Disordered Growth Hormone Secretion in HIV: Mechanisms and Novel Therapeutic Strategies

Steven Grinspoon, M.D.
Professor of Medicine
Harvard Medical School

24th Annual AACE Program

May 16, 2015
Nashville, TN

Disclosures

- Consultant, NovoNordisk
- Research support from Theratechnologies, Inc.

Outline

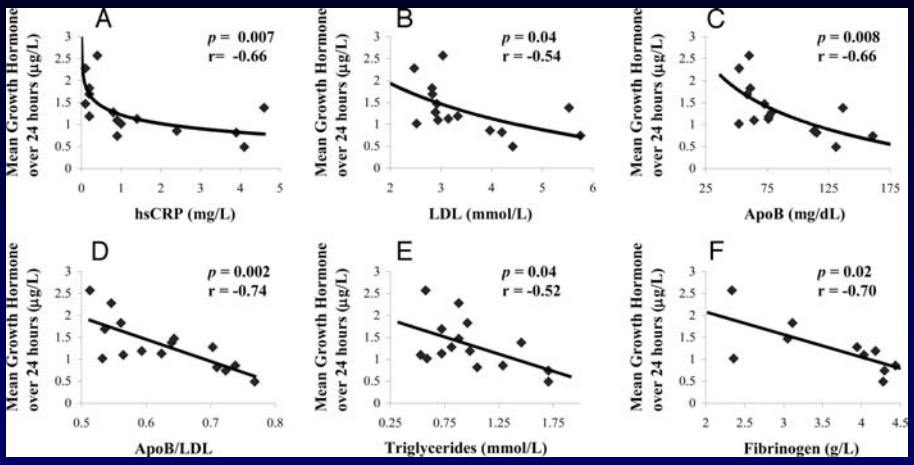
- Pituitary GHD is associated with metabolic consequences and inflammation
- Reduced GH is seen in obesity, in relationship to visceral adiposity, and independently contributes to CVD in this population
- Rationale for use of a GHRH analogue to augment pulsatile GH secretion in conditions of excess visceral adiposity
- Experience with tesamorelin in HIV-lipodystrophy
- Experience with tesamorelin in generalized obesity

GHD is Associated with Metabolic Risk

- Pituitary GHD is associated with
  - Increased abdominal fat accumulation
  - Dyslipidemia
  - Increased inflammation
  - Increased CVD risk
- Treatment of GHD with GH is an established therapy which improves these parameters

Molitch et al., 2011, JCEM 96:1587-1609.
Colao et al., 2008, JCEM 93:3416-3424.

GHD and Cardiovascular Risk Markers



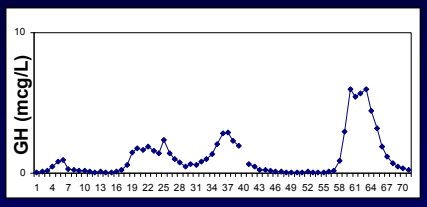
Miller et al. JCEM 2005

Outline

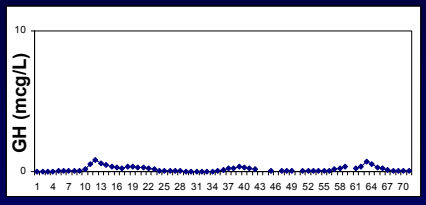
- Pituitary GHD is associated with metabolic consequences and inflammation
- Reduced GH is seen in obesity, in relationship to visceral adiposity, and independently contributes to CVD in this population
- Rationale for use of a GHRH analogue to augment pulsatile GH secretion in conditions of excess visceral adiposity
- Experience with tesamorelin in HIV-lipodystrophy
- Experience with tesamorelin in generalized obesity

GH Secretion is Perturbed in Obesity

- Intact pulse generation, but reduced pulse mass
- Functional deficiency syndrome – can be reversed with weight loss or GHRH



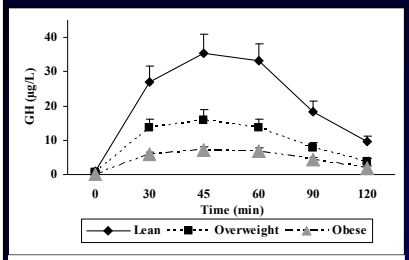
Lean

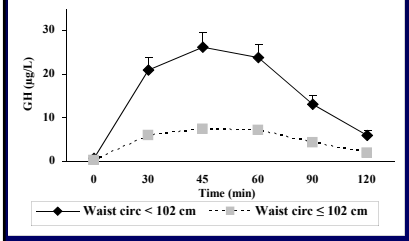


Obese

Iranmanesh et al., 1991, JCEM 73:1081-1088.
Bonert et al., 2004, JCEM 89:3397-3401.
Rasmussen et al., 1995, JCEM 80:1407-1415.
Grinspoon unpublished data.

Excess Visceral Fat Contributes to Reduced GH





Variables	Estimate	SEM	*P*
Age	0.03	0.27	0.90
BMI (kg.m2)	0.49	1.02	0.64
TAT (cm^2)	0.01	0.02	0.57
SAT (cm^2)	-0.06	0.04	0.16
VAT (cm^2)	-0.10	0.04	0.02

Makimura et al., 2008, JCEM 93: 4254-4260.

Prevalence of Relative GHD in Obesity

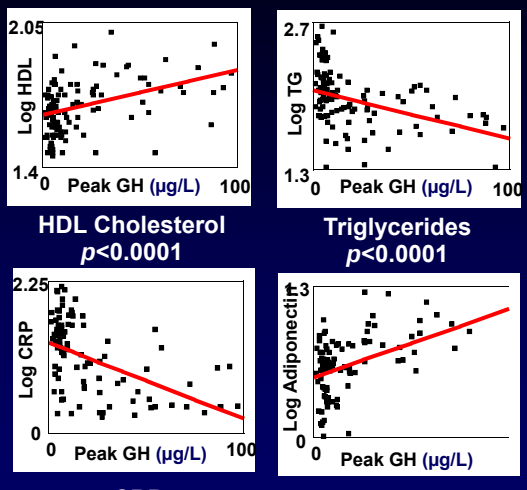
In 302 men and women without known endocrine abnormality, GHRH-Arginine stimulation tests were performed:

	BMI <25	BMI 25-30	BMI ≥30
N	65	36	201
GH ≤4.2 µg/l (%)	1 (1.5%)	2 (5.6%)	59 (29.4%)

- In response to glucagon stimulation test, similarly high failure rates were seen in obese subjects (Miller et al, unpublished data)

Makimura unpublished data

GH, Lipids, and Inflammation in Obesity



HDL Cholesterol ***p*<0.0001**

Triglycerides ***p*<0.0001**

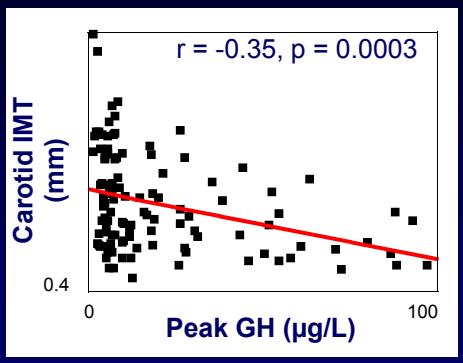
CRP ***p*<0.001**

Adiponectin ***p*<0.001**

Makimura et al., 2009, JCEM 94: 5131-5138.

Reduced GH is Associated with cIMT in Obesity

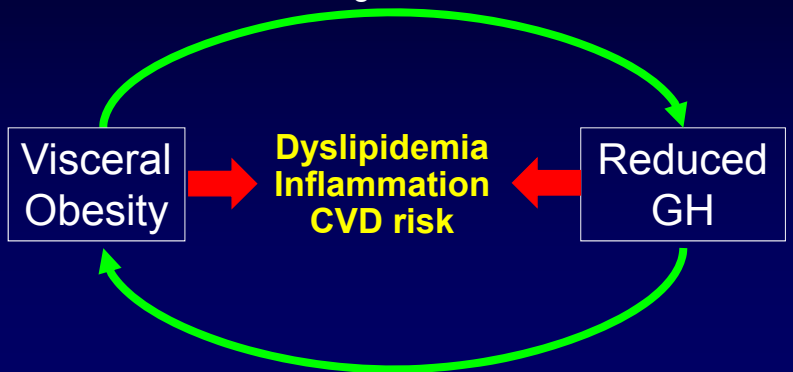
Relationship between cIMT and peak GH remained significant controlling for age, gender, race, smoking, lipids and glucose and BP



Makimura et al., 2009, JCEM 94: 5131-5138.

Mechanisms and Consequences of Reduced GH in Obesity

Decreased GHRH secretion
Increased somatostatin tone
Increased glucose/insulin/FFA



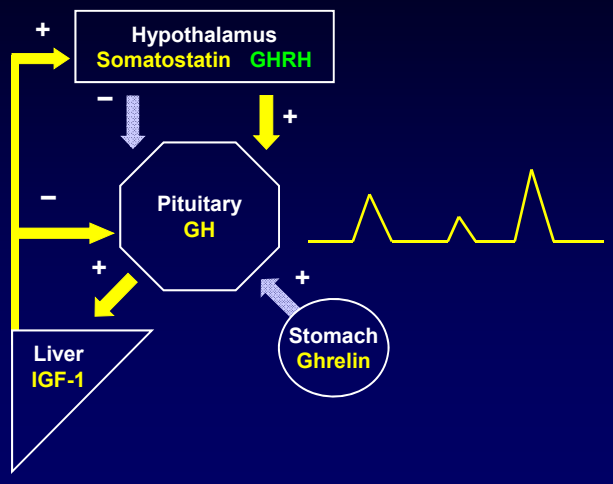
Decreased hormone-stimulated lipolysis
?Mitochondrial Dysfunction

Outline

- Pituitary GHD is associated with metabolic consequences and inflammation
- Reduced GH is seen in obesity, in relationship to visceral adiposity, and independently contributes to CVD in this population
- Rationale for use of a GHRH analogue to augment pulsatile GH secretion in conditions of excess visceral adiposity
- Experience with tesamorelin in HIV-lipodystrophy
- Experience with tesamorelin in generalized obesity

AUGMENT-GH 13

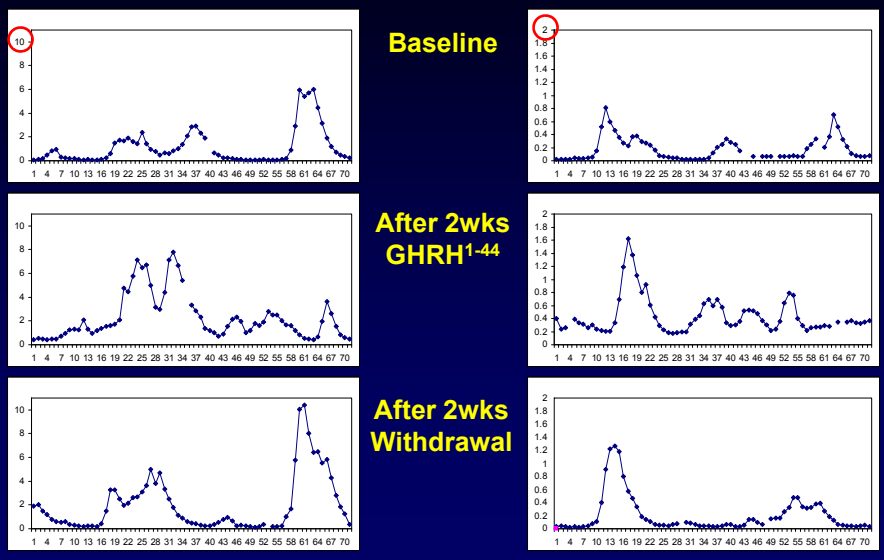
Rationale for Use of GHRH vs. GH



GHRH$^{1-44}$ (Tesamorelin):

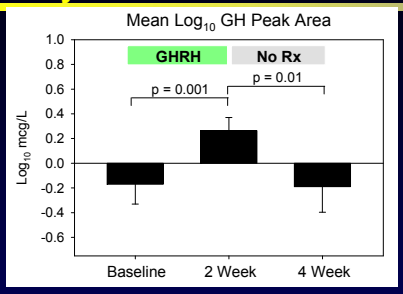
- A minimally modified GHRH$^{1-44}$ with trans 3-hexanoyl adduct on Tyr. This modification makes the analogue resistant to DPP IV mediated degradation.
- Increases GH in a physiologic, pulsatile manner unlike GH.

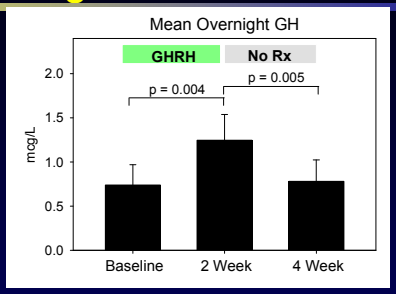
Representative GH Pulse Profiles in Response to GHRH$^{1-44}$



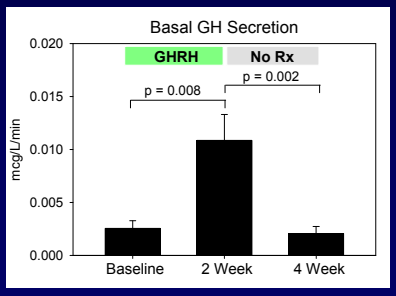
Stanley et al., 2010, JCEM 96: 150-158.

Effect of GHRH$^{1-44}$ on Pulsatile GH Secretion in Healthy Normal and Overweight Men



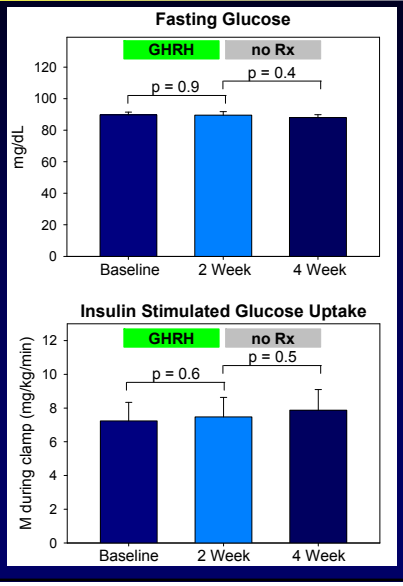


- **GHRH 2mg SC QD x 2 weeks**
- **↑ endogenous GH secretion**
- **↔ GH pulse frequency**
- **Increase in IGF-I (181 ± 22 mcg/L, *P* = 0.0001)**



Stanley et al., 2010, JCEM 96: 150-158.

Neutral Effects on Glucose Homeostasis



Stanley et al., 2010, JCEM 96: 150-158.

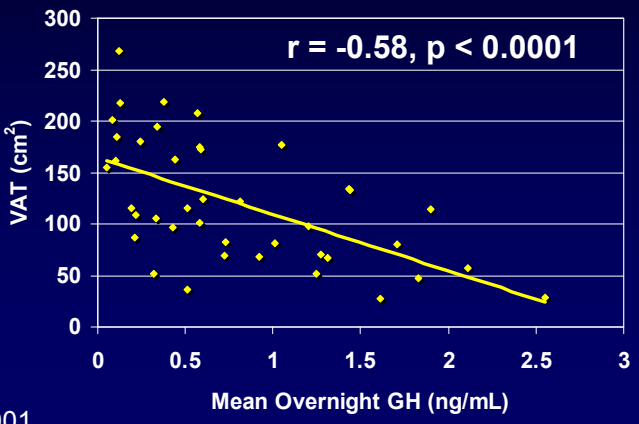
Outline

- Pituitary GHD is associated with metabolic consequences and inflammation
- Reduced GH is seen in obesity, in relationship to visceral adiposity, and independently contributes to CVD in this population
- Rationale for use of a GHRH analogue to augment pulsatile GH secretion in conditions of excess visceral adiposity
- Experience with tesamorelin in HIV-lipodystrophy
- Experience with tesamorelin in generalized obesity

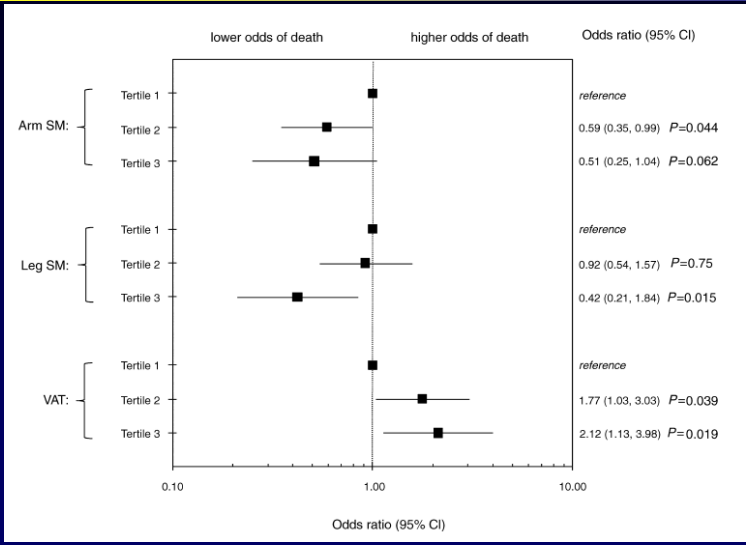
Relative GHD in HIV Lipodystrophy

Rietschel et al. JCEM 2001

•Common disorder seen in 25-50% of HIV Patients



VAT and Mortality in HIV



Scherzer et al., AIDS 2011.

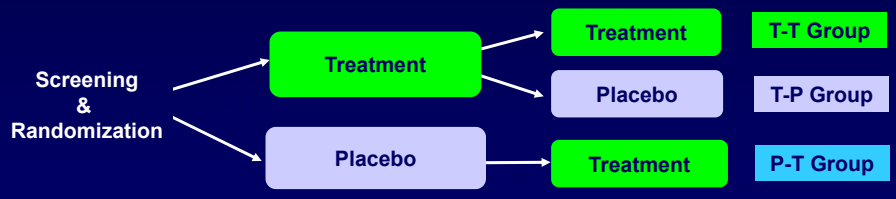
GHRH$^{1-44}$ in HIV Patients with Lipodystrophy

LIPO-010 (Main/Extension)
- **412 patients NEJM 2007, AIDS 2008**

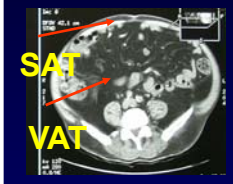
LIPO-1011 (Main/Extension)
- **404 patients JAIDS 2010**

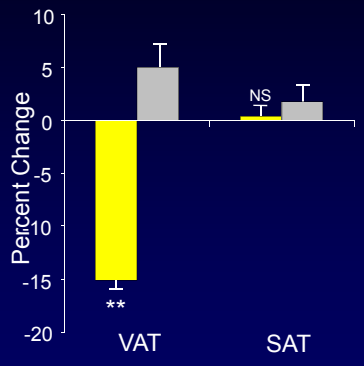
Combined Data Endo Soc 2010
- **816 patients JCEM 2010**

Re-randomization within 7 days after 26 weeks



GHRH$^{1-44}$ Decreases VAT and Preserves Abdominal SAT in HIV Lipodystrophy



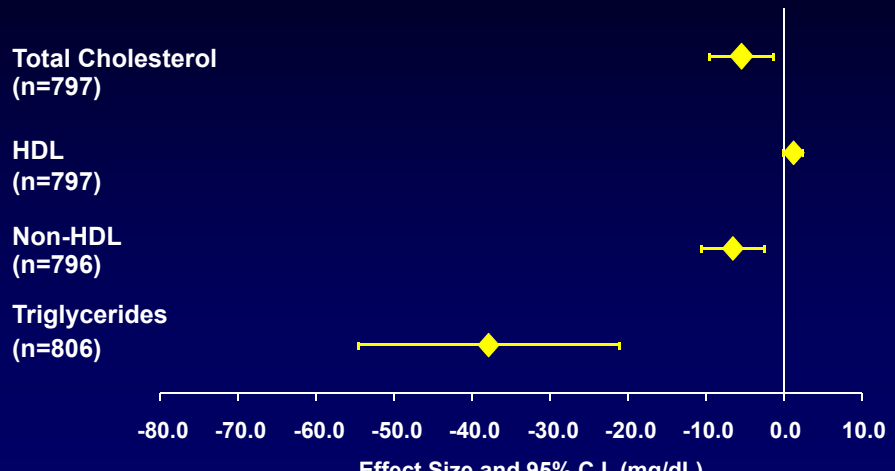


■ GHRH$^{1-44}$ ■ Placebo

Data are Mean ± SEM. **P<0.001 vs. Placebo. NS compared to Baseline.

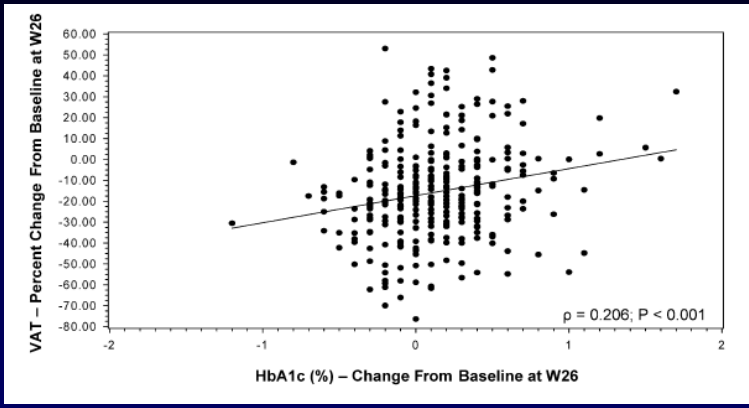
NEJM 2007; 357: 2359-2370.

Treatment Effects of GHRH$^{1-44}$ vs. Placebo on Lipids – Combined Phase III Studies in HIV



Falutz et al. JCEM. 2010;95:4291-304

VAT Reduction Predicts Metabolic Improvements



Changes in VAT significantly associated with changes in HbA1c, insulin, glucose, total cholesterol, triglyceride.

Stanley et al., 2012. CID.

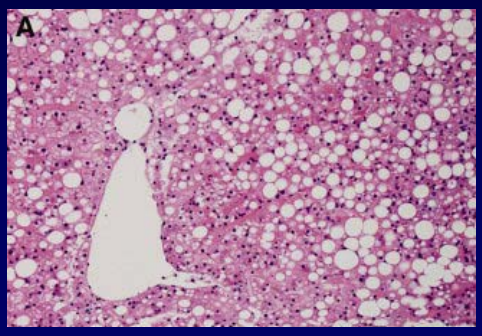
Safety Observations in Phase 3 HIV Studies

- No clinically meaningful changes were observed at Week 26 and Week 52 in patients receiving tesamorelin in:
  - Vital signs
  - Blood chemistry, hepatic enzymes, hematology, and urinalysis
  - Levels of pituitary hormones other than GH, including TSH, LH, and prolactin
  - Glucose
  - Mild hypersensitivity reactions in 3%

Falutz et al. JCEM. 2010;95:4291-304

Steatosis is Prevalent and Relates to VAT in HIV

- Hepatic TG accumulation is strongly associated with VAT
- Non-alcoholic fatty liver disease (NAFLD) is highly prevalent and seen in 30-40% of individuals with HIV
- No known treatment in HIV



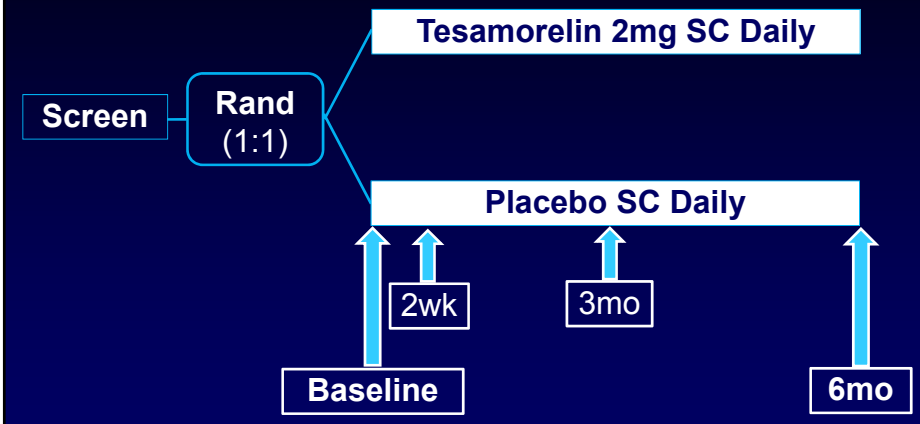
Brunt EM et al. *Hepatology.* 2011

[1]Guaraldi et al. *Clin Infect Dis.* 2008;47(2):250-257.
[2]Crum-Cianflone et al. *JAIDS.* 2009;50(5):464-473.
[3]Hadigan et al. *JAIDS.* 2007;46(3):312-317

Role of GH in NAFLD

- Evidence supporting role of GH in development of NAFLD
  - Transgenic mice that overexpress GH: decreased liver fat
  - Mice with liver-specific GH-receptor (GHR) knock-out: severe hepatic steatosis
  - Pituitary GH deficiency: higher prevalence of NAFLD
  - Replacement of GH in GHD: reduces transaminases and improves histological findings.

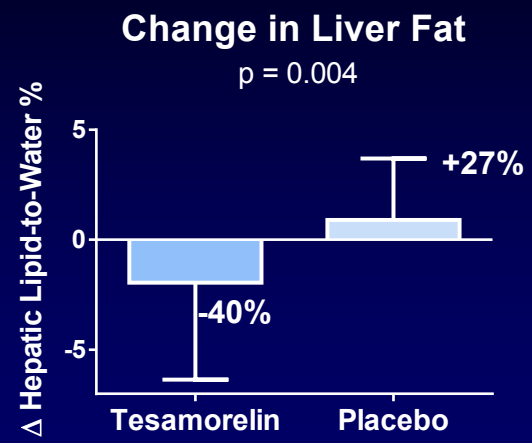
Effects of Tesamorelin on Steatosis in HIV Lipodystrophy



•**Baseline & 6mo:** CT for VAT/SAT, ^{1}H-MRS for liver fat, OGTT, cIMT, lipids, AST/ALT, adiponectin, clamp (subgroup)

Stanley JAMA 2014

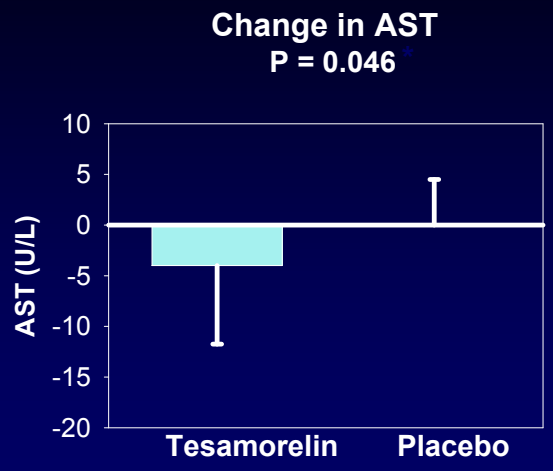
Effects on % Liver Fat by Spectroscopy



• Bars show median, error bars IQR

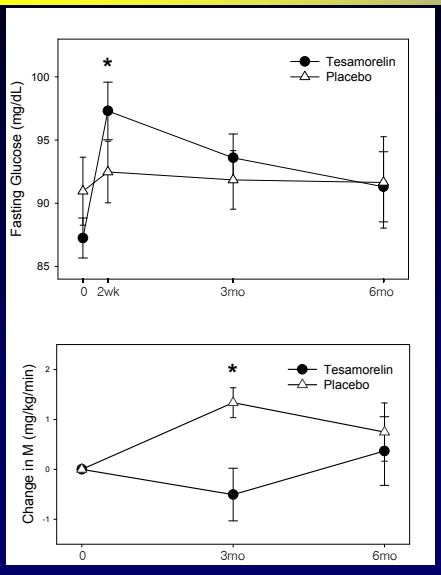
Stanley JAMA 2014

Effect on AST



Stanley JAMA 2014

Effects on Glucose Homeostasis



- Fasting insulin, HOMA-IR, 2-hour glucose not different from placebo; 0.2% increase in A1c in tesamorelin group

(M = insulin sensitivity measured by clamp, with higher M indicating better insulin sensitivity)

Stanley JAMA 2014

FDA Approves Tesamorelin for Reduction in Abdominal Fat in HIV Lipodystrophy in 2010

- Noted improvementt in VAT, lipids and QOL
- Subsequent data suggest Tesamorelin may reduce liver fat

Outline

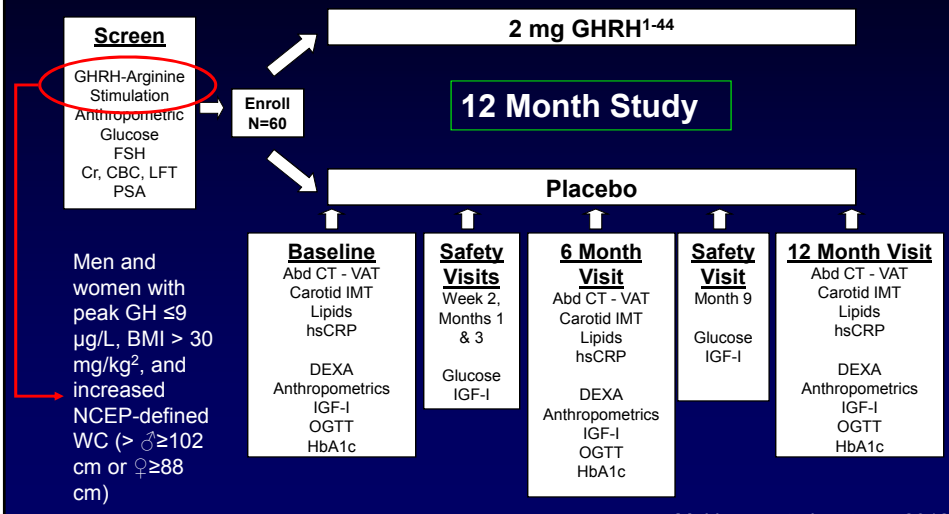
- Pituitary GHD is associated with metabolic consequences and inflammation
- Reduced GH is seen in obesity, in relationship to visceral adiposity, and independently contributes to CVD in this population
- Rationale for use of a GHRH analogue to augment pulsatile GH secretion in conditions of excess visceral adiposity
- Experience with tesamorelin in HIV-lipodystrophy
- Experience with tesamorelin in generalized obesity

Pilot Data on GHRH$^{1-44}$ Effects in Obesity

- 12-month, randomized, double-blind, placebo-controlled study
- GHRH$^{1-44}$ analog (Tesamorelin) vs. placebo
  - Dose reduction algorithm to maintain age-adjusted normal levels of IGF-1
- End points:
  - 1° end point: VAT
  - 2° end point: cIMT, hsCRP, lipid profile
- Longitudinal linear mixed effects modeling with all available data and last-observation carried forward

Makimura et al., *JCEM,* 2012.

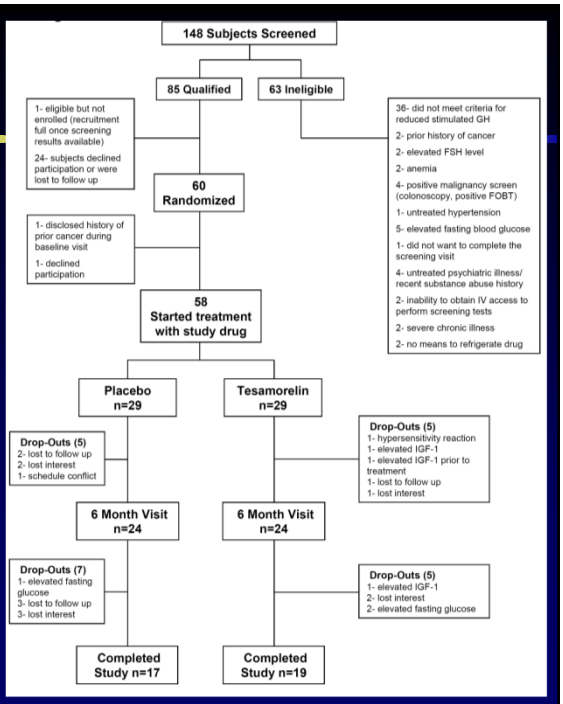
Study Schema



Makimura et al., *JCEM,* 2012.

Patient Flow

- Discontinuation rates similar in both arms
- 83% with post-baseline data available for ITT analysis with LOCF
- Compliance similar in each arm and > 90%
- Dose titration algorithm to keep IGF-1 within normal range



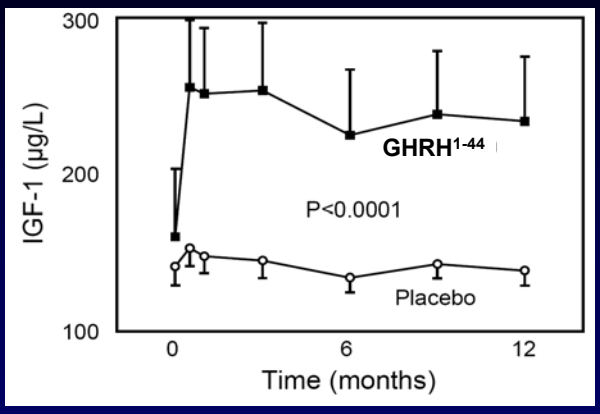
Makimura et al., *JCEM,* 2012.

Baseline Data

	GHRH$^{1-44}$ (N= 31)	Placebo (N= 29)	P value
Demographics			
Age (years)	42.5 ± 1.3	39.9 ± 1.8	0.25
Gender-M/F (% male)	20/11 (65.5%)	19/10 (64.5%)	0.94
Tobacco Use	18 (58%)	13 (45%)	0.31
Medication Use			
Lipid lowering therapy (%)	8 (26%)	12 (41%)	0.20
Anti-hypertensive (%)	10 (32%)	5 (17%)	0.18
Body Composition			
Body Mass Index (kg/m^2)	[37.5 (34, 41.4)]	[38.3 (34.4, 40.5)]	0.81
Waist Circumference (cm)	121 ± 2	121 ± 2	0.94
VAT (cm^2)	209 ± 13	193 ± 14	0.39
Growth Hormone Parameters			
Peak stimulated GH	4.22 ± 0.46	5.19 ± 0.47	0.15
IGF-1 (µg/L)	[101 (79, 145)]	[131 (107, 172)]	0.17

Makimura et al., *JCEM,* 2012.

Physiologic Increases in IGF-I

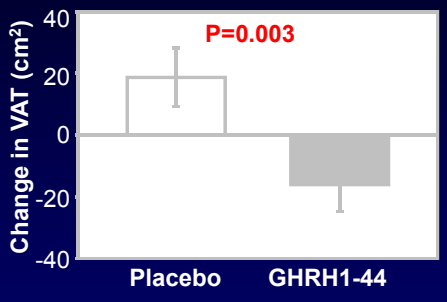


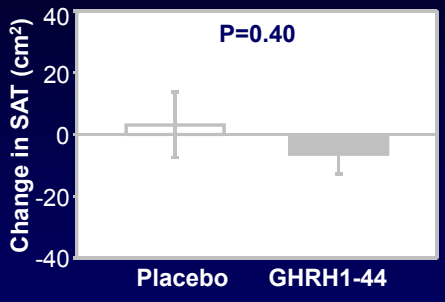
Change in IGF-I SD Scores (GHRH$^{1-44}$ *vs.* placebo):

- 1.14±0.25 (95% CI: 0.63, 1.65) *vs.* 0.12±0.13 (95% CI: 0.39, 0.15) at 6 mos
- 1.25±0.27 (95% CI: 0.69, 1.81) *vs.*0.05±0.14 (95% CI: 0.34, 0.25) at 12 mos

Makimura et al., *JCEM,* 2012.

Reductions in VAT without Significant Effects on SAT





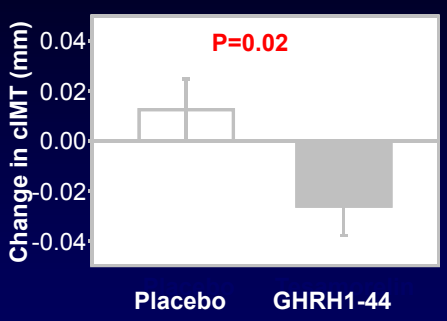
GHRH$^{1-44}$ decreased VAT (-19%) relative to placebo

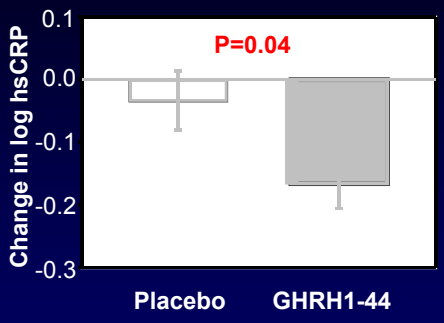
- VAT decreased -8% in GHRH$^{1-44}$
- VAT increased 11% in placebo

GHRH$^{1-44}$ does not significantly affect SAT

Makimura et al., *JCEM,* 2012.

Improvement in cIMT and hsCRP





GHRH$^{1-44}$ decreased cIMT by -6% compared to placebo

- cIMT inc 2% in placebo
- cIMT dec -4% in Tesamorelin

GHRH$^{1-44}$ decreased log hsCRP by -23% Compared to placebo

- hsCRP dec -6% in placebo
- hsCRP dec -30% in Tesamorelin

Makimura et al., *JCEM*, 2012.

Effects on Body Composition

	Baseline			Change (12 Months)		Effect Size (vs. Placebo)	
	GHRH$^{1-44}$	Placebo	P	GHRH$^{1-44}$	Placebo	Effect (95% CI)	P
BMI (kg/m^2)	38.2±0.9	37.9±0.7	0.81	-0.1±0.4	0.6±0.4	-0.6 (-1.4, 0.2)	0.14
Waist (cm)	121±2	121±2	0.94	-2±1	1±1	-3 (-5, -0.3)	0.03
Lean (kg)	71.8±2.5	70.7±2.2	0.74	1.0±0.5	-0.4 ±0.4	1.4 (0.2, 2.6)	0.03
Fat (kg)	42.6±1.9	44.0±2.0	0.26	-0.7±0.7	1.0 ±0.7	-1.7 (-3.4, -0.1)	0.04
Trunk fat (kg)	23.3±1.3	23.3±1.1	0.53	-0.6±0.4	0.7 ±0.4	-1.4 (-2.4, -0.3)	0.01

Makimura et al., *JCEM*, 2012.

Effects on Lipid Levels

	Baseline			Change (12 Months)		Effect Size (vs. placebo)	
	GHRH$^{1-44}$	Placebo	P	GHRH$^{1-44}$	Placebo	Effect (95% CI)	P
Tot Chol (mg/dl)	176±5	168±5	0.28	4±4	7±5	-2 (-13, 9)	0.69
TGL (mg/dl)	196±26	132±11	0.03	-26±16	12±8	-37 (-67, -7)	0.02
HDL (mg/dl)	35±1	36±2	0.61	4±1	3±1	1 (-3, 5)	0.66
LDL (mg/dl)	114±5	117±6	0.72	4±4	1±4	3 (-8, 14)	0.58

Makimura et al., *JCEM,* 2012.

Effects on Glucose

	Baseline			Change (12 Months)		Effect Size (vs. placebo)	
	GHRH$^{1-44}$	Placebo	P	GHRH$^{1-44}$	Placebo	Effect (95% CI)	P
FBG (mg/dl)	95±3	92±2	0.79	2±3	1±2	1 (-5, 8)	0.73
2-hr gluc (mg/dl)	138±7	134±6	0.71	-11±7	-3±8	-10 (-27, 7)	0.25
Insulin (µIU/ml)	9.3±1.1	8.6±0.9	0.78	4.0±3.3	1.8±1.0	-0.3 (-7.5, 7.0)	0.94
HOMA	2.25±0.29	1.98±0.21	0.69	1.46±1.08	0.50±0.26	-0.11 (-2.41, 2.19)	0.93
HbA1c	5.8±0.1	5.6±0.1	0.26	0.2±0.1	0.2±0.1	-0.002 (-0.2, 0.2)	0.98

Makimura et al., *JCEM,* 2012.

Safety

Event	GHRH$^{1-44}$ Number (%)	Placebo Number (%)	P value
Any adverse event	28 (90.3%)	26 (89.7%)	0.93
Serious adverse event	0 (0%)	0 (0%)	N/A
Hypertension	8 (29.6%)	5 (17.2%)	0.27
Hyperglycemia	3 (9.7%)	2 (6.9%)	0.70
Tingling/paresthesia	3 (9.7%)	1 (3.5%)	0.33
Peripheral edema	3 (9.7%)	1 (3.5%)	0.33
Injection-site pruritis	2 (6.5%)	1 (3.5%)	0.59
Injection-site reaction	2 (6.5%)	0 (0%)	0.16
Arthralgia	2 (6.5%)	0 (0%)	0.16
Carpal tunnel syndrome	1 (3.2%)	0 (0%)	0.33
Hypersensitivity Reaction	1 (3.2%)	0 (0%)	0.33
Malignancy	0 (0%)	0 (0%)	N/A

Makimura et al., *JCEM,* 2012.

Summary

- GH is reduced with excess visceral adiposity in association with metabolic perturbation and CVD risk
- GHRH selectively reduces visceral and liver fat in HIV-lipodystrophy, increasing physiologic pulsatile GH secretion, and is FDA approved for this indication
- GHRH has been shown to reduce VAT, and improve dyslipidemia, inflammation, and cIMT in generalized obesity but is not FDA approved for this purpose
- Further study is needed of the long-term effects of augmenting pulsatile GH on metabolic and CVD indices in obesity and other models of excess VAT