 concentrations have been directly linked to glucose utilization,[27,28] there was no relationship between thyroid hormone and GH secretion in this study.

Conclusion

In summary, weight loss in non-obese individuals is associated with a decreased serum insulin concentration, a reduced fat mass, and an increased GH pulse height, GH AUC, and mean GH concentration. Fat mass and serum insulin and C-peptide concentrations were all inversely associated with the mean GH pulse height. Fasting insulin and C-peptide were also inversely associated with GHRH-stimulated GH pulse height. Prior research has demonstrated that insulin inhibits GH production at the site of the rat pituitary.[4] Our data suggest that a reduction in systemic insulin concentrations may disinhibit GH secretion at the level of the pituitary or hypothalamus. While factors such as the fat mass, testosterone, or free fatty acid concentration may be important and influence GH secretion, we believe that the reduced GH pulse height observed in obesity may be secondary to hyperinsulinism associated with obesity.

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