Traditional And Novel Aspects of the Metabolic Actions of Growth Hormone:

PEDIATRIC ENDOCRINE NURSES SOCIETY

DENVER May 13, 2016

Mark A. Sperling MD
University of Pittsburgh & Icahn School of Medicine at Mt Sinai, NY

METABOLIC EFFECTS OF GROWTH HORMONE  MARK A SPERLING MD

PENS CONFERENCE MAY 13, 2016

LEARNING OBJECTIVES:
1. Describe the effects of GH on the metabolism of glucose, protein and fat under normal and pathologic conditions.
2. Explain the differences between the metabolic effects of GH deficiency or excess from those of IGF-I deficiency or excess
3. Discuss how to apply this information in counseling and managing patients on GH therapy

Growth Hormone And Diabetes Mellitus

• Historical Background
• 1930 Housay, B. Hyperglycemia plus other biochemical abnormalities improve after hypophysectomy in experimental diabetes in dogs.
• 1941 Young, F. Growth promotion and diabetogenic properties reside in growth hormone. GH is “pancreotrophic” and “diabetogenic.” Puppies given GH become gigantic but are resistant to diabetogenic action. Adult dogs are susceptible to diabetes including ketoacidosis, but have positive rather than negative nitrogen retention.
GH and Diabetes Mellitus (continued)

- Historical Background
- 1952 Poulsen, J. 30 year old woman with diabetes mellitus since age 9 developed Sheehan Syndrome. Insulin 100 U to 10/UD. Complete regression of retinopathy; death from renal failure at age 45.

Growth Hormone Actions

Significance of Metabolic Actions of Growth Hormone

Pathological
- Total lack of GH signaling
- Total excess of GH signaling

Comparison of Total Absence of GH Action (Laron) and GH Excess (Gigantism)

12 years 4 year 3 months
POOR GROWTH, EXCESS FAT, POOR MUSCLE DEVELOPMENT, POOR BONE MINERALIZATION, FASTING, HYPOGLYCEMIA

EXCESSIVE GROWTH, BIG MUSCLES AND BONE, LITTLE FAT, CHO INTOLERANCE.
CASE HISTORY-JLB

- BIRTHWEIGHT 8# 5OZ @ 42 WEEKS GESTATION VIA C-SECTION
- RECURRENT EPISODES OF HYPOGLYCEMIA WITH SEIZURES ESPECIALLY WITH ILLNESS (FASTING)
- BASAL IGF-1 UNDETECTABLE
- GROWTH HORMONE –BASAL 62NG/ML STIMULATED PEAK 218NG/ML
- BEGAN IGF-1 @13.5 YRS-HT 97.7CM,BONE AGE 8YR
- TREATED WITH IGF-1 UNTIL AGE 20 YRS-HEIGHT 132.6 CM

5 Years 3 Months

Gigantism, Big Muscles & Bone, Little Fat

Significance of Metabolic Actions of Growth Hormone

Physiological

• Carbohydrate metabolism in puberty
• Protein metabolism in puberty
• Lipid metabolism in puberty
### Glucose and Insulin Responses to OGTT In Pre-Pubertal and Pubertal Subjects

<table>
<thead>
<tr>
<th></th>
<th>PRE-PUBERTAL GLUCOSE Dose</th>
<th>PUBERTAL GLUCOSE Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.75 g/kg (N = 9)</td>
<td>1.75 g/kg (N = 10)</td>
</tr>
<tr>
<td>Fasting Blood Glucose (mg/dL)</td>
<td>82.0±3.1 (N = 8)</td>
<td>84.3±3.0</td>
</tr>
<tr>
<td>Peak Blood Glucose (mg/dL)</td>
<td>151.6±8.5 (N = 8)</td>
<td>152.2±7.9</td>
</tr>
<tr>
<td>Area Glucose mg/dL x 4hr</td>
<td>421.1±17.0 (N = 8)</td>
<td>432.7±17.9</td>
</tr>
<tr>
<td>Area Insulin µU/mL x 4hr</td>
<td>118.5±17.3 (N = 8)</td>
<td>299.1±77.6</td>
</tr>
</tbody>
</table>


### Changes in Insulin Sensitivity During Puberty: Assessed Via Euglycemic Clamp

Adapted from Bloch S, Clemens P, Sperling M. J Pediatrics. 1987; 110:481-87

### Longitudinal Study of Insulin Sensitivity

Pre-Pubertal vs Pubertal Time-Points (N=9)

**Insulin Response to Standard Hyperglycemic Clamp**

![Graph showing plasma insulin response](image)


**Change in Plasma BCAA During Hyperglycemic Clamp**

![Graph showing change in branched chain amino acids](image)


**Whole Body Protein Synthesis Rates**

![Graph showing synthesis rates](image)


* p<0.03 vs D1
Fat Versus Glucose Oxidation

Rates of total body lipolysis (glycerol Ra) and substrate oxidation (ratio of fat to glucose oxidation [FOX/GOX]) and free fatty acid (FFA) levels at the pre-pubertal vs. pubertal time point

Growth Hormone Treatment in Adolescent Males with Idiopathic Short Stature

• Objective
  - Assess longitudinally the effects of GH supplementation (0.3mg/kg/week for 4 months) in adolescent males (11-17 yrs) with ISS on body composition, metabolism & insulin sensitivity.

• Methods
  - Body composition assessed via dexta; glucose, protein and fat turnover via stable isotopes; insulin sensitivity via euglycemic / heperinsulenic clamp @40mu/m²/min.

GH Supplementation
Body Composition and Hormonal Profile

Before and after 4 months of GH (0.3 mg/kg/wk) supplementation

<table>
<thead>
<tr>
<th></th>
<th>Pre-GH (n=8)</th>
<th>Post-GH (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>14 ± 1.8 (SD)</td>
<td>14.4 ± 1.8 (SD)</td>
<td>0.001</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>255 ± 29 (33.3 ± 3.8)</td>
<td>477 ± 55 (62.3 ± 7.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>28.0 ± 2.63</td>
<td>32.3 ± 2.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>8.3 ± 1.3</td>
<td>6.1 ± 1.0</td>
<td>0.036</td>
</tr>
<tr>
<td>% body fat</td>
<td>22.8 ± 4.1</td>
<td>15.4 ± 2.4</td>
<td>0.032</td>
</tr>
</tbody>
</table>

**GH Supplementation**

Fasting Lipid Profile

<table>
<thead>
<tr>
<th></th>
<th>Pre-GH (n=8)</th>
<th>Post-GH (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol [mg/dl (mmol/liter)]</td>
<td>177 ± 12 (4.58 ± 0.31)</td>
<td>157 ± 9 (4.07 ± 0.23)</td>
<td>0.024</td>
</tr>
<tr>
<td>LDL [mg/dl (mmol/liter)]</td>
<td>118 ± 11 (3.06 ± 0.28)</td>
<td>84 ± 13 (2.18 ± 0.34)</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL [mg/dl (mmol/liter)]</td>
<td>44 ± 2 (1.14 ± 0.05)</td>
<td>45 ± 7 (1.17 ± 0.18)</td>
<td>0.839</td>
</tr>
<tr>
<td>Triglycerides [mg/dl (mmol/liter)]</td>
<td>76 ± 10 (0.86 ± 0.11)</td>
<td>115 ± 13 (1.30 ± 0.15)</td>
<td>0.057</td>
</tr>
<tr>
<td>Free fatty acids (mM)</td>
<td>0.41 ± 0.06</td>
<td>0.38 ± 0.37</td>
<td>0.644</td>
</tr>
</tbody>
</table>


**GH Supplementation**

**Conclusion**

- Treatment with GH for only 4 months in males with ISS mimics puberty in significant changes of body composition, insulin resistance, higher insulin and higher IGF-1.


**Impact of GH Withdrawal on Lipid Profile in Adolescents With CO GHD**

![Impact of GH Withdrawal on Lipid Profile](image)

Elevated Markers of Cardiovascular Risk in Adults With CO GHD

Study Design
- Single-center study
- 14 patients with CO GHD (6 males and 8 females, aged 18 to 36 years) treated with GH for 2 to 16 years with treatment withdrawn ≥ 3 years before study entry

Summary of Metabolic Effects

<table>
<thead>
<tr>
<th>GH</th>
<th>Testosterone</th>
<th>Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein Anabolism</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Lipolysis/Lipid oxidation</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>FFM/%FM</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Linear Growth</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Summary of Effects of Increased Physiological Growth Hormone Secretion in Puberty

- Increased GH secretion during puberty leads to
  - Insulin resistance for carbohydrate metabolism, but not for protein metabolism.
  - The resistance to insulin’s effect on glucose is normally overcome by increased insulin secretion.
  - The increased insulin synergizes with growth hormone to enhance protein anabolism—sex steroids further enhance this effect (Testosterone > Estradiol).
  - Growth hormone enhances lipolysis and fat oxidation sparing glucose and amino acids for anabolism and growth.
The Lesson from Pubertal Insulin Resistance

Those who cannot compensate for the pubertal/pregnancy induced insulin resistance by increasing insulin secretion develop varying degrees of glucose intolerance, explaining the pubertal peak of DM incidence, increased requirement for insulin during puberty and pregnancy, as well as gestational diabetes.

Does GH Therapy Induce Diabetes Mellitus?

- Retrospective analysis of KIGS data base
- Compared incidence of T1DM and T2 DM with available reference data
- 85 of 22,333 children (0.36%) reported with abnormal GT; 43 confirmed abnormal
- 11 turned out to have T1DM, 18 T2DM, 14 IGT
- Incidence of T1DM did not differ from expected population values
- Incidence of T2DM 34.4/100,000 GH Rx yrs was 6 fold higher than without GH Rx
- T2 DM did NOT resolve after GH Dc
- Conclusion: GH accelerates appearance of T2 DM in predisposed individuals

Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment


Safety and Benefits of Growth Hormone Therapy

Safety of Growth Hormone Treatment in Children Born Small for Gestational Age: The US Trial and KIGS Analysis

W.S. Cutfield', A. Lindberg', R. Rapaport', M.P. Wajcman', P. Swanger"

'Aglaia Analytics, University of Auckland, Auckland, New Zealand; "Section of Pediatrics, Affiliated Bronx College of Medicine, Children’s Hospital at Mott, New York, NY, USA

Conclusions: As expected, a reduction in insulin sensitivity occurred during GH treatment of children born SGA; however, glucose tolerance remained normal. No adverse events were reported more commonly in children born SGA than in those with ISS. Minor differences in adverse events reporting within organ systems between children born SGA and those with ISS are probably due to variable under-reporting of adverse events. GH appears to be a safe drug to use at current doses as a growth-promoting agent in short children born SGA.
Long-term safety of recombinant human growth hormone in children.

Between 1985 and 2006, the National Cooperative Growth Study (NCGS) monitored the safety and efficacy of recombinant human growth hormone (rhGH) in 54,996 children.

Thirty-three patients developed type 1 diabetes mellitus (DM) (37 expected; SIR, 0.90; 95% CI, 0.62-1.26). Type 2 DM and non-specified DM were reported in 20 and eight patients, respectively.

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**EFFECT OF FASTING AND REFEEDING ON SOMATOMEDIN-C**

Dietary Components that Regulate Serum Somatomedin-C Concentrations in Humans
William L Isley et al
SUMMARY OF METABOLIC EFFECTS OF GROWTH HORMONE (GH)

1. GH IS AN IMPORTANT REGULATOR OF CARBOHYDRATE, PROTEIN AND FAT METABOLISM

2. GH IS AN ESSENTIAL COUNTER-REGULATORY HORMONE TO PREVENT HYPOGLYCEMIA

3. GH INTEGRATES THE FUEL REQUIREMENTS FOR GROWTH, INCLUDING THE PUBERTAL GROWTH SPURT AND DURING PREGNANCY TO PREVENT FETAL HYPOGLYCEMIA

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Potential Consequences of No Treatment or Treatment Withdrawal in Adults With CO GHD

<table>
<thead>
<tr>
<th>Potential Consequences</th>
<th>Untreated</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stature</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Muscle and lean body mass</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bone mass and bone density</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Frequency of fractures</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fat mass (abdominal visceral fat)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Total cholesterol (total-C), low-density–lipoprotein cholesterol (LDL-C), and serum triglycerides</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>High-density–lipoprotein cholesterol (HDL-C)</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
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SOME NEWER METABOLIC FUNCTIONS OF GH
GHR DELETION IN LIVER VIA ALBUMIN PROMOTER-DRIVEN CRE

Control
GHRLD

Control
GHRLD

Control
GHRLD

Control
GHRLD

Control
GHRLD

Control
GHRLD

Control
GHRLD

Control
GHRLD

Control
GHRLD
Distinct GH receptor signaling modes regulate skeletal muscle development and insulin sensitivity in mice: J Clin Invest. 2010; 120(11):4007–4020

Mahendra D. Mavalli,1 Douglas J. DiGirolamo,1 Yong Fan,2 Ryan C. Riddle,1 Kenneth S. Campbell,3 Thomas van Groen,4 Hoang J. Tran,4,5 Mark A. Spiegel,2 Karyn A. Esser,3 Marcas M. Bamman,7 and Thomas L. Clemens1,8

• Strikingly, mice lacking GHR developed metabolic features that were not observed in the IGF-1R mutants, including marked peripheral adiposity, insulin resistance, and glucose intolerance. These results identify distinct signaling pathways through which GHR regulates skeletal muscle development and modulates nutrient metabolism.

Intermuscular infiltration of fat tissues in mice with muscle-specific GHR deletion
Effects of GHR deletion on WAT distribution at different depots. WAT was harvested from visceral (epididymal) and subcutaneous (subQ) sites from 8 to 10-week old female GHRFD and littermate controls. As shown, more WAT is accumulated at subQ site in GHRFD mice, compared to abdominal location which is the major fat depot in littermate controls.

![Graph showing the ratio of fat weight (visceral to subQ) for Control and GHRFD mice. P<0.02 control vs GHRFD.]

Aged GHRLD mice develop hepatocellular adenoma.

**IMPAIRED GROWTH HORMONE RESPONSES TO GROWTH HORMONE-RELEASING FACTOR IN OBESITY**

A Pituitary Defect Reversed with Weight Reduction

Timothy Wadsworth, M.D., Michael Boulton, M.D., Stephen N. Joyce, M.D.,
Michael G. Tommasi, M.B., Jean Roux, Ph.D., Wynne Vale, Ph.D.,
and Lawrence A. Thompson, M.D.

Abstract. To investigate whether the impaired growth hormone secretion associated with obesity is a result of a hypothalamic or a pituitary disorder and whether it is a cause or a consequence of obesity, we studied plasma GH levels and GH responses to growth hormone-releasing factor in normal obese patients before and after weight reduction by diet and exercise. A significant reduction in GH levels during measurement was observed in the group of patients studied postoperatively, whereas in patients studied preoperatively GH levels were comparable to normal levels. In contrast, the GH response to growth hormone-releasing factor was increased in normal levels before weight reduction, whereas in patients studied postoperatively, GH levels were not significantly different from normal levels. These findings support the hypothesis that the reduced GH response to growth hormone-releasing factor is a cause of obesity and that weight reduction reverses this defect. The observation that the GH response to growth hormone-releasing factor is increased in normal levels before weight reduction suggests that the decreased response to growth hormone-releasing factor may result from a pituitary disorder. Further studies are needed to determine the exact nature of this disorder and to determine the role of the pituitary in obesity.

CONCLUSIONS AND FUTURE DIRECTIONS:

1. GH SIGNALING IN LIVER IS AN IMPORTANT REGULATOR OF HEPATIC LIVER METABOLISM AND IS INVOLVED IN THE GENESIS OF NAFLD.

2. GH IS ESSENTIAL FOR NORMAL MUSCLE FORMATION AND FAT DISTRIBUTION PATTERNS.

3. OBESITY IS A STATE OF GH DEFICIENCY, BOTH IN TERMS OF SECRETION AND ACTION. HENCE, OBESITY-ASSOCIATED NAFLD MAY BE AMENABLE TO GH THERAPY.

REFERENCES:


Fan Y et al Evolution of hepatic steatosis to fibrosis and adenoma formation in liver-specific growth hormone receptor knockout mice Frontiers Endocrinol (Lausanne) 2014 Dec 18;5:218

Sperling MA. Long-term therapy with GH: Bringing Sagacity to SAGHE J Clin Endocrinol Metab. 2012 Jan;97(1):81-3

Fan Y et al Liver-specific deletion of the growth hormone receptor reveals essential role of growth hormone signaling in hepatic lipid metabolism J Biol Chem 2009; 284(30):19937-44

Mavalli MD et al Distinct growth hormone receptor signaling modes regulate skeletal muscle development and insulin sensitivity in mice J Clin Invest 2010 Nov;120(11):4007-20

Once we accept our limits, we go beyond them. 
Albert Einstein

BrainyQuote