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Relationship of Adiponectin to Endogenous GH Pulse Secretion Parameters in Response to Stimulation with a Growth Hormone Releasing Factor

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Abstract

Objective—Obesity is associated with both reduced growth hormone (GH) and adiponectin. However, the relationship between adiponectin and parameters of endogenous GH secretion remains unknown. The aim of this study was to determine the relationship between total and high molecular weight (HMW) adiponectin and parameters of endogenous pulsatile GH secretion and to determine the effects of tesamorelin, a synthetic GH releasing hormone (GHRH¹⁻⁴⁴), on total and HMW adiponectin.

Design—A 2-week interventional study with tesamorelin was conducted at an academic medical center in 13 men with BMI 20–35 kg/m². Overnight frequent blood sampling and measurement of total and HMW adiponectin at baseline and after treatment was performed to assess the effects of augmenting endogenous pulsatile GH secretion.

Results—Total, but not HMW, adiponectin was positively associated with log₁₀Peak GH area ($r=+0.73$; $P=0.005$), basal GH secretion ($r=+0.67$; $P=0.01$), and total GH production ($r=+0.57$; $P=0.04$), but was not associated with the number of secretion events ($P=0.85$). Two-week treatment with tesamorelin increased endogenous GH release and IGF-1, but neither total (change -0.16 ± 0.64 ; $P=0.40$), nor HMW (change $+0.03\pm0.70$; $P=0.87$) adiponectin changed significantly with treatment. Sub-analyses in overweight and obese men yielded similar results.

Conclusions—Our study demonstrates a strong relationship between specific parameters of endogenous GH pulsatility and adiponectin. However, short-term augmentation of GH pulsatility over 2-weeks does not change adiponectin. Therefore, the relationship between GH and adiponectin is most likely mediated by specific covariates related to adiposity or other factors.

Keywords

growth hormone; growth hormone releasing hormone; adiponectin; tesamorelin

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Introduction

Adiponectin is an adipocyte derived hormone which is negatively associated with insulin resistance, cardiovascular disease and inflammation. Expression of adiponectin mRNA in adipose tissue and serum levels of adiponectin are reduced in obesity^{1,2} and increase with weight loss³. In addition to a reduction in adiponectin, obesity is also associated with decreased spontaneous^{4,5} and stimulated⁶ growth hormone (GH) secretion which is reversed with weight loss⁷.

In vitro studies have demonstrated GH stimulation of adiponectin gene expression⁸ and adiponectin secretion⁹, whereas other in vitro investigations demonstrate a suppressive effect of GH on adiponectin secretion¹⁰. Likewise, in vivo studies have yielded conflicting results. Previous studies have demonstrated low levels of adiponectin in association with GH deficiency in children¹¹ and adults¹². However, other studies have demonstrated similar levels of adiponectin comparing adults with GH deficiency and controls¹³. Thus the effect of GH on adiponectin in humans is not yet clear.

In a prior study of otherwise healthy obese men and women, we demonstrated a significant positive association between peak GH secretion on standard GH releasing hormone (GHRH)-arginine stimulation test and total serum adiponectin¹⁴. However, the specific relationship between adiponectin and parameters of endogenous pulsatile GH secretion have not been further defined, and it remains unknown whether total adiponectin, or high molecular weight (HMW) adiponectin, is related to specific parameters of endogenous GH pulse secretion (e.g. pulse area vs. frequency). The aim of this study was therefore to further evaluate the association of GH with adiponectin in a more detailed manner, evaluating specific parameters of GH pulsatility and response of adiponectin to tesamorelin, a novel GH releasing factor, over a 2-week treatment period.

Methods

Study design

Thirteen healthy men from the Boston area were recruited through the Massachusetts General Hospital (MGH) research volunteer database between March 2009 and March 2010. Data from these patients were previously published in a study evaluating the efficacy of tesamorelin (GHRH¹⁻⁴⁴) to improve endogenous pulsatile GH secretion without effects on insulin sensitivity¹⁵. However, data on adiponectin were not previously examined. Healthy adult men between 18-60 y with BMI 20-35 kg/m² were studied to assess the effects of tesamorelin. Exclusion criteria included any history of pituitary disease or cranial irradiation; use of corticosteroids, gonadal steroids, or antidiabetic agents; and any condition for which GH treatment might be contraindicated. No subjects had previously received GHRH or GH treatment. Written informed consent was obtained from each subject before testing, in accordance with the Subcommittee on Human Studies at the MGH.

This was a 4-week, open-label study with tesamorelin daily for 14-days followed by a 14-day withdrawal period as previously described¹⁵. After a screening visit to determine eligibility, subjects returned for 3 overnight visits at baseline, 2 weeks, and 4 weeks. Subsequent to completion of the baseline visit, subjects initiated treatment with the study drug, tesamorelin (Theratechnologies, Inc., Montreal, Canada), injected subcutaneously in the abdomen at a dose of 2mg daily $\times$ 14 days. The subjects were free living with an ad lib diet during the course of the study.

At each overnight visit, subjects had dinner at 1700 and began fasting at 1800. Samples were drawn every 10 minutes from 2000 until 0740 to assess endogenous overnight GH secretion.

For two patients, data were available at a frequency of every 20 minutes at each visit. Data showed similar significant effects of tesamorelin on GH pulsatility excluding these patients from the dataset (data not shown); thus data from all 13 patients who completed the study were included in the analysis. GH secretion parameters were analyzed using the automated deconvolution algorithm AutoDecon, which has been well-validated for deconvolution analysis of endogenous GH pulsatility¹⁶.

Biochemical analyses

Serum GH was measured using the Beckman Access Ultrasensitive human GH assay (Beckman Coulter, Chaska, MN) with an intra-assay variation of 1.90-2.78% and inter-assay variation from 1.77-2.65% and an effective analytical sensitivity of 0.01 µg/l. Serum IGF-1 levels were measured with Immulite 2000 (Siemens Healthcare Diagnostics, Deerfield, IL), with an intra-assay CV of 2.3-3.9% and inter-assay CV of 3.7-8.1% and an analytical sensitivity of 20 µg/l. Serum total and HMW adiponectin was measured by ELISA using commercial kits from ALPCO Diagnostic Systems (Salem, NH). The intra-assay variability for total adiponectin is 5.0-5.4% and HMW adiponectin is 3.3-5.0% while the inter-assay variability for both total and HMW adiponectin are 6%. The minimal detectable concentration is 0.05 µg/ml. Fasting glucose and lipid profile were determined using standard methodology. Insulin was measured using the Beckman Access paramagnetic-particle chemiluminescence immunoassay (Beckman Coulter, Chaska, MN).

Body composition and bionutrition analyses

Whole body DEXA was performed using Discovery A densitometer (Hologic, Bedford, MA) to determine total body and regional fat mass. Four-day food record was completed before each overnight visit to determine diet composition.

Statistical analyses

Results are presented as mean ± SD unless stated otherwise. Univariate regression analyses were performed to assess the relationship between baseline total and HMW adiponectin and various parameters of baseline pulsatile GH secretion using the Pearson correlation coefficient. To assess the effects of tesamorelin, changes between baseline, 2-week (post-treatment) and 4-week (post-withdrawal) visits were analyzed using 2-tailed paired t-testing. In addition, overweight and obese subjects (BMI ≥25 kg/m²)(n=8) were analyzed separately in a sub-analyses. Multivariate regression analyses using standard least squares modeling was used to determine the relationship between GH pulse dynamics and adiponectin while controlling for BMI or body fat percentage in independent models. Statistical analysis was performed using JMP 5.0.1.2 (SAS Institute, Cary, North Carolina, USA). Statistical significance was defined as P<0.05. Due to the small number of subjects and possibility of Type 2 error, we also noted apparent trends and report any P-values of <0.1.

Results

Clinical characteristics of study subjects

Details of the subject characteristics are reported in **Table 1**. Subjects were 45±12 years (median age: 49 years [25-75%: 34.5 to 55 years]), with an average BMI of 27.3±4.5 kg/m². Seventy-seven percent of subjects were Caucasian. Total adiponectin was 3.7±1.2 µg/ml, and HMW adiponectin was 1.8±0.6 µg/ml. At baseline, total, but not HMW adiponectin were related to BMI (r=-0.63, P=0.02) and percent body fat (r=-0.64, P=0.02).

Association of adiponectin to parameters associated with pulsatile GH secretion

Total serum adiponectin was positively associated with $\log_{10}$ Peak GH area ($r=+0.73$; $P=0.005$), basal GH secretion ($r=+0.67$; $P=0.01$), and total GH production ($r=+0.57$; $P=0.04$), (**Figure 1**), and trended to an association with overnight mean GH ($r=+0.50$; $P=0.09$) and GH nadir ($r=+0.49$; $P=0.09$), but was not associated with GH half life ($P=0.87$) or the number of secretion events ($P=0.85$). Total adiponectin was not associated with IGF-1 ($P=0.94$). In multivariate regression analyses, the relationship between total adiponectin and GH pulse secretion parameters was no longer significant controlling for BMI or percent body fat in independent models (all $P>0.1$).

HMW adiponectin was not associated with basal GH secretion, total GH production, GH AUC, overnight mean GH, GH nadir, GH half life or the number of secretion events (all $P>0.1$). There was a possible trend toward association with $\log_{10}$ Peak Area ($r=+0.50$, $P=0.08$). HMW adiponectin was also not associated with IGF-1 ($P=0.73$).

Effects of tesamorelin treatment

Treatment with tesamorelin for 2-weeks led to the expected increase in IGF-1 (change $+181\pm 79$ $\mu\text{g/l}$; $P<0.0001$) (**Figure 2A**), GH AUC (change $+365.5\pm 379.9$ $\mu\text{g/l}$ per 12 hours; $P=0.005$) and mean overnight GH levels (change $+0.51\pm 0.52$ $\mu\text{g/l}$; $P=0.004$), without a change in body composition, diet composition, or insulin sensitivity as previously reported¹⁵. However, 2-week treatment with tesamorelin did not have any significant effect on total (change -0.16 ± 0.64 $\mu\text{g/ml}$; $P=0.40$), HMW adiponectin (change $+0.03\pm 0.70$ $\mu\text{g/ml}$; $P=0.87$) (**Figure 2B, C**) or the ratio of HMW:total adiponectin (change -0.00 ± 0.13 ; $P=1.00$).

There was no correlation between change in GH AUC and change in total ($P=0.14$) or HMW adiponectin ($P=0.69$).

Sub-analyses in overweight and obese subjects

Additional analyses limited to overweight and obese subjects ($\text{BMI} \geq 25$ kg/m^2) ($n=8$) were performed given the known association between reduced GH secretion and obesity^{4,5,6}. Treatment with tesamorelin for 2-weeks led to the expected increase in IGF-1 (change $+171\pm 82$ $\mu\text{g/l}$; $P=0.0006$) as previously reported¹⁵. However, 2-week treatment with tesamorelin did not have any effect on total (change -0.20 ± 0.77 $\mu\text{g/ml}$; $P=0.48$), HMW adiponectin (change -0.21 ± 0.62 $\mu\text{g/ml}$; $P=0.37$) or the ratio of HMW:total adiponectin (change -0.05 ± 0.13 ; $P=0.28$) in a sub-set analysis limited to overweight and obese subjects.

Discussion

This study demonstrates, for the first time, a significant association between specific parameters of endogenous GH secretion and adiponectin in otherwise healthy subjects. However, intervention with a GHRH¹⁻⁴⁴ analog, tesamorelin, had no effect on adiponectin, in spite of a significant increase in IGF-1 and measures of GH pulsatility. Importantly we utilized a short-term study design, which was of sufficient duration to show a significant effect on endogenous GH pulsatility, but short-enough such that body composition remained unchanged. The short duration of treatment enabled us to uniquely assess the effect of increased endogenous GH pulsatility in an experimental model in which body composition and GH effects could be dissociated.

In vitro studies demonstrate GH stimulates adiponectin gene expression through the JAK2 pathway⁸ and GH stimulates secretion of adiponectin in cultured adipocytes⁹. In contrast, however, Nilsson et al. demonstrate that GH suppresses adiponectin secretion in vitro in cultured human adipose cells, and that transgenic mice over expressing GH have reduced

adiponectin, while GH-receptor deficient mice have increased adiponectin¹⁰. Studies evaluating the relationship between GH and adiponectin using GH treatment have similarly yielded conflicting results. GH treatment has been associated with an increase in adiponectin in children with Prader-Willi Syndrome¹⁷. However, GH treatment in small-for-gestational-age children¹⁸, children with Turner's syndrome¹⁹ and adults with acquired GH deficiency²⁰ resulted in no significant change in serum adiponectin levels. These studies evaluating the relationship between GH and adiponectin may be misleading, however, given the complex background of metabolic changes associated with pathologic conditions of GH deficiency and excess and confounding by changes in body composition which may occur in longer-term studies with GH.

Studies of genetic models resulting in GH resistance such as Laron dwarfism²¹ and GH deficiency due to GHRH receptor mutations²² have also been performed and demonstrate increased adiponectin. However, among patients in these models of deficient GH signaling and/or absent GH secretion since birth with severely reduced IGF-1, the relationship of GH to adiponectin may be affected by compensatory changes associated with growth and development. For example, the increase in adiponectin seen in these genetic models of GH deficiency may be a compensatory mechanism to increase GH. Adiponectin receptors AdipoR1 and R2 expression have been demonstrated in the human pituitary gland, including somatotrophs²³, and treatment of somatotrophs with adiponectin has been shown to increase GH secretion in vitro²⁴. In addition, given the differences in metabolic physiology seen in these genetic models, the relevance to obese subjects who have a functional or relative GH deficiency is unknown.

Our study is the first to evaluate the relationship between GH and adiponectin in otherwise healthy normal weight and obese subjects assessing detailed parameters of GH pulsatility and body composition simultaneously, both at baseline and in response to a physiologic stimulus to increase endogenous GH pulsatility. We demonstrate a significant association between total adiponectin and parameters of GH pulsatility including basal GH secretion, total GH production, log₁₀Peak GH area with a trend to an association with GH AUC, overnight mean GH and GH nadir.

In contrast to the observation that adiponectin was strongly related to indices of GH secretion at baseline, neither total, HMW or the ratio of HMW:total adiponectin changed in response to tesamorelin, despite a significant increase in endogenous GH pulsatility. Specifically, tesamorelin increased basal GH secretion, total GH, and log₁₀Peak GH area, parameters which were clearly associated with adiponectin at baseline. We also performed sub-analyses limited to overweight and obese subjects and demonstrated a similar lack of effect of tesamorelin on adiponectin, suggesting the lack of significant effect is not explainable by differences in BMI. Of note, this model permitted us to determine the effects of an increase in GH pulse secretion independent of any change in adiposity, or insulin sensitivity, two factors known to affect adiponectin. Indeed, the relationship seen at baseline between GH secretion parameters and adiponectin was not significant controlling for indices of body weight or body fat, suggesting that the relationship between GH and adiponectin is mediated by adiposity, and not reflective of a direct relationship between adiponectin and pulsatile GH secretion. It is possible that changes in adiponectin in response to augmentation of pulsatile GH secretion might take longer than two weeks, but we believe this is an adequate time to see a change if GH directly affected circulating adiponectin levels.

Taken together, our data suggest a positive association between GH and adiponectin levels in humans but do not support a strong direct effect of GH on circulating adiponectin. Our study investigated detailed measures of GH pulsatility and was relatively small in size. Therefore, it is possible that we failed to find an effect due to Type 2 error. Using paired t-

testing, our sample size provides 80% power to detect a treatment effect of 1 µg/ml, and the magnitude of effect of GH on adiponectin may be less than this, particularly given the numerous other physiologic determinants of adiponectin. However, as can be seen from the data, there was not even a trend to any change in adiponectin, suggesting a larger study may not have yielded different results. It is also possible that giving GH to subjects with low adiponectin might have different results, but again such a study would have to be performed short-term to dissociate the effects of GH on body composition. Indeed longer term studies of GH augmentation have shown improvements in adiponectin, but body composition also changed¹⁷. Our study in healthy volunteers, with normal glucose and insulin, avoids much of the confounding associated with disorders of GH deficiency and excess. Our data are limited to men to avoid the confounding by gender with respect to GH secretion, and thus further detailed studies investigating the relationship between adiponectin and GH pulse secretion will be needed in women.

In summary, our data demonstrate a positive relationship between adiponectin and parameters of GH pulse secretion, but do not demonstrate an effect of short-term augmentation in GH pulsatility on circulating adiponectin. The data suggest the relationship between GH and adiponectin is not direct but rather may be mediated by other factors that relate both to GH and adiponectin, including adiposity. Additional studies will be needed to further characterize the relationship between GH and adiponectin, and to determine its pathophysiological significance in human obesity.

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Figure 1.

Univariate regression analysis demonstrating relationships between total adiponectin and (A) $\log_{10}$ Peak GH area ($r=0.73$, $P=0.005$), (B) basal GH secretion ($r=0.67$, $P=0.01$), and (C) total GH production ($r=0.57$, $P=0.04$).

Figure 2.
Change in IGF-I (A), total adiponectin (B) and high molecular weight adiponectin (C) after 2-week treatment with tesamorelin followed by 2-week withdrawal.

Table 1

Clinical characteristics of study subjects.

All subjects (N=13)	
Age (years)	45 ± 12
Race (N [%])	
Caucasian	10 [77%]
Non-Caucasian	3 [23%]
BMI (kg/m ²)	27.3 ± 4.5
Waist Circumference (cm)	95 ± 13
Visceral Adipose Tissue (cm ²)	110 ± 71
Fasting glucose (mg/dl)	89.8 ± 6.3
Fasting insulin (μU/ml)	6.09 ± 5.05
GH AUC(μg/l per 12 hours)	531.4 ± 597.7
Overnight mean GH (μg/l)	0.74 ± 0.83
IGF-1 (μg/l)	148 ± 53
Adiponectin (μg/ml)	3.7 ± 1.2
HMW Adiponectin (μg/ml)	1.8 ± 0.6