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Effects of Growth Hormone Releasing Hormone on Visceral Fat, Metabolic and Cardiovascular Indices in Human Studies

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Abstract

Increased visceral adipose tissue (VAT) is associated with reductions in endogenous GH secretion, possibly as a result of hyperinsulinemia, increased circulating free fatty acid, increased somatostatin tone, and reduced ghrelin. Reduced GH may, in turn, further exacerbate visceral fat accumulation because of decreased hormone sensitive lipolysis in this depot. Data from multiple populations demonstrate that both reduced GH and increased VAT appear to contribute independently to dyslipidemia, increased systemic inflammation, and increased cardiovascular risk. The reductions in GH in states of visceral adiposity are characterized by reduced basal and pulsatile GH secretion with intact pulse frequency. Treatment with GH releasing hormone (GHRH) provides a means to reverse these abnormalities, increasing endogenous basal and pulsatile GH secretion without altering pulse frequency. This review describes data from HIV-infected individuals and individuals with general obesity showing that treatment with GHRH significantly reduces visceral fat, ameliorates dyslipidemia, and reduces markers of cardiovascular risk. Further research is needed regarding long term efficacy and safety of this treatment modality.

Keywords

growth hormone; visceral obesity; obesity; growth hormone releasing hormone; cardiovascular risk

Introduction

Beyond its effects on bone growth and musculoskeletal anabolism, growth hormone (GH) plays an important role in the regulation of lipid metabolism, body fat distribution, inflammation and vascular health. These effects were first illustrated by data from individuals with frank GH deficiency (GHD) due to pituitary insufficiency. In 1990, Rosen

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and Bengtsson demonstrated that individuals with hypopituitarism had increased cardiovascular mortality compared to the general population (1). As these individuals were receiving adrenal, thyroid, and gonadal steroid replacement but not GH replacement, Rosen and Bengtsson suggested that GHD may contribute to elevated cardiovascular mortality (1). Further investigation in patients with GH deficiency has supported this hypothesis, demonstrating higher BMI, increased central adiposity, higher triglyceride (TG), decreased high-density lipoprotein (HDL), increased rate of hypertension, elevated inflammatory markers such as c-reactive protein (CRP), and increased carotid intima-media thickness (cIMT) (2–6). In further support of these findings, GH replacement in individuals with hypopituitarism increases muscle mass, decreases overall fat and visceral adiposity, improves dyslipidemia, reduces systemic inflammation, and decreases cIMT (3, 7–11). The benefits of GH replacement on body composition were first demonstrated by Jorgensen et al., who reported that GH treatment to normalize insulin-like growth factor 1 (IGF-1) in patients with GHD increased muscle volume and strength and decreased fat mass (10). Subsequently, in the first randomized, placebo-controlled study of GH in adults with GHD, Jorgensen et al. demonstrated that GH treatment resulted in marked reductions in visceral fat in addition to the overall reductions in fat and improvements in muscle mass and muscle strength (11). Further studies have shown not only improvements in body composition, but also improvements in lipids and measures of cardiovascular health (3, 7–11).

More recently, relative states of GH deficiency have been described in individuals with obesity, particularly those with increased visceral adipose tissue. As this review details, studies in viscerally obese populations have mirrored those in hypopituitary patients, demonstrating dyslipidemia, increased systemic inflammation, and increased cardiovascular risk in association with reduced GH secretion. These findings have prompted the investigation of strategies to augment growth hormone in viscerally obese individuals in order to ameliorate cardiovascular and metabolic risk. Recombinant human GH (rhGH) has shown some benefit in this regard (12–15) but has adverse effects on glucose homeostasis. This review will discuss an alternative strategy, the use of a GH releasing hormone (GHRH) analogue to augment endogenous GH secretion in order to reverse the relative GH deficiency associated with visceral adiposity.

Obesity-Related Changes in the GH/IGF-1 Axis

Both endogenous GH secretion and GH response to provocative testing are blunted in obesity (16–21). Importantly, GH secretion is restored with weight loss, suggesting that the relative GH deficiency associated with obesity is functional and reversible (21, 22). Whereas the inverse relationship between adiposity and GH secretion has been recognized for decades, visceral fat mass is now understood to be the most important determinant of reduced GH secretion in obesity. In a cohort of 42 healthy non-obese adults, Vahl et al. first demonstrated this link, showing intra-abdominal fat mass to be the dominant determinant of 24-hour endogenous GH secretion (23). Further studies have confirmed that visceral fat, rather than overall adiposity, is the measure of body composition most strongly associated with growth hormone secretion. In a cohort of non-obese women who underwent 24-hour frequent sampling for GH concentrations, Miller et al. demonstrated that truncal fat was a strong independent predictor of 24 hour mean GH, whereas total body fat and BMI were not

significantly associated with GH (24). Similarly, in a male cohort that underwent GH provocative testing, we demonstrated that measures of central adiposity -- waist circumference, trunk fat by dual energy x-ray absorptiometry (DXA), and visceral adipose tissue (VAT) measured by CT -- were significantly associated with peak stimulated GH levels, whereas BMI was not associated with GH independent of measures of abdominal obesity (25). In a multivariate model including waist and hip circumference, age, and BMI, peak GH decreased by 1.02 μ g/L for every 1cm increase in waist circumference ($p=0.02$) (25). In a separate model including age, BMI, and measures of abdominal fat area by single-slice computed tomography, peak GH decreased by 1 μ g/L for every 10cm² increase in VAT area ($P=0.02$), whereas subcutaneous adipose tissue (SAT) and total adipose tissue area were not associated with peak GH (25). The independent negative association between visceral adiposity and peak stimulated GH has also been demonstrated in adolescents (26).

Studies of endogenous GH secretion have shown that the number of GH pulses is not altered in obesity, whereas the magnitude of both basal and pulsatile secretion is significantly diminished (24). Multiple mechanisms may contribute to reduced GH secretion in visceral obesity. In a study of men receiving a hypercaloric diet, Cornford et al. demonstrated that reductions in GH are strongly associated with increased insulin levels (27). Moreover, decreased GH is seen within a few days of hypercaloric diet, temporally consistent with the increase in circulating insulin but before significant changes in body composition (27). *In vitro* studies also support a role for insulin in the suppression of GH secretion, demonstrating that insulin decreases pituitary mRNA expression of GH, GHRH receptor, and ghrelin receptor (28, 29). Free fatty acids (FFA) also inhibit GH secretion (30). In obese subjects treated with either placebo or acipimox, the latter of which inhibits lipolysis and decreases FFA, acipimox treatment resulted in significant increases in GH response to provocative testing (31). Relative reductions in ghrelin and increases in somatostatin tone may also play a role in decreased GH secretion in states of visceral obesity.

Although GH is not reduced in all obese individuals, the rate of functional GH deficiency among obese individuals is substantial. In data from 302 men and women undergoing standard GHRH-arginine provocative testing in our unit, 29.4% of obese individuals meet a strict definition of GH deficiency using a peak GH cut-off of 4.2 μ g/L, determined by Corneli et al. to be an optimal cutoff for defining GH deficiency in obese individuals (32), (Makimura and Grinspoon, unpublished data). Similar prevalence of GHD -- between 25--30% - has been reported in other obese cohorts (33, 34). Importantly, GH reductions in obesity are not consistently associated with reductions in IGF-1. Further, IGF binding protein 1 (IGFBP-1) levels are inversely associated with insulin levels and thus decreased in obesity, such that even obese individuals with reduced total IGF-1 may have normal or increased bioavailable IGF-1. Consequently, the consequences of reduced GH in obesity are likely due to the actions of GH itself, rather than those of IGF-1.

Metabolic Correlates of Relative GH Deficiency in Obesity

Obesity-related reductions in GH are significantly associated with measures of metabolic and cardiovascular risk. Multiple studies have demonstrated that both endogenous and stimulated GH secretion are positively associated with adiponectin and negatively associated

with triglyceride, low-density lipoprotein cholesterol (LDL), c-reactive protein (CRP) and other markers of systemic inflammation (24, 35). These associations appear to be independent of overall adiposity (33, 35, 36). Utz et al. demonstrated that women with obesity-associated GHD had higher serum concentrations of CRP and tumor necrosis factor receptor 2 (TNFR2) and lower high-density lipoprotein cholesterol (HDL) than women without GHD, even after controlling for BMI and a measure of central adiposity (33). In a large cohort of men and women undergoing provocative GH stimulation testing, we have demonstrated that peak stimulated GH is inversely associated with LDL and HDL particle size, independent of adiposity and traditional cardiovascular risk factors, suggesting a more atherogenic lipoprotein profile in obese individuals with relative GHD (37). Further, we have demonstrated that peak stimulated GH is independently negatively associated with cIMT in modeling controlling for traditional cardiovascular risk factors including smoking, lipids, glucose, and blood pressure (35). In this cohort, obese individuals without reductions in GH had cIMT similar to normal weight controls, whereas obese individuals with relative GHD had higher cIMT (Figure 1) (35), suggesting that reductions in GH may be an important mediator of the relationship between obesity and cardiovascular disease.

The adverse metabolic effects of increased visceral fat *per se* are also relevant to a discussion of GH and metabolic health, as GH deficiency is associated with increased visceral fat whereas therapy to augment GH significantly reduces visceral fat. Visceral fat accumulation is strongly associated with increased metabolic and cardiovascular risk (38–42), whereas subcutaneous fat, particularly that stored in the gluteofemoral region, appears to be beneficial with respect to metabolic health (43, 44). Specifically, VAT quantity is an independent risk factor for the development of diabetes, assessed prospectively, whereas neither BMI nor overall adiposity contributes to diabetes risk, and increasing lower body fat is protective against diabetes (45). Additionally, VAT quantity is an independent risk factor of non-calcified coronary artery plaque and its progression over time, independent of known CVD risk factors (40, 46). Finally, VAT is also associated with overall mortality, independent of overall adiposity (47). The importance of VAT in driving the metabolic comorbidities of obesity is highlighted by interventional studies of liposuction compared to omentectomy. Removal of subcutaneous fat through large volume liposuction has no benefit on blood pressure, lipids, or glucose (48, 49), whereas omentectomy may result in improvements in glucose (50).

Together, the strong association between increased visceral fat and reduced growth hormone, and the contribution of both to metabolic perturbations and cardiovascular risk, may create a vicious cycle for some patients. Visceral fat accumulation may reduce GH secretion through multiple mechanisms, including increased insulin and FFA, decreased ghrelin, and increased somatostatin tone, and relative GH deficiency may, in turn, exacerbate visceral adiposity because of decreased hormone sensitive lipolysis. Reduced GH appears to have independent adverse effects on cardiovascular and metabolic risk, as does visceral fat. Consequently, this self-reinforcing cycle of increased VAT and decreased GH may significantly contribute to cardiovascular and metabolic risk in states of visceral obesity (Figure 2).

Rationale for the Use of Growth Hormone Releasing Hormone in Obesity

Given the evidence suggesting an independent contribution of reduced GH to metabolic dysregulation and cardiovascular risk in obesity, a logical hypothesis is that augmenting GH in obesity may ameliorate these risks. Indeed, studies of rhGH treatment in obese individuals have demonstrated benefit, including decreased visceral fat and overall adiposity, increased lean mass, reductions in LDL and triglyceride, and reductions in CRP (12, 13, 15, 51, 52). Most of these studies have also demonstrated worsening of glucose tolerance, however, with increased insulin and increased 2-hour glucose levels following oral glucose tolerance test (OGTT) (12, 15, 51). Consequently, exacerbation of insulin resistance limits the clinical utility of rhGH in the obese population.

Important differences exist between endogenous GH secretion and rhGH administration. Whereas endogenous GH is secreted in a pulsatile manner, with approximately 95% of overall GH being secreted during GH pulses (53), rhGH administration results in apulsatile GH concentrations and in relatively elevated levels for much of the day. Both animal and human data suggest that the pattern of GH delivery to target tissues is relevant to the physiological actions of GH. In rodent models, GH secretion is pulsatile in males but relatively apulsatile in females, and these distinct patterns of secretion are thought to differentially affect growth as well as expression of numerous hepatic enzymes (54–57). Sensitivity to the pattern of GH delivery to target tissues is mediated at least in part by signal transducer and activator of transcription 5b (STAT5b), the primary GH responsive transcription factor. In a rodent model, continuous GH exposure decreases the tyrosine phosphorylation (activation) of STAT5b to 10–20% of the maximal level found after exposure to a single GH pulse (58). Although human data are limited, physiology studies demonstrate that continuous GH appears to increase IGF-1 to a greater degree than pulsatile GH, whereas pulsatile GH concentrations stimulate a greater degree of lipolysis than do apulsatile concentrations (59–62). Thus, the pulsatility of endogenous GH secretion in humans may be an important determinant of its physiologic effects.

The use of GHRH analogue rather than rhGH provides a strategy that preserves endogenous pulsatile GH secretion. Moreover, administration of GHRH preserves the negative feedback of IGF-1 on pituitary GH secretion, thus possibly reducing side effects from excess administration. Whereas GHRH therapy would be ineffective in conditions of complete pituitary GHD, the relative GHD of obesity, in which pituitary function is intact, is amenable to GHRH therapy.

Endogenous GHRH is a 44 amino acid hypothalamic peptide. GHRH^{1–29} has been used extensively for provocative GH testing, and multiple GH formulations, including GHRH^{1–29} and GHRH^{1–40} have previously been tested in humans (63–66). The only marketed GHRH formulation that is currently available is tesamorelin (Theratechnologies, Inc., Montreal, Canada), a minimally modified GHRH^{1–44} with C-terminal amidation that confers resistance to DPP IV mediated degradation. In a study of healthy men who received tesamorelin for two weeks, followed by a 2 week withdrawal period, we have demonstrated that tesamorelin increases both basal and pulsatile GH secretion without changing GH pulse frequency (Figure 3) (67). In this study, fasting glucose and insulin stimulated glucose uptake as

measured by euglycemic hyperinsulinemic clamp did not change with tesamorelin treatment (67), suggesting that augmentation of endogenous pulsatile growth hormone secretion with tesamorelin may not have adverse effects on insulin sensitivity like those seen with rhGH.

Experience with Growth Hormone Releasing Hormone in HIV-Infection

Investigation of GHRH in HIV-infection has provided a foundation for further investigation in general obesity. A significant percentage of HIV-infected individuals experience increased visceral fat accumulation in association with increased metabolic and cardiovascular risk. As in general obesity, increased visceral adiposity in HIV-infected individuals is strongly associated with decreased endogenous and stimulated GH secretion, independent of age, BMI, and total body fat (68, 69). Further, reductions in GH in these patients are independently associated with dyslipidemia and other metabolic perturbations (70). rhGH administration has shown benefit to decrease visceral fat and improve lipids in this population, but treatment consistently exacerbates insulin resistance, limiting its clinical application (14, 71–73). Given the rationale for use of GHRH discussed above, we investigated GHRH in this population with the hypothesis that GHRH would have similar efficacy to rhGH but improved side effect profile, particularly with regard to effects on insulin resistance.

After an initial study demonstrating benefit of GHRH^{1–29} in this population (74), tesamorelin has been investigated extensively (75–79) and received FDA approval in 2010 for treatment of excess visceral fat in HIV-infection. In Phase 3 studies including 806 HIV-infected individuals with increased abdominal adiposity, tesamorelin treatment for 6 months significantly decreased VAT (-24 ± 41 vs. 2 ± 35 cm², tesamorelin vs. placebo, $p < 0.001$, treatment effect 15.4%) compared to placebo, with no effect on subcutaneous adipose tissue (SAT) (Figure 4) (79). There was a significant decrease in whole body fat mass, and an increase in whole body lean mass, yielding a net neutral effect on BMI (79). Following the initial 26 weeks of treatment, subjects who received placebo were switched to tesamorelin (P-T), and those who initially received tesamorelin were re-randomized to receive tesamorelin (T-T) vs. placebo (T-P). During the subsequent study phase, from 26 to 52 weeks, VAT reductions in the P-T group mimicked those initially seen in the tesamorelin treated patients, whereas subjects in the T-T group sustained decreases in VAT and those in the T-P group experienced a return of VAT to baseline (Figure 3) (79). Tesamorelin also significantly decreased triglyceride compared to placebo (-37 ± 139 vs. 6 ± 112 mg/dL, $P < 0.001$) (79). Fasting insulin and fasting and 2-hour glucose following OGTT were not significantly affected by tesamorelin treatment, although there was a modest but statistically significant increase in HbA1c (net treatment effect 0.12%, $P < 0.001$) in the tesamorelin group compared to the placebo group after 26 weeks. After 52 weeks, this difference in HbA1c was no longer evident (79), suggesting neutrality with respect to glucose homeostasis over the long term.

Tesamorelin also significantly improved quality of life related to body image. Significant adverse events and adverse events resulting in study discontinuation were not different between treatment groups, but the rate of overall adverse events was higher in patients receiving tesamorelin (79). In particular, injection site erythema, injection site pruritis,

peripheral edema, and myalgias were seen in a small number of patients and were significantly more common in the tesamorelin group than in the placebo group (79). Of note, approximately half of patients receiving tesamorelin developed IgG antibodies to the drug, but the antibody positivity had no effect on the effects of tesamorelin to increase IGF-1 or decrease VAT (79).

Further analysis of Phase 3 data for tesamorelin has demonstrated that much of tesamorelin's benefit is significantly associated with magnitude of VAT reduction. Adiponectin significantly increased in response to tesamorelin treatment (75), and these changes were significantly negatively associated with changes in VAT, independent of changes in IGF-1 (80). Further, changes in circulating tissue plasminogen activator (tPA) antigen, and plasminogen activator inhibitor-1 (PAI-1) were positively associated with change in VAT adjusting for changes in IGF-1 (80). In an analysis comparing individuals who responded to tesamorelin with $\geq 8\%$ VAT loss vs. those with $< 8\%$ VAT loss, responders experienced significant reductions in triglyceride and preservation of glucose homeostasis, whereas those without VAT loss did not have a significant change in triglyceride and experienced a worsening of fasting insulin, fasting glucose, and HbA1c (81). Changes in triglyceride, total cholesterol, and measures of glycemia were significantly associated with changes in VAT, suggesting that VAT reduction may mediate improvements in these variables (81).

We have recently demonstrated that tesamorelin may also reduce liver fat in HIV-infected individuals. In 50 individuals with abdominal obesity randomized to receive tesamorelin vs. identical placebo for 6 months, liver fat as measured by ^1H -magnetic resonance spectroscopy (^1H -MRS) significantly decreased in the tesamorelin group as compared to placebo (Figure 5), and this change was significantly associated with reduction in VAT but not with changes in IGF-1 (82). There was a significant decrease in aspartate aminotransferase (AST) in the tesamorelin group, but no changes in alanine aminotransferase (ALT). With respect to glucose homeostasis, fasting glucose increased in the tesamorelin group at 2 weeks of treatment but returned to baseline after 3 and 6 months of treatment, and insulin sensitivity as measured by euglycemic hyperinsulinemic clamp worsened at 3 months but returned to baseline after 6 months of treatment (82).

Investigation of Growth Hormone Releasing Hormone in Obesity

Based on the rationale for GHRH treatment described above and the evidence of efficacy in the HIV-infected population, we investigated the effects of tesamorelin vs. placebo in abdominally obese men and women. Although testing for relative GH deficiency is not a prerequisite for treatment with GHRH in patients with HIV lipodystrophy, we selected for subjects with relative reductions in GH secretory capacity for this initial study of GHRH in obesity. A peak stimulated GH of $\geq 9 \mu\text{g/L}$ on standard GHRHarginine testing was chosen as a cut-off as this is the first centile limit of peak stimulated GH in otherwise healthy normal-weight subjects (83). In 60 abdominally obese subjects with peak stimulated GH $\geq 9 \mu\text{g/L}$, tesamorelin significantly decreased VAT area (-16 ± 9 vs. $19 \pm 9 \text{ cm}^2$, $p = 0.003$, Figure 6) without effects on abdominal SAT area (83). As in the HIV-infected population, there was a significant decrease in fat mass (treatment effect -1.7 kg [95% CI $-3.4, 0.1$], $p = 0.04$) and a

significant increase in lean mass (treatment effect +1.4kg [95% CI 0.2, 2.6], $p = 0.03$), with no overall effect on BMI (treatment effect -0.6kg/m^2 [95% CI $-1.4, 0.2$], $p = 0.14$). Triglycerides decreased significantly (treatment effect -37mg/dL [95% CI $-67, -7$], $p = 0.02$) with no significant effects on other measures of lipid. Carotid IMT decreased significantly (treatment effect -0.04mm [95% CI $-0.07, -0.01$], $p = 0.02$, Figure 5), as did log CRP. There were no differences in fasting glucose, 2-hour glucose following OGTT, or HbA1c following tesamorelin treatment. There was no significant difference between adverse events in each group. Overall, these data suggest a potential benefit of GHRH to reduce visceral adiposity, decrease triglyceride, and reduce measures of cardiovascular risk in obese patients with reduced GH secretory capacity. Further studies are required to confirm these benefits and to determine the potential safety and efficacy of GHRH in abdominally obese individuals not selected for relative reductions in GH.

Summary

Growth hormone is reduced in states of visceral adiposity, and evidence suggests that both reduced GH and increased VAT independently increase cardiovascular risk. Treatment with rhGH reduces VAT and decreases triglyceride, but may have adverse effects on glucose homeostasis as well as other possible side effects resulting from excess GH. GHRH provides an alternative treatment strategy which augments endogenous pulsatile GH secretion and preserves IGF-1 feedback to reduce GH secretion, possibly limiting side effects. Although side effects of increased GH, including joint pain and peripheral edema, are seen in a limited number of subjects in studies of GHRH, the drug is generally well tolerated. Careful studies of changes in glucose homeostasis have shown initial worsening of insulin sensitivity and fasting glucose, with return to baseline after longer term treatment. Our data suggest that GHRH reduces markers of cardiovascular risk, although longer-term studies would be needed to assess effects on CV events. An increased risk of malignancy has not been noted with GHRH treatment, although a long-term Phase 4 study is ongoing in the HIV-infected population. With both GHRH and rhGH, however, it is critical to follow IGF-1 levels during treatment to ensure that increases in IGF-1 remain in the physiologic range. GHRH is not approved for use in obesity, and further studies are needed to confirm its beneficial effects and to ensure safety in this population. In sum, data suggest that GHRH, or other means of augmenting physiologic growth hormone secretion, may yield cardiovascular and metabolic benefit in this population.

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References

1. Rosen T, Bengtsson B-A. Premature mortality due to cardiovascular disease in hypopituitarism. *The Lancet*. 1990; 336(8710):285–288. 1990/8/4;
2. Rosen T, Eden S, Larson G, Wilhelmsen L, Bengtsson BA. Cardiovascular Risk Factors in Adult Patients with Growth Hormone Deficiency. *Acta Endocrinologica*. 1993; 128(2):67.
3. Colao A, Di Somma C, Rota F, Pivonello R, Savanelli MC, Spiezia S, et al. Short-term effects of growth hormone (GH) treatment or deprivation on cardiovascular risk parameters and intima-media thickness at carotid arteries in patients with severe GH deficiency. *J Clin Endocrinol Metab*. 2005 Apr; 90(4):2056–2062. [PubMed: 15671089]
4. Colao A, Di Somma C, Spiezia S, Rota F, Pivonello R, Savastano S, et al. The natural history of partial growth hormone deficiency in adults: a prospective study on the cardiovascular risk and atherosclerosis. *J Clin Endocrinol Metab*. 2006 Jun; 91(6):2191–2200. [PubMed: 16537686]
5. Abs R, Feldt-Rasmussen U, Mattsson AF, Monson JP, Bengtsson BA, Goth MI, et al. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults - a KIMS database analysis. *Eur J Endocrinol*. 2006 Jul; 155(1):79–90. [PubMed: 16793953]
6. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011 Jun; 96(6):1587–1609. [PubMed: 21602453]
7. Colao A, Di Somma C, Spiezia S, Savastano S, Rota F, Savanelli MC, et al. Growth hormone treatment on atherosclerosis: results of a 5-year open, prospective, controlled study in male patients with severe growth hormone deficiency. *J Clin Endocrinol Metab*. 2008 Sep; 93(9):3416–3424. [PubMed: 18593773]
8. Miller KK, Wexler T, Fazeli P, Gunnell L, Graham GJ, Beauregard C, et al. Growth hormone deficiency after treatment of acromegaly: a randomized, placebo-controlled study of growth hormone replacement. *J Clin Endocrinol Metab*. 2010 Feb; 95(2):567–577. [PubMed: 20061426]
9. Pasarica M, Zachwieja JJ, Dejonge L, Redman S, Smith SR. Effect of growth hormone on body composition and visceral adiposity in middle-aged men with visceral obesity. *J Clin Endocrinol Metab*. 2007 Nov; 92(11):4265–4270. [PubMed: 17785361]
10. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, et al. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet*. 1989 Jun 3; 1(8649):1221–1225. [PubMed: 2566779]
11. Jorgensen JO, Vahl N, Hansen TB, Thuesen L, Hagen C, Christiansen JS. Growth hormone versus placebo treatment for one year in growth hormone deficient adults: increase in exercise capacity and normalization of body composition. *Clin Endocrinol (Oxf)*. 1996 Dec; 45(6):681–688. [PubMed: 9039333]
12. Bredella MA, Gerweck AV, Lin E, Landa MG, Torriani M, Schoenfeld DA, et al. Effects of GH on body composition and cardiovascular risk markers in young men with abdominal obesity. *J Clin Endocrinol Metab*. 2013 Jul 3.
13. Johannsson G, Marin P, Lonn L, Ottosson M, Stenlof K, Bjorntorp P, et al. Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. *J Clin Endocrinol Metab*. 1997; 82(3):727–734. [PubMed: 9062473]
14. Lo J, You SM, Canavan B, Liebau J, Beltrani G, Koutkia P, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *Jama*. 2008 Aug 6; 300(5):509–519. [PubMed: 18677023]
15. Bredella MA, Lin E, Brick DJ, Gerweck AV, Harrington LM, Torriani M, et al. Effects of GH in women with abdominal adiposity: a 6-month randomized, double-blind, placebo-controlled trial. *Eur J Endocrinol*. 2012 Apr; 166(4):601–611. [PubMed: 22275471]
16. Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. *J Clin Endocrinol Metab*. 1991; 73:1081–1088. [PubMed: 1939523]

17. Riedel M, Hoeft B, Blum WF, von zur Muhlen A, Brabant G. Pulsatile growth hormone secretion in normal-weight and obese men: differential metabolic regulation during energy restriction. *Metabolism*. 1995 May; 44(5):605–610. [PubMed: 7752908]
18. Ghigo E, Procopio M, Boffano GM, Arvat E, Valente F, Maccario M, et al. Arginine potentiates but does not restore the blunted growth hormone response to growth hormone-releasing hormone in obesity. *Metabolism*. 1992; 41(5):560–563. [PubMed: 1588839]
19. Veldhuis JD, Iranmanesh A, Ho KK, Waters MJ, Johnson ML, Lizarralde G. Dual defects in pulsatile growth hormone secretion and clearance subserve the hyposomatotropism of obesity in man. *J Clin Endocrinol Metab*. 1991; 72(1):51–59. [PubMed: 1986027]
20. Kopelman PG, Noonan K, Goulton R, Forrest AJ. Impaired growth hormone response to growth hormone releasing factor and insulin-hypoglycaemia in obesity. *Clin Endocrinol (Oxf)*. 1985 Jul; 23(1):87–94. [PubMed: 2863016]
21. Williams T, Berelowitz M, Joffe SN, Thorner MO, Rivier J, Vale W, et al. Impaired growth hormone responses to growth hormone-releasing factor in obesity. A pituitary defect reversed with weight reduction. *N Engl J Med*. 1984 Nov 29; 311(22):1403–1407. [PubMed: 6436706]
22. Rasmussen MH, Hvidberg A, Juul A, Main KM, Gotfredsen A, Skakkebaek NE, et al. Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor-I levels in obese subjects. *J Clin Endocrinol Metab*. 1995 Apr; 80(4):1407–1415. [PubMed: 7536210]
23. Vahl N, Jorgensen JO, Skjaerbaek C, Veldhuis JD, Orskov H, Christiansen JS. Abdominal adiposity rather than age and sex predicts mass and regularity of GH secretion in healthy adults. *Am J Physiol*. 1997 Jun; 272(6 Pt 1):E1108–E1116. [PubMed: 9227458]
24. Miller KK, Biller BM, Lipman JG, Bradwin G, Rifai N, Klibanski A. Truncal adiposity, relative growth hormone deficiency, and cardiovascular risk. *J Clin Endocrinol Metab*. 2005 Feb; 90(2):768–774. [PubMed: 15572428]
25. Makimura H, Stanley T, Mun D, You SM, Grinspoon S. The effects of central adiposity on growth hormone (GH) response to GH-releasing hormone-arginine stimulation testing in men. *J Clin Endocrinol Metab*. 2008 Nov; 93(11):4254–4260. [PubMed: 18765508]
26. Misra M, Bredella MA, Tsai P, Mendes N, Miller KK, Klibanski A. Lower growth hormone and higher cortisol are associated with greater visceral adiposity, intramyocellular lipids, and insulin resistance in overweight girls. *Am J Physiol Endocrinol Metab*. 2008 Aug; 295(2):E385–E392. [PubMed: 18544645]
27. Cornford AS, Barkan AL, Horowitz JF. Rapid suppression of growth hormone concentration by overeating: potential mediation by hyperinsulinemia. *J Clin Endocrinol Metab*. 2011 Mar; 96(3):824–830. [PubMed: 21209037]
28. Luque RM, Kineman RD. Impact of obesity on the growth hormone axis: evidence for a direct inhibitory effect of hyperinsulinemia on pituitary function. *Endocrinology*. 2006 Jun; 147(6):2754–2763. [PubMed: 16513828]
29. Luque RM, Gahete MD, Valentine RJ, Kineman RD. Examination of the direct effects of metabolic factors on somatotrope function in a non-human primate model, *Papio anubis*. *J Mol Endocrinol*. 2006 Aug; 37(1):25–38. [PubMed: 16901921]
30. Casanueva FF, Villanueva L, Dieguez C, Diaz Y, Cabranes JA, Szoke B, et al. Free fatty acids block growth hormone (GH) releasing hormone-stimulated GH secretion in man directly at the pituitary. *J Clin Endocrinol Metab*. 1987 Oct; 65(4):634–642. [PubMed: 2888782]
31. Cordido F, Peino R, Penalva A, Alvarez CV, Casanueva FF, Dieguez C. Impaired growth hormone secretion in obese subjects is partially reversed by acipimox-mediated plasma free fatty acid depression. *J Clin Endocrinol Metab*. 1996 Mar; 81(3):914–918. [PubMed: 8772550]
32. Corneli G, Di Somma C, Baldelli R, Rovere S, Gasco V, Croce CG, et al. The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. *Eur J Endocrinol*. 2005 Aug; 153(2):257–264. [PubMed: 16061832]
33. Utz AL, Yamamoto A, Hemphill L, Miller KK. Growth hormone deficiency by growth hormone releasing hormone-arginine testing criteria predicts increased cardiovascular risk markers in normal young overweight and obese women. *J Clin Endocrinol Metab*. 2008 Jul; 93(7):2507–2514. [PubMed: 18445664]

34. Di Somma C, Pivonello R, Pizza G, De Rosa A, Lombardi G, Colao A, et al. Prevalence of the metabolic syndrome in moderately-severely obese subjects with and without growth hormone deficiency. *J Endocrinol Invest.* 2010 Mar; 33(3):171–177. [PubMed: 19794297]
35. Makimura H, Stanley T, Mun D, Chen C, Wei J, Connelly JM, et al. Reduced growth hormone secretion is associated with increased carotid intima-media thickness in obesity. *J Clin Endocrinol Metab.* 2009 Dec; 94(12):5131–5138. [PubMed: 19837914]
36. Carmichael JD, Danoff A, Milani D, Roubenoff R, Lesser ML, Livote E, et al. GH peak response to GHRH-arginine: relationship to insulin resistance and other cardiovascular risk factors in a population of adults aged 50–90. *Clin Endocrinol (Oxf).* 2006 Aug; 65(2):169–177. [PubMed: 16886956]
37. Makimura H, Feldpausch MN, Stanley TL, Sun N, Grinspoon SK. Reduced growth hormone secretion in obesity is associated with smaller LDL and HDL particle size. *Clin Endocrinol (Oxf).* 2012 Feb; 76(2):220–227. [PubMed: 21819438]
38. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet.* 2005 Nov 5; 366(9497):1640–1649. [PubMed: 16271645]
39. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med.* 2008 Nov 13; 359(20):2105–2120. [PubMed: 19005195]
40. Ohashi N, Yamamoto H, Horiguchi J, Kitagawa T, Kunita E, Utsunomiya H, et al. Association between visceral adipose tissue area and coronary plaque morphology assessed by CT angiography. *JACC Cardiovasc Imaging.* 2010 Sep; 3(9):908–917. [PubMed: 20846624]
41. Liu J, Fox CS, Hickson D, Bidulescu A, Carr JJ, Taylor HA. Fatty liver, abdominal visceral fat, and cardiometabolic risk factors: the Jackson Heart Study. *Arterioscler Thromb Vasc Biol.* 2011 Nov; 31(11):2715–2722. [PubMed: 21885852]
42. Liu J, Fox CS, Hickson DA, May WD, Hairston KG, Carr JJ, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab.* 2010 Dec; 95(12):5419–5426. [PubMed: 20843952]
43. McLaughlin T, Lamendola C, Liu A, Abbasi F. Preferential Fat Deposition in Subcutaneous Versus Visceral Depots Is Associated with Insulin Sensitivity. *Journal of Clinical Endocrinology & Metabolism.* 2011; 96(11):E1756–E1760. [PubMed: 21865361]
44. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond).* 2010 Jun; 34(6):949–959. [PubMed: 20065965]
45. Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA.* 2012 Sep 19; 308(11):1150–1159. [PubMed: 22990274]
46. Imai A, Komatsu S, Ohara T, Kamata T, Yoshida J, Miyaji K, et al. Visceral abdominal fat accumulation predicts the progression of noncalcified coronary plaque. *Atherosclerosis.* 2012 Jun; 222(2):524–529. [PubMed: 22498255]
47. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. *Obesity (Silver Spring).* 2006 Feb; 14(2):336–341. [PubMed: 16571861]
48. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med.* 2004 Jun 17; 350(25):2549–2557. [PubMed: 15201411]
49. Mohammed BS, Cohen S, Reeds D, Young VL, Klein S. Long-term effects of large-volume liposuction on metabolic risk factors for coronary heart disease. *Obesity (Silver Spring).* 2008 Dec; 16(12):2648–2651. [PubMed: 18820648]
50. Thorne A, Lonnqvist F, Apelman J, HELLERS G, Arner P. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *Int J Obes Relat Metab Disord.* 2002 Feb; 26(2):193–199. [PubMed: 11850750]
51. Mekala KC, Tritos NA. Effects of recombinant human growth hormone therapy in obesity in adults: a meta analysis. *J Clin Endocrinol Metab.* 2009 Jan; 94(1):130–137. [PubMed: 18940879]

52. Richelsen B, Pedersen SB, Borglum JD, Moller-Pedersen T, Jorgensen J, Jorgensen JO. Growth hormone treatment of obese women for 5 wk: effect on body composition and adipose tissue LPL activity. *Am J Physiol.* 1994 Feb; 266(2 Pt 1):E211–E216. [PubMed: 8141279]
53. Hartman ML, Faria AC, Vance ML, Johnson ML, Thorner MO, Veldhuis JD. Temporal structure of in vivo growth hormone secretory events in humans. *Am J Physiol.* 1991 Jan; 260(1 Pt 1):E101–E110. [PubMed: 1987784]
54. Eden S. Age- and sex-related differences in episodic growth hormone secretion in the rat. *Endocrinology.* 1979 Aug; 105(2):555–560. [PubMed: 572295]
55. Mode A, Gustafsson JA, Jansson JO, Eden S, Isaksson O. Association between plasma level of growth hormone and sex differentiation of hepatic steroid metabolism in the rat. *Endocrinology.* 1982 Nov; 111(5):1692–1697. [PubMed: 7128531]
56. Gustafsson JA, Eden S, Eneroth P, Hokfelt T, Isaksson O, Jansson JO, et al. Regulation of sexually dimorphic hepatic steroid metabolism by the somatostatin-growth hormone axis. *J Steroid Biochem.* 1983 Jul; 19(1B):691–698. [PubMed: 6136633]
57. Waxman DJ, O'Connor C. Growth hormone regulation of sex-dependent liver gene expression. *Mol Endocrinol.* 2006 Nov; 20(11):2613–2629. [PubMed: 16543404]
58. Gebert CA, Park SH, Waxman DJ. Down-regulation of liver JAK2-STAT5b signaling by the female plasma pattern of continuous growth hormone stimulation. *Mol Endocrinol.* 1999 Feb; 13(2):213–227. [PubMed: 9973252]
59. Jaffe CA, Turgeon DK, Lown K, Demott-Friberg R, Watkins PB. Growth hormone secretion pattern is an independent regulator of growth hormone actions in humans. *Am J Physiol Endocrinol Metab.* 2002 Nov; 283(5):E1008–E1015. [PubMed: 12376329]
60. Surya S, Horowitz JF, Goldenberg N, Sakharova A, Harber M, Cornford AS, et al. The pattern of growth hormone delivery to peripheral tissues determines insulin-like growth factor-1 and lipolytic responses in obese subjects. *J Clin Endocrinol Metab.* 2009 Aug; 94(8):2828–2834. [PubMed: 19470622]
61. Faje AT, Barkan AL. Basal, but not pulsatile, growth hormone secretion determines the ambient circulating levels of insulin-like growth factor-I. *J Clin Endocrinol Metab.* 2010 May; 95(5):2486–2491. [PubMed: 20190159]
62. Cersosimo E, Danou F, Persson M, Miles JM. Effects of pulsatile delivery of basal growth hormone on lipolysis in humans. *Am J Physiol.* 1996 Jul; 271(1 Pt 1):E123–E126. [PubMed: 8760089]
63. Duck SC, Schwarz HP, Costin G, Rapaport R, Arslanian S, Hayek A, et al. Subcutaneous growth hormone-releasing hormone therapy in growth hormone-deficient children: first year of therapy. *J Clin Endocrinol Metab.* 1992 Oct; 75(4):1115–1120. [PubMed: 1400880]
64. Ross RJ, Rodda C, Tsagarakis S, Davies PS, Grossman A, Rees LH, et al. Treatment of growth-hormone deficiency with growth-hormone-releasing hormone. *Lancet.* 1987; 1(8523):5–8. [PubMed: 2879138]
65. Smith PJ, Brook CG. Growth hormone releasing hormone or growth hormone treatment in growth hormone insufficiency? *Arch Dis Child.* 1988 Jun; 63(6):629–634. [PubMed: 2898924]
66. Thorner M, Rochiccioli P, Colle M, Lanes R, Grunt J, Galazka A, et al. Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. *Geref International Study Group. J Clin Endocrinol Metab.* 1996; 81(3):1189–1196. [PubMed: 8772599]
67. Stanley TL, Chen CY, Branch KL, Makimura H, Grinspoon SK. Effects of a Growth Hormone-Releasing Hormone Analog on Endogenous GH Pulsatility and Insulin Sensitivity in Healthy Men. *J Clin Endocrinol Metab.* 2011 Jan; 96(1):150–158. [PubMed: 20943777]
68. Rietschel P, Hadigan C, Corcoran C, Stanley T, Neubauer G, Gertner J, et al. Assessment of growth hormone dynamics in human immunodeficiency virus-related lipodystrophy. *J Clin Endocrinol Metab.* 2001 Feb; 86(2):504–510. [PubMed: 11158000]
69. Koutkia P, Meininger G, Canavan B, Breu J, Grinspoon S. Metabolic regulation of growth hormone by free fatty acids, somatostatin, and ghrelin in HIV-lipodystrophy. *Am J Physiol Endocrinol Metab.* 2004 Feb; 286(2):E296–E303. [PubMed: 14559725]

70. Lo J, You SM, Wei J, Canavan B, Grinspoon S. Relationship of peak growth hormone to cardiovascular parameters, waist circumference, lipids and glucose in HIV-infected patients and healthy adults. *Clin Endocrinol (Oxf)*. 2009 Apr 17.
71. Kotler DP, Muurahainen N, Grunfeld C, Wanke C, Thompson M, Saag M, et al. Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004 Mar 1; 35(3):239–252. [PubMed: 15076238]
72. Kotler DP, Muurahainen N, Grunfeld C, Wanke C, Thompson M, Saag M, et al. Effects of growth hormone on visceral adipose tissue and dyslipidemia in HIV, an erratum. *J Acquir Immune Defic Syndr*. 2006 Nov 1; 43(3):378–380. [PubMed: 17079997]
73. Grunfeld C, Thompson M, Brown SJ, Richmond G, Lee D, Muurahainen N, et al. Recombinant human growth hormone to treat HIV-associated adipose redistribution syndrome: 12 week induction and 24-week maintenance therapy. *J Acquir Immune Defic Syndr*. 2007 Jul 1; 45(3):286–297. [PubMed: 17592343]
74. Koutkia P, Canavan B, Breu J, Torriani M, Kissko J, Grinspoon S. Growth Hormone-Releasing Hormone in HIV-Infected Men With Lipodystrophy: A Randomized Controlled Trial 10.1001/jama.292.2.210. *JAMA*. 2004 Jul 14; 292(2):210–218. 2004. [PubMed: 15249570]
75. Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med*. 2007 Dec 6; 357(23):2359–2370. [PubMed: 18057338]
76. Falutz J, Allas S, Kotler D, Thompson M, Koutkia P, Albu J, et al. A placebo-controlled, dose-ranging study of a growth hormone releasing factor in HIV-infected patients with abdominal fat accumulation. *AIDS*. 2005 Aug 12; 19(12):1279–1287. [PubMed: 16052083]
77. Falutz J, Allas S, Mamputu JC, Kotler D, Somero M, Berger D, et al., editors. 15th Conference on Retroviruses and Opportunistic Infections. Boston, MA: 2008. Data on 52-Week Safety and Efficacy of Tesamorelin, A Growth Hormone-Releasign Factor Analogue, in HIV-infected Patients with Abdominal Fat Accumulation.
78. Falutz J, Allas S, Mamputu JC, Potvin D, Kotler D, Somero M, et al. Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. *AIDS*. 2008 Sep 12; 22(14):1719–1728. [PubMed: 18690162]
79. Falutz J, Mamputu JC, Potvin D, Moyle G, Soulban G, Loughrey H, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab*. 2010 Sep; 95(9):4291–4304. [PubMed: 20554713]
80. Stanley TL, Falutz J, Mamputu JC, Soulban G, Potvin D, Grinspoon SK. Effects of tesamorelin on inflammatory markers in HIV patients with excess abdominal fat: relationship with visceral adipose reduction. *AIDS*. 2011 Jun 19; 25(10):1281–1288. [PubMed: 21516030]
81. Stanley TL, Falutz J, Marsolais C, Morin J, Soulban G, Mamputu JC, et al. Reduction in visceral adiposity is associated with an improved metabolic profile in HIV-infected patients receiving tesamorelin. *Clin Infect Dis*. 2012 Jun; 54(11):1642–1651. [PubMed: 22495074]
82. Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial. *JAMA*. 2014 Jul 23–30; 312(4):380–389. [PubMed: 25038357]
83. Makimura H, Feldpausch MN, Rope AM, Hemphill LC, Torriani M, Lee H, et al. Metabolic effects of a growth hormone-releasing factor in obese subjects with reduced growth hormone secretion: a randomized controlled trial. *J Clin Endocrinol Metab*. 2012 Dec; 97(12):4769–4779. [PubMed: 23015655]
84. Johnson ML, Pipes L, Veldhuis PP, Farhy LS, Nass R, Thorner MO, et al. AutoDecon: a robust numerical method for the quantification of pulsatile events. *Methods Enzymol*. 2009; 454:367–404. [PubMed: 19216935]

Highlights

- GH is reduced in states of visceral obesity and may contribute to increased CV risk.
- GHRH provides a strategy to increase endogenous pulsatile growth hormone secretion.
- GHRH reduces visceral fat and ameliorates dyslipidemia in HIV-infected individuals.
- Data suggest that GHRH may have metabolic and cardiovascular benefit in obesity.

Figure 1.

Carotid intima-media thickness in normal weight (white bar), obese without relative GHD (hashed bar), and obese with relative GHD (black bar). Relative GHD was defined as peak stimulated GH of 4.2 $\mu\text{g/liter}$ or less on standard GHRH-arginine stimulation test (32). cIMT is significantly different across groups by overall ANOVA ($P = 0.01$). Between-group comparisons with Tukey-Kramer post hoc tests show that cIMT is similar between normal-weight and obese GHS subjects but significantly different between normal-weight and obese subjects with relative GHD ($P < 0.05$). Reproduced with permission from The Journal of Clinical Endocrinology & Metabolism by ENDOCRINE SOCIETY (35); permission conveyed through Copyright Clearance Center, Inc.

Figure 2.
Self-reinforcing cycle of increased visceral fat and reduced GH in states of abdominal obesity.

Figure 3.

Effects of tesamorelin on mean overnight GH, GH basal secretion, and mean log₁₀ GH pulse area. GH secretion parameters were determined by automated deconvolution of every 10 minute frequently sampled GH concentrations from 8:00 pm to 7:40 am using AutoDecon (84). Subjects were 13 healthy men with BMI 20–35kg/m². Error bars represent standard error of the mean (SEM). Reproduced with permission from The Journal of Clinical Endocrinology & Metabolism by ENDOCRINE SOCIETY (67); permission conveyed through Copyright Clearance Center, Inc.

Figure 4.

Percent changes in VAT and SAT from baseline to 26 and 52 weeks in combined Phase 3 studies of tesamorelin. Data are mean $\pm$ SEM. At 52 weeks, T-T indicates subjects who remained on tesamorelin for 52 weeks; T-P indicates subjects who received tesamorelin for the first 26 weeks and placebo for the final 26 weeks, and P-T indicates subjects who received placebo for the first 26 weeks and tesamorelin for the final 26 weeks. **, $P < 0.001$ vs. Placebo; §, $P < 0.001$ vs. baseline and vs. T-P; †, $P < 0.001$ vs. baseline. Reproduced with permission from The Journal of Clinical Endocrinology & Metabolism by ENDOCRINE SOCIETY (79); permission conveyed through Copyright Clearance Center, Inc.

Figure 5.

Change in liver fat as measured by MR Spectroscopy (HCL/W%) in the tesamorelin and placebo groups in a 6 month investigation of the effects of tesamorelin on liver fat in HIV-infected subjects with abdominal adiposity (82). Medians with bars for IQR are shown.

Figure 6.

Effects of tesamorelin vs. placebo on abdominal VAT area (upper panel), and cIMT (lower panel). Error bars represent SEM. Statistical significance was determined by longitudinal linear mixed-effects modeling with the last value carried forward. Reproduced with permission from The Journal of Clinical Endocrinology & Metabolism by ENDOCRINE SOCIETY (83); permission conveyed through Copyright Clearance Center, Inc.