Effects of a Growth Hormone-Releasing Hormone Analog on Endogenous GH Pulsatility and Insulin Sensitivity in Healthy Men

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Context and Objective: Strategies to augment pulsatile GH may be beneficial in patients with excess visceral adiposity, in whom GH secretion is reduced. The objective of this study was to determine the effects of a novel GHRH (GHRH1–44) analog, tesamorelin, on endogenous GH pulsatility and insulin sensitivity in healthy men.

Design, Participants, and Intervention: Thirteen males (mean age 45 ± 3 yr and body mass index 27.3 ± 1.2 kg/m²) received tesamorelin 2 mg sc once daily for 2 wk, with assessment made at baseline, after 2 wk of treatment, and after 2 wk of withdrawal.

Outcome Measures: The primary end point was change in mean overnight GH as determined by overnight frequent sampling. Secondary end points included insulin-stimulated glucose uptake as measured by euglycemic hyperinsulinemic clamp; IGF-I; and GH secretion parameters, including pulse area, pulse frequency, and basal secretion.

Results: Tesamorelin treatment increased mean overnight GH (change +0.5 ± 0.1 µg/liter, P = 0.004), average log₁₀ GH peak area (change +0.4 ± 0.1 log₁₀ µg/liter, P = 0.001), and basal GH secretion (change +0.008 ± 0.003 µg/liter · min, P = 0.008). IGF-I increased by 181 ± 22 µg/liter (P < 0.0001). Neither fasting glucose (P = 0.93) nor insulin-stimulated glucose uptake (P = 0.61) was significantly affected by tesamorelin.

Conclusions: Once-daily short-term treatment with a GHRH1–44 analog, tesamorelin, augments basal and pulsatile GH secretion. Moreover, although tesamorelin significantly increases IGF-I, peripheral insulin-stimulated glucose uptake appears to be preserved. (J Clin Endocrinol Metab 96: 150–158, 2011)

G H is secreted in a pulsatile manner, with discrete secretory bursts accounting for 90–95% of total GH release in humans (1, 2). Although the physiological importance of pulsatile vs. tonic secretion has yet to be fully elucidated in humans, rodent models demonstrate that many effects of GH depend on its pattern of delivery to peripheral tissues. Hepatic synthesis of coagulation factors and hepatic expression of numerous enzymes differ, depending on whether the liver is exposed to pulsatile or continuous GH (3–6). Data in humans, although limited, suggest that pulsatile GH may be required to increase lipolysis (7, 8), whereas continuous exposure to GH is a more important determinant of IGF-I (7, 9, 10).

Multiple physiological and pathological states, including aging (11, 12), obesity (13), and lipodystrophic conditions with excess visceral obesity, as in HIV-infected patients (14), are associated with reduced GH secretion. Treatment with exogenous recombinant human GH

Abbreviations: BMI, Body mass index; CV, coefficient of variation; DEXA, dual-energy x-ray absorptiometry; FFA, free fatty acid; HOMA-IR, homeostasis model assessment insulin resistance index; LBM, lean body mass; M, glucose disposal; MGH, Massachusetts General Hospital; M/I, M corrected for insulin; rhGH, recombinant human GH; VAT, visceral adipose tissue.
(rhGH) may have beneficial effects in these populations, including improvement of body composition (15–17). Treatment with rhGH, however, results in nonpulsatile circulating GH levels and may adversely affect insulin sensitivity (18, 19). Given the evidence that a pulsatile pattern of secretion may be important for many of the physiological actions of GH, a strategy to augment physiological pulsatile GH secretion may be desirable and may have less effect on insulin sensitivity than rhGH. In the current study, we investigated the short-term effects of a GHRH analog, tesamorelin, which has been shown to reduce visceral adipose tissue (VAT) in patients with HIV-associated abdominal adiposity (20, 21). The effects of tesamorelin on endogenous GH secretion dynamics have not been previously described. We hypothesized that tesamorelin would increase mean overnight GH concentrations primarily by increasing GH pulse area as opposed to altering pulse frequency. Moreover, we hypothesized that this strategy to augment pulsatile secretion would not adversely affect insulin sensitivity as measured by euglycemic hyperinsulinemic clamp.

Subjects and Methods

Subject selection
Fifteen healthy men from the Boston area were recruited through the Massachusetts General Hospital (MGH) research volunteer database. Recruitment began in March 2009, and the last subject was randomized in March 2010. The study was approved by the MGH Institutional Review Board, and written, informed consent was obtained from each subject before study procedures.

Inclusion criteria included male sex, age between 18 and 60 yr, and body mass index (BMI) of 20–35 kg/m². Exclusion criteria included any history of pituitary disease or cranial irradiation as well as use of corticosteroids, gonadal steroids, or antidiabetic agents. In addition, subjects were excluded for any condition for which GH treatment might be contraindicated, including history of malignancy, carpal tunnel syndrome, severe chronic illness, renal disease, liver disease, or prostate-specific antigen greater than 5 ng/ml on screening. No subject had previously received GHRH or GH treatment.

Study design
This was a 4-wk, interventional study of an open-label GHRH (1–44) analog, tesamorelin, 2 mg sc daily for 14 d followed by a 14-d withdrawal period. All assessments were conducted after a 12-h fast. After a screening visit to determine eligibility, subjects returned for inpatient assessments of insulin sensitivity and endogenous GH secretion at baseline and 2 wk (after 14 d treatment with tesamorelin) and 4 wk (after 14 d withdrawal from treatment, see Fig. 1A). The time line of the inpatient visits is shown in Fig. 1B. All baseline measurements were taken before administration of tesamorelin. At the 2-wk visit, the euglycemic hyperinsulinemic clamp was performed before the subjects’ last injection of tesamorelin, which was given at approximately 1200 h. Thus, at the 2-wk visit, frequent sampling for GH concentrations began approximately 8 h after the final injection of tesamorelin, and fasting glucose, IGF-I, and free fatty acid values were drawn approximately 20 h after the last injection (Fig. 1B).

Study drug
GHRH (1–44) (tesamorelin; Theratechnologies, Inc., Montreal, Québec, Canada) was administered at a dose of 2 mg daily × 14 d, injected sc in the abdomen. Tesamorelin is an amidated GHRH (1–44) peptide that is stabilized against dipeptidyl peptide IV degradation. The measured half-life of tesamorelin after 14 d sc administration in humans is 26–38 min (investigator’s brochure; Theratechnologies). The first dose of the study drug was given at the conclusion of the baseline visit, and the last dose was given after the insulin clamp at the 2-wk visit. Two subjects opted to come to the Clinical Research Center for nurse-administered injections, and the remaining subjects were taught to reconstitute and self-administer the injections at home. Subjects were instructed to administer the study drug in the morning. Subjects were asked to keep injection diaries, and empty vials were returned and counted at the 2-wk visit as a measure of compliance.

Hyperinsulinemic euglycemic clamp
After a 12-h fast, subjects received a primed infusion of 40 mU/m²min regular insulin for 120 min. The priming dose was 200 mU/m²min given over the first 2 min. A variable infusion of 20% dextrose maintained plasma glucose concentrations at the euglycemic value of 5 mmol/liter (90 mg/dl). Blood glucose was determined every 5 min using a B-Glucose analyzer (Hemocue, Lake Forest, CA). Insulin samples were collected every 20 min. Insulin stimulated glucose disposal (M) was determined using the method of DeFronzo et al. (22) for the interval between 100 and 120 min. M was corrected for insulin (M/I) and indexed to fat-free mass [M/I per lean body mass (LBM), mg/kg of fat-free mass per minute per micromolars per millilitre insulin].

FIG. 1. Study schema (A) and schedule of the inpatient assessments conducted at baseline, 2 wk, and 4 wk (B). QD, Every day; NPO, nil per os.
Assessment of GH secretion

Subjects had dinner at 1700 h and began fasting at 1800 h. Blood samples were drawn every 10 min from 2000 until 0740 h to assess endogenous overnight GH secretion. For two patients, data were available at a frequency of every 20 min at each visit. Results were similar, excluding these patients from the data set (data not shown), with no changes in significance; thus, data from all 13 patients who completed the study were included in the primary analysis. GH secretion parameters, including basal secretion, pulse frequency (number of peaks per 12 h), pulse area, and half-life, were determined using the automated deconvolution algorithm AutoDecon (23), which has been well-validated for deconvolution analysis of endogenous GH pulsatility. In a secondary analysis, the Cluster algorithm, which does not use deconvolution methodology, was also used to determine basal secretion, pulse area, and pulse frequency. Pulse data presented below reflect analysis using AutoDecon unless otherwise noted. Due to significant intra-individual variation in pulse area, pulse area is logarithmically transformed using log10, and the mean of the pulse areas (mean log10 GH pulse area) is calculated for each overnight GH profile. For two GH profiles in which three consecutive samples were missing, the last GH value was carried forward ×1 to allow for analysis.

Bio-nutrition and body composition analysis

Whole-body dual-energy x-ray absorptiometry (DEXA) was performed using a Discovery A densitometer (Hologic, Bedford, MA) to determine total body and regional fat mass. Single-slice computed tomography scans were performed at the L4 pedicle to assess sc and VAT area as previously described (24, 25). Subjects had standard anthropometric measurements including waist circumference. Dietary intake, including macronutrient content, was assessed at each visit by 4-d food records analyzed by registered dietitians at the MGH Clinical Research Center.

Laboratory methods

Fasting glucose was measured using standard methodology at the MGH clinical laboratory. Insulin was measured using the paramagnetic particle, chemiluminescent Access immunoassay system (Beckman Coulter, Chaska, MN), with a sensitivity of 0.03 μU/ml and a precision of 3–5.6%. GH was measured using the paramagnetic particle, chemiluminescent Beckman Access ultra-sensitive human GH assay (Beckman Coulter), with an intra-assay variation of 1.90–2.78% and an inter-assay variation of 1.77–2.65% at concentrations of 2–10 μg/liter. At a concentration of 0.005 μg/liter, intra-assay coefficient of variation (CV) is 6.4%, and the interassay CV is 5.8%. The effective analytic sensitivity of the human GH assay is 0.01 μg/liter. Serum IGF-I levels were measured with Immulite 2000 (Siemens Healthcare Diagnostics, Deerfield, IL), with an analytical sensitivity of 20 μg/liter, the intra-assay CV ranging from 2.3 to 3.9%, and the interassay CV ranging from 3.7 to 8.1%. Free fatty acid (FFA) concentrations were measured with colorimetric assay (ZenBio, Research Triangle Park, NC), with an intra-assay variability of 4.96% and an interassay variability of 10.93%.

Statistical analysis

To assess the effects of tesamorelin, changes between baseline, 2-wk (after treatment), and 4 wk (after withdrawal) visits were analyzed using two-tailed paired t testing. Statistical analysis was performed using JMP 5.0.1.2 (SAS Institute, Cary, NC).

<table>
<thead>
<tr>
<th>TABLE 1. Baseline characteristics</th>
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<tr>
<td>Age (yr)</td>
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<td>Race [n (%)]</td>
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<tr>
<td>Waist circumference (cm)</td>
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<tr>
<td>VAT area (cm²)</td>
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<td>Fat by DEXA (%)</td>
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</table>

Values are mean ± SEM.

Statistical significance was defined as P < 0.05. Results are mean ± SEM unless otherwise stated. A subanalysis was performed among patients with BMI greater than 25 kg/m² (n = 8).

Results

Of 15 men recruited for the study, two discontinued for personal reasons after the baseline visit. Data from these subjects were not included in analyses. The remaining 13 subjects successfully completed the protocol. Compliance with the study drug, confirmed by vial count, was excellent at 98%.

Baseline characteristics

Mean age of the subjects was 45 ± 3 yr, and mean BMI was 27.3 ± 1.2 kg/m² (Table 1). In univariate analysis, VAT was negatively associated with mean overnight GH (r = −0.71, P = 0.007), basal GH secretion (r = −0.65, P = 0.02), and mean log10 GH peak area (r = −0.72, P = 0.006). There was no association between VAT and GH half-life or number of GH peaks. Similarly, BMI was related to mean overnight GH (r = −0.72, P = 0.006), basal GH secretion (r = −0.69, P = 0.009), and mean log10 peak GH area (r = −0.77, P = 0.002) and showed no relationship with GH half-life or number of GH peaks. As expected, insulin-stimulated glucose uptake was negatively associated with both VAT (r = −0.76, P = 0.003) and BMI (r = −0.76, P = 0.003) at baseline.

Effects of tesamorelin on endogenous GH secretion and IGF-I

GH pulse parameters at the baseline, 2-wk, and 4-wk visits are shown in Table 2 for the entire cohort. Tesamorelin treatment for 14 d increased mean overnight GH concentration by 0.5 ± 0.1 μg/liter (P = 0.004, Table 2 and Fig. 2). Likewise, GH area under the curve increased by 366 ± 105 μg/liter per 12 h (P = 0.005). The overall increase in GH secretion was comprised of both increased basal GH secretion (+0.008 ± 0.003 μg/liter · min in-
crease, \( P = 0.008 \) and increased average pulse area, with an increase in mean \( \log_{10} \) GH pulse area of \( 0.4 \pm 0.1 \log_{10} \mu g/liter \) (\( P = 0.001 \), as shown in Fig. 2). Nonlogarithmically transformed pulse area data were also analyzed to provide clinical context; in this analysis, mean pulse area increased from \( 2.2 \pm 0.6 \) to \( 3.4 \pm 0.7 \mu g/liter \) after tesamorelin (\( P = 0.002 \)). In deconvolution analysis performed by AutoDecon (23), there was no significant change in number of GH pulses (\( P = 0.68 \)) or GH half-life (\( P = 0.60 \)) after tesamorelin administration. Maximum overnight GH value also did not change (\( P = 0.98 \)), suggesting that tesamorelin increased pulse area without significantly affecting maximal GH secretory capacity. GH secretion parameters returned to baseline after 2 wk of tesamorelin withdrawal, with the exception of GH half-life, which appeared to be longer at 4 wk compared with baseline (+3 ± 1 min, \( P = 0.01 \)). There were no other significant differences between baseline and 4-wk GH secretion characteristics. A representative subject’s GH profiles from baseline, 2 wk, and 4 wk are shown in Fig. 3.

Analysis using the Cluster algorithm confirmed significant increases in basal GH secretion and GH pulse area after tesamorelin treatment (Table 3). In Cluster analysis, however, the number of overnight GH pulses also significantly increased after tesamorelin (Table 3).

**IGF-I** increased significantly after tesamorelin treatment (+181 ± 22 \( \mu g/liter \), \( P < 0.0001 \)) and subsequently decreased after 2 wk of withdrawal to values that did not significantly differ from baseline (Table 2).

### Table 2. Effects of tesamorelin on GH pulse parameters (deconvolution analysis) and insulin sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (( n = 13 ))</th>
<th>Mean overnight GH (( \mu g/liter ))</th>
<th>Basal secretion (( \mu g/liter \cdot min ))</th>
<th>GH half-life (min)</th>
<th>GH peaks (n per 12 h)</th>
<th>GH AUC (( g/liter ) per 12 h)</th>
<th>Mean ( \log_{10} ) GH peak area (( log_{10} \mu g/liter ))</th>
<th>GH maximum (( \mu g/liter ))</th>
<th>GH nadir (( \mu g/liter ))</th>
<th>IGF-I (( \mu g/liter ))</th>
<th>Fasting glucose (mg/dl)</th>
<th>M (mg/kg · min)</th>
<th>M/L per LBM (mg/kg LBM per ( \mu U/ml ) insulin per min)</th>
<th>HOMA-IR</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>2 wk</td>
<td>4 wk</td>
<td>Baseline</td>
<td>2 wk</td>
<td>4 wk</td>
<td>Baseline</td>
<td>2 wk</td>
<td>4 wk</td>
<td>Baseline</td>
<td>2 wk</td>
<td>4 wk</td>
<td>Baseline</td>
<td>2 wk</td>
</tr>
<tr>
<td>Mean overnight GH (( \mu g/liter ))</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.2 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.003 ± 0.001</td>
<td>0.011 ± 0.002</td>
<td>0.002 ± 0.001</td>
<td>0.011 ± 0.003</td>
<td>0.001 ± 0.0002</td>
<td>13.6 ± 0.8</td>
<td>14.9 ± 2.5</td>
<td>16.3 ± 1.3</td>
<td>12.7 ± 0.8</td>
</tr>
<tr>
<td>Basal secretion (( \mu g/liter \cdot min ))</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>8 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>0.05 ± 0.02</td>
<td>0.28 ± 0.10</td>
<td>0.05 ± 0.02</td>
<td>138 ± 15</td>
<td>308 ± 34</td>
<td>0.17 ± 0.03</td>
<td>0.19 ± 0.03</td>
<td>0.22 ± 0.05</td>
<td>0.13 ± 0.02</td>
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<tr>
<td>GH half-life (min)</td>
<td>13.6 ± 0.8</td>
<td>14.9 ± 2.5</td>
<td>16.3 ± 1.3</td>
<td>12.7 ± 0.8</td>
<td>12.8 ± 3.4</td>
<td>15.1 ± 1.4</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>531 ± 166</td>
<td>897 ± 211</td>
<td>549 ± 170</td>
<td>172 ± 42</td>
<td>423 ± 136</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. M is insulin-stimulated glucose uptake calculated between 100 and 120 min of the euglycemic hyperinsulinemic clamp procedure. M/L per LBM is insulin-stimulated glucose uptake indexed to fat-free mass and divided by serum insulin concentration. GH pulse parameters determined by the automated deconvolution algorithm AutoDecon. AUC, Area under the curve.

\( a \) \( P < 0.005 \) compared with baseline by paired \( t \) test.

\( b \) \( P < 0.05 \) compared with baseline by paired \( t \) test.

Effects of tesamorelin on insulin sensitivity and FFA

As shown in Table 2 and Fig. 4, there were no significant changes in fasting glucose (\( P = 0.93 \)) or insulin-stimulated glucose uptake (\( P = 0.61 \)) as determined by euglycemic hyperinsulinemic clamp. Results were similar when insulin-stimulated glucose uptake was adjusted for insulin level and indexed to LBM (\( P = 0.62 \), Table 2). Homeostasis model assessment insulin resistance index (HOMA-IR) did not significantly change, although there was a trend toward increased HOMA-IR with tesamorelin treatment (\( P = 0.08 \), Table 2). Fasting FFA did not change after tesamorelin treatment (428 ± 46 \( \mu M \) at baseline vs. 392 ± 33 \( \mu M \) at 2 wk, \( P = 0.37 \) by paired \( t \) test).
Body composition and dietary intake

As expected, given the short duration of the study, there were no significant changes in subjects’ BMI, iliac waist circumference, or percent body fat as measured by DEXA during the study (data not shown). There were also no significant changes in caloric or macronutrient intake over the course of the study as measured by the 4-d food diary (data not shown).

Subanalysis in subjects with BMI greater than 25 kg/m² (n = 8)

Because individuals with excess visceral adiposity are likely to be overweight or obese, the subgroup of subjects with BMI greater than 25 kg/m² was examined separately. This subgroup was similar in age to the larger group but had an average BMI of 30.1 ± 1.1 kg/m² (Table 1). GH pulse parameters for this subgroup at the baseline, 2-wk, and 4-wk visits are shown in Table 2. After 14 d of tesamorelin treatment, mean overnight GH concentration tended to increase (+0.4 ± 0.2 µg/liter, P = 0.09), and significant increases were seen in GH basal secretion (+0.010 ± 0.003 µg/liter · min, P = 0.01) and \( \log_{10} \) mean pulse area (+0.5 ± 0.2 \( \log_{10} \) µg/liter, P = 0.009). As in the entire cohort, there were no significant changes in half-life or pulse frequency (Table 2). All GH secretion parameters returned to baseline after 2 wk of treatment withdrawal. IGF-I increased significantly following treatment, (+171 ± 29 µg/liter, P = 0.0006) and subsequently decreased after 2 wk of withdrawal to values that did not significantly differ from baseline. There were no significant changes in fasting glucose (P = 0.85) or insulin-stimulated glucose uptake (P = 0.29) after 2 wk of treatment. HOMA-IR did not significantly change (P = 0.11, Table 2).

Discussion

In this study we demonstrate that once-daily sc administration of a GHRH (1–44) analog, tesamorelin, augments...
GH secretion by increasing both basal secretion and GH pulse area, without changing pulse frequency as assessed by deconvolution analysis. Moreover, although mean GH concentrations and IGF-I levels increase to a significant degree, we did not observe changes in insulin-stimulated glucose uptake like those that might be expected with rhGH administration (18, 19). The above holds true, even among those with significantly increased BMI at baseline. GHRH analogs have shown benefit in numerous conditions, including aging (26, 27), HIV-lipodystrophy (20, 28), and childhood short stature (29, 30). Subjects in the current study were healthy and male to avoid confounding by gender in the assessment of GHRH effects on GH pulsatility. We recruited subjects who were on average overweight and obese in association with excess VAT, stimulation preserves the negative feedback of IGF-I on pituitary somatroph function is intact, but pulsatile GH secretion is reduced due to physiological factors related to excess abdominal fat (14, 34). Evidence that this is a functional deficiency related to weight and nutritional status derives from studies in which GH secretion normalizes in obese patients after significant weight loss (33). For conditions of obesity and particularly of excess VAT accumulation, GHRH analogs may have potential advantages over rhGH. First, unlike exogenous rhGH, GHRH administration preserves the negative feedback of IGF-I on pituitary GH secretion, which may limit side effects of GH excess.

### Table 3: Effects of tesamorelin on GH pulse parameters as determined by cluster analysis

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n = 13)</th>
<th>BMI &gt;25 kg/m² (n = 8)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 wk</td>
</tr>
<tr>
<td>Basal secretion (μg/liter · min)</td>
<td>0.018 ± 0.007</td>
<td>0.041 ± 0.011</td>
</tr>
<tr>
<td>GH peaks (n per 12 h)</td>
<td>5 ± 0</td>
<td>7 ± 0</td>
</tr>
<tr>
<td>Mean log₁₀ GH peak area (log₁₀ μg/liter)</td>
<td>−0.40 ± 0.16</td>
<td>−0.09 ± 0.15</td>
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</table>

Values are mean ± SEM. GH pulse parameters were determined by Cluster analysis.

*P < 0.05 compared with baseline by paired t test.

FIG. 4. Effects of tesamorelin on fasting glucose and insulin-stimulated glucose uptake (M) as measured by euglycemic hyperinsulinemic clamp. Error bars represent SEM.
Second, as previously shown with other GHRH compounds (26), and now shown with a novel GHRH (1–44) analog, tesamorelin, in a study that was large enough to allow us to specifically examine effects in obese patients per se, GHRH administration preserves the pulsatile pattern of endogenous GH secretion.

Although further investigation into the importance of the secretory pattern of GH in humans is needed, data strongly suggest that pulsatile secretion is required for some of the physiologic effects of GH. In vitro studies demonstrate that a critical GH responsive transcription factor, signal transducer and activator of transcription-5b, is maximally activated by pulsatile GH delivery, whereas continuous GH delivery decreases signal transducer and activator of transcription-5b activation to 10–20% of the maximal level (35, 36). In humans, Jaffe et al. (9) using pulsatile and continuous GH delivery paradigms to administer equivalent doses of rhGH, demonstrate that continuous GH increases IGF-I to a greater degree than pulsatile administration, whereas pulsatile GH has greater effects on markers of bone turnover. In addition, the activity of P-450 cytochromes, CYP1A2 and CYP3A4, differs according to pattern of GH administration, with the former decreasing to a greater degree in response to pulsatile GH and the latter increasing in response to continuous GH but decreasing with pulsatile GH (9). Further studies are necessary to determine the effects of tesamorelin on transcription factors and cytochrome markers of GH action.

In this study we used AutoDecon (23) in our primary analysis because we wanted to assess the effects of tesamorelin on pituitary GH secretion using deconvolution analysis to define and differentiate discrete pituitary secretory episodes from background basal secretion. However, this technique may not assess biological action in the periphery, which may relate to the specific pattern of peaks and troughs better detected by a pulse detection algorithm. For this reason we reanalyzed our data using Cluster in a secondary analysis, confirming the result obtained using deconvolution analysis. Significant changes in basal and peak GH secretion were seen, similar to that shown by deconvolution analysis. Using Cluster, fewer peaks were detected, and an increase in number of peaks was noted after tesamorelin treatment. Tesamorelin clearly augments basal and peak GH secretion, confirmed by two independent methods and may increase GH pulsatility. Further studies are needed in this regard. Calculated basal secretion using AutoDecon (23) is below the minimum detectable concentration of the assay for some subjects, as the program approximates a best-fit theoretical curve to the data. The calculation of pulse area by AutoDecon does not include and is independent of any changes in the basal secretion area.

The GHRH analog tested in the current short-term physiology study has shown significant beneficial effects to decrease VAT in individuals with HIV-associated abdominal fat accumulation, without clinically meaningful changes in long-term glucose homeostasis over 12 months (20, 21, 37). However, the effects of tesamorelin on short-term glucose homeostasis using euglycemic hyperinsulinemic clamp to assess effects on peripheral insulin sensitivity were not previously known. Our data demonstrate that insulin-stimulated glucose uptake did not significantly change nor show any trend toward decrease after 2 wk of tesamorelin administration. Importantly, adverse effects of rhGH on insulin sensitivity are usually greatest at the beginning of treatment (15, 38), suggesting that a treatment period of 2 wk should be optimal to observe changes in insulin sensitivity. Due to the size of our cohort, however, we cannot rule out the possibility of type 2 error. HOMA-IR did show a trend toward increase in our study, although changes were not statistically significant. Differential effects of tesamorelin on these indices may reflect differential effects of short-term tesamorelin on hepatic vs. peripheral insulin sensitivity. Further long-term studies will be needed to investigate this possibility.

The half-life of tesamorelin is short, estimated at 26–38 min, yet effects to stimulate pituitary secretion were clearly seen after 2 wk of once-daily dosing, with assessment of overnight GH starting 8 h after the last dose. Although the increases in GH pulsatility may have been due to the last dose of GHRH administered per se, we performed the study over 2 wk because prior pharmacokinetic studies demonstrate achievement of steady-state increases in IGF-I after 2 wk of administration. Why tesamorelin is able to increase GH pulsatility when given once a day, despite its short half-life, is unknown but may reflect dissociation time from the GHRH receptor, longer biological half-life at the pituitary, or unknown factors. Further studies are needed to better understand the biological effects of GHRH (1–44) on pituitary GH secretion.

Tesamorelin administration in the current short-term, physiology study was well tolerated, with no serious adverse events related to treatment. Definitive studies on safety require larger study periods and greater number of subjects, and these issues were not the intent of the current study. Larger and longer studies might be useful to evaluate the effects of GH augmentation with tesamorelin on metabolic end points such as lipid metabolism, body composition including ectopic accumulation of fat in liver and muscle, subclinical inflammation, and carotid intima-media thickness, all of which have shown an inverse association with GH dynamics (39–42).
Overall, we demonstrate that short-term use of a GHRH (1–44) analog, tesamorelin, augments endogenous GH pulsatility and increases IGF-I without apparent changes in insulin-stimulated glucose uptake among healthy men, including those with overweight and obesity. To the extent that reduced GH is associated with increased cardiovascular risk indices in obesity (40, 42, 43), augmentation of GH using a GHRH strategy may prove beneficial to enhance pulsatile GH secretion in this population. Our data suggest that pituitary GH secretion is diminished in overweight and obese patients in association with excess VAT, but pituitary GH reserve is sufficiently intact to respond to GHRH administration at the dose given, at least over the short term. Further studies of the physiological effects of this compound on women are necessary. In addition, longer-term studies may be useful to assess the efficacy and safety of GHRH to augment GH secretion in obesity.

Acknowledgments

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