Abdominal Fat Accumulation in HIV-infected Patients – Mechanisms and Novel Treatment Strategies

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Disclosures

Consultant: Serono, Theratechnologies
GH and GHRH are not FDA approved for use in treatment of central obesity
Research Funding by R01 DK 63639, R01 HL085268 and Theratechnologies
HIV Lipodystrophy Syndrome

- Occurs to some degree in more than half of HIV pts treated with HAART
- Characterized by fat redistribution, not severe generalized obesity
  - increased visceral adiposity
  - decreased subcutaneous peripheral fat
  - dyslipidemia and insulin resistance
- Mechanism unknown (direct or indirect effect of ART on adipogenesis and substrate metabolism)
HIV-Associated Lipodystrophy
Effect of Initiating HAART

Pre HAART

HAART for 9 months
Body Composition Changes Over 9 Months

<table>
<thead>
<tr>
<th></th>
<th>Pre HAART</th>
<th>HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>79.2</td>
<td>79.8</td>
</tr>
<tr>
<td>Abdominal CT (L4-L5; cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– VAT</td>
<td>307</td>
<td>403</td>
</tr>
<tr>
<td>– SAT</td>
<td>147</td>
<td>106</td>
</tr>
<tr>
<td>Total fat by DEXA (kg)</td>
<td>17.9</td>
<td>17.3</td>
</tr>
<tr>
<td>– trunk</td>
<td>12.3</td>
<td>13.8</td>
</tr>
<tr>
<td>– limbs</td>
<td>4.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>
MI rates in HIV+ (8500) and non-HIV-infected patients (1,000,000) between 1996-2004

RR 1.77 vs. non-HIV, P<0.0001

Triant et al JCEM 2007 from the MGH and BWH RPDR Database
<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV (N=3851)</th>
<th>Non-HIV (N=1044589)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>818</td>
<td>21.24†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>443</td>
<td>11.50†</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>896</td>
<td>23.27†</td>
</tr>
</tbody>
</table>

**Attenuation of Risk When Adjusting for:**

- HTN 4%
- Dyslipidemia 10%
- Diabetes 10%
Relationship of GH to Increased Weight and WC
Reduced GH Secretion in Obesity

Makimura et al. JCEM 2008
Multivariate Analysis of Peak Stimulated GH Level and Regional Fat Distribution (n = 75)

Abdominal CT model. $P < 0.0001$ for model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.27</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.49</td>
<td>1.02</td>
<td>0.64</td>
</tr>
<tr>
<td>TAT (cm²)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.57</td>
</tr>
<tr>
<td>SAT (cm²)</td>
<td>-0.06</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>-0.10</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Makimura et al. JCEM 2008
Relationship Between CV Risk Parameters and Mean GH

Miller et al. JCEM 2005
Questions

1. Are HIV patients who present with increased visceral adiposity relatively GH deficient?
2. Does this contribute to increased CVD?
3. Is there a benefit to augmenting GH secretion in this population?
4. What is the optimal way to do this?
The Growth Hormone Axis

Hypothalamus
- SS
- GHRH

Pituitary
+ GH

Liver
- IGF-1

Stomach
Ghrelin

Growth
IGF-1 Synthesis
Lipolysis
Muscle Mass
GH Deficiency in HIV Lipodystrophic Patients vs. BMI Matched Controls

Failure Rate (%)

- Cutoff of 3.3 ng/mL
- Cutoff of 5 ng/mL
- Cutoff of 7.5 ng/mL
- Cutoff of 9 ng/mL

*P<0.05 compared to HIV + Non-Lipo
†P<0.05 compared to Control

Koutkia et al. JCEM 2005
Correlation of Visceral Adiposity and GH Secretion

$r= -0.58, \ P<0.0001$

Rietschel et al. JCEM 2001
Potential Schema for the Mechanisms of Reduced GH Secretion in HIV Lipodystrophy

- Increased Somatostatin Tone
- Ghrelin
- Growth Hormone
- Free Fatty Acids
- Intact GHRH Pulse Initiation

Comparison between Normal and HIV Lipodystrophy:
- Normal: Increased GH secretion
- HIV Lipodystrophy: Decreased GH secretion

AJP 2004
Strategies for Restoring GH in HIV Lipodystrophy

- Growth Hormone
- Growth Hormone Releasing Hormone
TH9507

• Synthetic human GHRH$^{1-44}$ analog
  – Hydrophobic chain at N-terminus
• Increased in vitro half life as compared to natural GHRH, but half life is short, on order of 10-20 minutes
• Raises GH secretion in a pulsatile manner resulting in increased IGF-I levels generally within the physiological range (effects on pulsatility significantly outlast its circulating half life, eg given daily with effects on pulsatility that last far beyond 10 minute half life)
• Well tolerated at single doses up to 2 mg/day including with regard to glycemic control in type 2 diabetic patients (Clemmons Endo Soc 2004)
Effect of Short Term GHRH$^{1-44}$ (Tesamorelin) in Healthy Men
Effect of GHRH$^{1-44}$ on GH Secretion

**GH AUC (total overnight secretion)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 Week</th>
<th>4 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/mL</td>
<td>500</td>
<td>1000</td>
<td>1500</td>
</tr>
<tr>
<td>p</td>
<td>0.007</td>
<td>0.006</td>
<td>0.007</td>
</tr>
</tbody>
</table>

**Basal GH Secretion**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 Week</th>
<th>4 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/mL/min</td>
<td>0.000</td>
<td>0.005</td>
<td>0.010</td>
</tr>
<tr>
<td>p</td>
<td>0.15</td>
<td>0.06</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Number of Overnight GH Pulses**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 Week</th>
<th>4 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>8</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>p</td>
<td>0.42</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

**Mean Log$_{10}$ GH Peak Area**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 Week</th>
<th>4 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log$_{10}$ ng/mL</td>
<td>-0.6</td>
<td>-0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>p</td>
<td>0.002</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

**Number of Overnight GH Pulses**

<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>#</td>
<td>8</td>
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<td>6</td>
</tr>
<tr>
<td>p</td>
<td>0.42</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Stanley JCEM 2010
Representative GH Pulse Profiles

Lean Male

Baseline

After 2wks

GHRH^{1-44}

After 2wks

Withdrawal

Obese Male

Baseline

Withdrawal

Stanley JCEM 2010
Effect of GHRH$^{1-44}$ on IGF-I

IGF-I increase of 181 ± 22 ng/mL after 2 weeks of GHRH$^{1-44}$
Effect of GHRH$^{1-44}$ on Glucose Homeostasis

No significant changes in fasting glucose or insulin-stimulated glucose uptake as measured by euglycemic hyperinsulinemic clamp.

Stanley JCEM 2010
Tesamorelin in HIV-Infected Patients with Abdominal Fat Accumulation (Phase III Program)

LIPO-010 (Main/Extension)
- First patient: June 2005
- 412 patients NEJM 2007, AIDS 2008

CTR-1011 (Main/Extension)
- First patient: February 2007
- 404 patients JAIDS 2010
- Combined Data Endo Soc 2010
  816 patients

Screening & Randomization

Treatment
Placebo

2:1

0
Week

26

Main Study

Treatment
Placebo

Extension Study

Treatment
Placebo

T-T Group
T-P Group
P-T Group

Re-randomization within 7 days after 26 weeks
Patient Disposition (Lipo 10)

412 Randomized

273 TH9507
211 Completed

137 Placebo
115 Completed
Eligibility Criteria

• HIV positive adults
• Stable ART for at least 8 weeks, CD4 > 100 cells/mm³ and viral load < 10,000 copies
• Abdominal fat accumulation occurring in the context of treatment for HIV infection
  – WC ≥ 95 cm and WHR ≥ 0.94 for males
  – WC ≥ 94 cm and WHR ≥ 0.88 for females
• Fasting glucose ≤ 150 mg/dL
• Stable lipid-lowering agents permitted
• Use of antidiabetic, insulin sensitizing, GH or GH agonists exclusionary

NEJM 2007
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TH9507 (n=273)</th>
<th>Placebo (n=137)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (y)</td>
<td>47±7</td>
<td>48±7</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td>29.2±4.2</td>
<td>29.2±4.2</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>VAT (cm^2)</strong></td>
<td>178±77</td>
<td>171±77</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>SAT (cm^2)</strong></td>
<td>231±127</td>
<td>239±133</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/L)</strong></td>
<td>5.1±1.1</td>
<td>5.0±1.0</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>[197±44]</td>
<td>[195±38]</td>
<td></td>
</tr>
<tr>
<td><strong>Triglyceride (mmol/L)</strong></td>
<td>2.9±2.1</td>
<td>2.6±1.6</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>[252±188]</td>
<td>[234±145]</td>
<td></td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>5.4±0.7</td>
<td>5.4±0.7</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>(mmol) [mg/dL]</strong></td>
<td>[97±14]</td>
<td>[99±15]</td>
<td></td>
</tr>
</tbody>
</table>
Effects of GHRH on % Change of VAT and SAT

Similar effects in analyses limited to females

NEJM 2007
Effects of GHRH on Lipid Profiles

- Total Cholesterol (mmol/L)
- HDL (mmol/L)
- Triglycerides (mmol/L)
- Cholesterol: HDL

TH9507 vs. Placebo:
- Total Cholesterol: **P<0.001 vs. placebo
- HDL: *P=0.01 vs. placebo
- Triglycerides: **P<0.001 vs. placebo

NEJM 2007

-19%, 59 mg/dL
Change in Lipid Parameters
Week 26 (combined data: 816 patients)

- Total Cholesterol
- HDL
- Non-HDL
- Triglycerides

Effect Size and 95% C.I. (mg/dL)

JCEM 2010
Effects of TH9507 on IGF-I Levels

![Graph showing the effects of TH9507 on IGF-I levels.](image)

- **Baseline**: TH9507 and Placebo levels are comparable.
- **13 Week**: TH9507 shows a significant increase compared to Placebo.
- **26 Week**: TH9507 levels remain high, while Placebo levels decrease.

Statistical significance:

\[ P < 0.001 \]

**Legend**

- **TH9507**
- **Placebo**

**NEJM 2007**
## Change in Glucose Parameters at Week 26 (Combined Main Studies)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Mean ± SD</th>
<th>Change from Baseline to Week 26 Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>98.2 ± 14.38</td>
<td>2.7 ± 15.89</td>
</tr>
<tr>
<td>2-hr OGTT glucose (mg/dL)</td>
<td>112.7 ± 36.90</td>
<td>3.2 ± 37.63</td>
</tr>
<tr>
<td>Insulin (μIU/mL)</td>
<td>21.9 ± 29.24</td>
<td>0.03 ± 29.29</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>5.5 ± 8.30</td>
<td>-0.02 ± 8.50</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.3 ± 0.50</td>
<td>0.14 ± 0.40¹</td>
</tr>
</tbody>
</table>

1 Statistically significantly different between the tesamorelin and placebo groups.

JCEM 2010
## Change in Glucose Parameters at Week 52 (Combined Extension Studies)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Change from Baseline to Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T-T (N=246)</td>
<td>T-P (N=135)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>97.1 ± 13.09</td>
<td>102.2 ± 16.86</td>
</tr>
<tr>
<td>2- hr OGTT glucose (mg/dL)</td>
<td>111.6 ± 33.60</td>
<td>112.4 ± 39.88</td>
</tr>
<tr>
<td>Fasting insulin (µIU/mL)</td>
<td>19.5 ± 20.22</td>
<td>25.9 ± 31.38</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.8 ± 5.74</td>
<td>7.3 ± 10.95</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.2 ± 0.50</td>
<td>5.3 ± 0.47</td>
</tr>
</tbody>
</table>

JCEM 2010
Effects of Tesamorelin on Inflammatory Markers at Week 26

Change in Adiponectin (mcg/mL)

<table>
<thead>
<tr>
<th></th>
<th>Tesamorelin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

Change in CRP (mg/L)

<table>
<thead>
<tr>
<th></th>
<th>Tesamorelin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 compared to placebo
Change in Abdomen Profile Score

![Bar charts showing change in abdomen profile score for TH9507 and Placebo groups.](chart.png)

- **Patient-Reported Profile**
  - Mean Score Change: TH9507, Placebo, P = 0.03
  - Mean Score Change: TH9507, Placebo, P = 0.04

- **Physician-Reported Profile**
  - Mean Score Change: TH9507, Placebo, P = 0.03
  - Mean Score Change: TH9507, Placebo, P = 0.04

*NEJM 2007*
# Correlation Between Change in Self Image and VAT

## Correlation between Percent change in VAT and Changes in Belly Image Parameters at Week 26 in the Primary Efficacy Phase

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tesamorelin (N=542)</th>
<th>Placebo (N=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Belly Image Parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belly Size</td>
<td>-0.179</td>
<td>-0.059</td>
</tr>
<tr>
<td>Belly Appearance Distress</td>
<td>-0.229</td>
<td>0.047</td>
</tr>
<tr>
<td>Patient-Reported Belly Profile</td>
<td>0.341</td>
<td>0.016</td>
</tr>
<tr>
<td>Physician-Reported Belly Profile</td>
<td>0.219</td>
<td>0.096</td>
</tr>
</tbody>
</table>

1 Spearman’s rank correlation (ρ).

---

*Endo Soc 2010*
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>TH9507 (n=273)</th>
<th>Placebo (n=137)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>82%</td>
<td>75%</td>
<td>0.12</td>
</tr>
<tr>
<td>SAE’s</td>
<td>4%</td>
<td>2%</td>
<td>0.29</td>
</tr>
<tr>
<td>Specific AE’s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
<td>18%</td>
<td>0.58</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13%</td>
<td>10%</td>
<td>0.43</td>
</tr>
</tbody>
</table>

- 2-3% on TH9507 experienced urticaria and/or rash

NEJM 2007
Tesamorelin in HIV-Infected Patients with Abdominal Fat Accumulation

Randomize

2 mg TH9507

Placebo

Placebo

2 mg TH9507

2 mg TH9507

6 Months

6 Months

JAIDS 2008
Effects of TH9507 on % Change in VAT from Baseline
Theoretical Effects of WC Reduction in Response to Tesamorelin

![Graph showing theoretical effects of WC reduction in response to Tesamorelin.](image)

Tesamorelin –4.7 cm and all VAT

Pischon NEJM 2008; JCEM 2010
The FDA approves Egrifta, the first drug to treat HIV patients with lipodystrophy

LA Times Nov 10, 2010
Conclusions and Future Directions

• HIV-infected patients demonstrate increased VAT, loss of SAT and a lipodystrophic pattern associated with a number of metabolic abnormalities that increase CVD risk

• HIV patients with increased VAT have reduced pulsatile GH secretion

• Augmenting GH via GHRH improves a number of CVD parameters in this population

• Obesity in the general population is associated with similar functional GH deficiency. Is there utility of GHRH to selectively improve visceral fat, with potentially beneficial effects on lipids and other CVD parameters?
Patients in the Normal, IGT/IFG or Diabetes Category Based on FBG and 2h-OGTT Over 26 Weeks Combined Main Phase

ADA definition 2006/2010:
**IGT/IFG**: 140 mg/dL ≤ 2 hours OGTT ≤ 199 mg/dL or 100 mg/dL ≤ fasting glucose ≤ 125 mg/dL
**Diabetes**: 2 hours OGTT ≥ 200 mg/dL or fasting glucose ≥ 126 mg/dL
Mean Overnight GH in HIV-Infected Patients and BMI-Matched Control Subjects

*\(P<0.05\) compared to Non-Lipo
†\(P<0.05\) compared to Control

Rietschel et al. JCEM 2001