The Skinny on Endocrine Mediated Weight Gain

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BMI Trend Predictions

$66\text{ Billion/year by 2030}$

$50\%$ (164 million) of US population by 2030

*Lancet 2011*

Factors Influencing Obesity

Our clinical understanding of obesity is constantly challenged by our molecular/in vitro understanding of endocrinology

- Endocrine and paracrine signaling of endocrine hormones /energy signaling

- Integrated sensors of metabolism require further understanding and allows for targeted therapies

- Adapted/maladapted counterregulatory responses re-define a broader perspective of endocrine mediated weight gain
Common Clinical Endocrinopathies

- Weight Gain
- Drugs
- Genetic
- Diabetes Mellitus Type 2 / PCOS
- Social/Diet
- Cushing’s
- Growth Hormone Deficiency
- Hypothyroidism
# Regulation of Metabolic Processes

<table>
<thead>
<tr>
<th>Anabolic ↑ I: G</th>
<th>Metabolic Process</th>
<th>Catabolic ↓ I:G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glycogen synthesis (liver and muscle)</td>
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<tr>
<td></td>
<td>Glycogen breakdown</td>
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<td></td>
<td>Gluconeogenesis</td>
<td>↑</td>
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<tr>
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<td>Fatty acid synthesis and triglycerides (hepatocytes and adipose tissue)</td>
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<td>Muscle protein synthesis</td>
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<tr>
<td></td>
<td>Lipogenesis and triglyceride formation</td>
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<tr>
<td></td>
<td>Lipolysis</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Free fatty acid oxidation</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Ketone body formation</td>
<td>↑</td>
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<tr>
<td></td>
<td>Muscle proteolysis</td>
<td>↑</td>
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</tbody>
</table>
Adipocyte: Integrated Energy Model

- Leptin
- Angiotensinogen
- Resistin
- C-reactive protein
- TNF–α
- PAI -1
- Serum Amyloid-A
- IL-6
- Estrogens
- Cortisol
- Adiponectin (ACRP-30)
- Visfatin

Does this patient have an endocrinopathy?

Amy is a 32 year old female.

CC: weight gain
Tempo: 35 pounds in 4 months

PMHx: Major Depression

SocHx: no exercise, specific diet, works 9 hours a day, single mother
Drinks 3 beers per week

FMHx: Autoimmune thyroid disease

Twin sister

Meds: health food store stuff

“Will I gain more weight”

“I know/I think it is my thyroid”

“I don’t eat that much”

“Is there a pill for me”
Clinical Rethinking of Weight Gain

Weight Gain

orexins
cholecystokinin
Agouti related peptide
NPY
glucagon
insulin
resistin
leptin
ghrelin
T3
TSH
ACTH
cortisol
Clinical Disorders of Hypothyroidism

- **Primary**
  - Overt (AI, RAI, etc)
    - TSH >10
  - Mild (MTF)
    - TSH 5-10
- **Secondary**
  - Pituitary
    - Free t4 and T3
- **Central**
  - Hypothalamic

Williams Textbook of Endocrinology, 11th ed
Thyroid Hormone Metabolism

3,5,3',5'-Tetraiodothyronine (thyroxine, T₄)

D₂, D₁ - I(5')
D₃, (D₁) - I(5)

3,5,3'-Triiodothyronine (T₃)

D₃, (D₁) - I(5)

3,3',5'-Triiodothyronine (reverse T₃)

-D₁, D₂ - I(5')

3,3'-Diiodothyronine
It has been clear for some time that thyroid function is not grossly impaired in most patients with obesity

• TSH “mildly elevated” in <20% of obese individuals

Emerson, Thyroid 2010
Kaptein et al., JCEM 2009
Michalaki, Thyroid, 2006
**Biochemical Hypothyroidism**

<table>
<thead>
<tr>
<th>Assertion of disease/therapy</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes excessive weight gain</td>
<td>Minimal : 5-7% of TBW</td>
</tr>
<tr>
<td>Weight gain will increase TSH</td>
<td>Maybe: is this disease or compensation?</td>
</tr>
<tr>
<td>T3 therapy in single or combination is needed</td>
<td>Clinical trials demonstrate poor outcomes</td>
</tr>
<tr>
<td>Continued symptoms with “normal” labs means continued hypothyroidism</td>
<td>No (mostly), yes (maybe)</td>
</tr>
</tbody>
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Thyroid Hormone and Obesity

• Is thyroid status disturbed in obesity?
  1. Are local thyroid hormone concentrations thyrotoxic (or in excess of what is appropriate)?
     - TSH and maybe free T4
     - i.e., does obesity cause TH resistance thus compensatory mild elevations of TSH and T4?
Is Obesity an Anthropometric Thyroidopathy?

Mild Thyroid Failure?

Versus

Inappropriate TSH secretion?

Emerson, Thyroid 2010
Kaptein et al., JCEM 2009
Relationship of BMI to TSH in MTF

DanThyrStudy

Knudsen, et al. JCEM 2005
Relationship of BMI to Free T4 in MTF

DanThyrStudy Knudsen, et al. JCEM 2005
Mild Thyroid Failure

• Modest increases in TSH have been associated with modest weight gain in adults (The DanTHyr Study)

• Framingham Offspring Study also demonstrated this phenomenon

• Treatment of MTF does not appear to be associated with weight loss

Knudsen, et al. JCEM 2005
Fox et al. Arch Intern Med 2008
Thyroid Disease as an Endocrinopathy

- orexins
- cholecystokinin
- Agouti related peptide
- NPY
- glucagon
- insulin
- resistin
- leptin
- ghrelin
- T3
- TSH
- ACTH
- cortisol
Serum T3 and Caloric Intake

- Fasting and caloric restriction
  - reduces free and total T3
  - rT3 levels remain the same

- Overfeeding normal weight or obese subjects
  - Increases free T3 levels

- T3 levels may be lower in dieting obese
- T3 levels may be elevated in non-dieting obese due to energy needed to maintain weight

- Conclusion: Food intake must be considered with interpretation of lab data

Glass, 1981
Thyroid Hormone and Appetite Regulation

• TH resistance associated with hyperphagic behavior
  – cocaine and amphetamine related transcripts (reduce food intake)
  – NPY (neuropeptide Y) increases in hyperthyroidism, increases appetite
  – Antagonism of NPY regulated by 5′ adenosine monophosphate-activated protein kinase (AMPK)
Thyroid Hormone and Appetite Regulation

Amin, J Thyroid Research, 2011
Thyroid Hormone and Appetite Regulation--Fasting

Amin, J Thyroid Research, 2011
Thyroid and Leptin

Feldt-Rassmussen, 2007, Thyroid
Thyroid Hormone and Ghrelin

- Ghrelin (unacylated): Anti-leptin action
  - Levels are low in obese state
  - Stimulates food intake and adiposity via activation of NPY and Agouti Related Peptide
  - Stimulates GH release
  - Levels are inversely related to T3 levels
  - Modulates insulin sensitivity
  - Effects islet cell survival and proliferation

Altinova, Thyroid, 2006
AMPK: Cellular Energy Sensor

Duntas, Clin Endocr, 2011
Energy Metabolism Regulator: Peroxisome Proliferator-activated receptor-γ coactivator-1α (PGC-1α)

Liang, Adv Physiol Edu, 2006
Thyroid: Miracle Cure or Scapegoat?
Thyroid: Miracle Cure or Scapegoat? however . . .

T₄/T₃
Simplified Clinical Tools

TSH

(0.5-5.0 mU/L)
Thyroid Hormone Actions/Targets

- Obesity-thermogenic
- Hypercholesterolemia
- Heart failure
- Impaired cognition
- Thyroid cancer
- Affective disorders

Ribeiro, Thyroid 2008
Williams Textbook of Endocrinology, 11th ed
Thyroid Hormone Actions/Targets

- Bone
- Heart
- Liver
- Muscle
- Brain

No FDA approved targeted therapies (yet): TRα/TRβ receptor
Thyroid Mimetics

• TRα/TRβ effects
  – Triatricol and 3,5-diiodothyropropionic acid (DIPTA)—worsened heart failure (increased HR and bone turnover)

• TRβ specific effects
  – Primary lipid lowering
  – Calorigenic effects
Thyroid Mimetics

- TRβ specific effects
  - Primary lipid lowering
    - Sobetirome – phase 1 22% reduction LDL-C
    - Eprotirome
      - LDL-C and Lp(a) reduction
      - Combo with statin in heterozygous FH
      - Combination with ezetimibe
      - Phase 3 trials under way soon...
Can we answer these questions?

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FMHx: Autoimmune thyroid disease

Twin sister

Meds: health food store stuff

“Will I gain more weight” maybe

“I know/I think it is my thyroid” maybe

“I don’t think I eat too much” maybe

“Is there a pill for me” maybe/not yet
Clinical Disorders of Hypercortisolism

• **Cushing’s Syndrome**
  – ACTH dependent
    • Pituitary
    • Ectopic ACTH/CRH
    • Macronodular adrenal hyperplasia
  – ACTH independent
    • Adrenal adenoma or carcinoma
    • PPNAH/Carney’s
    • iatrogenic

• **Pseudo-Cushing’s**
  – Alcholism
  – Depression
  – Obesity
Clinical Disorders of Hypercortisolism

Stressors (hypoglycemia, hypotension, surgery, fever, injury) → Circadian regulation → Hypothalamus → CRH → Vasopressin → Pro-inflammatory cytokines

CRH → ACTH → Adrenals → Cortisol

Leptin ↑ Food intake ↓ Energy expenditure ↑ Lipolysis ↓ Lipogenesis → Insulin sensitivity

IL-6 ↑ Food intake ↑ Energy expenditure ↓ Lipolysis ↓ Lipogenesis

TNF-α ↑ Food intake ↑ Energy expenditure ↓ Lipolysis ↓ Lipogenesis → Insulin sensitivity ↓ GLUT4 ↓ LPL

Angiotensinogen ↑ Angiotensin II ↑ Adipose blood flow ↓ Lipolysis ↓ Re-esterification

Insulin Resistance

Hypertension

Obesity

Hypertension

Hyperlipidemia

Adipsin/ASP ↓ Diacylglycerol acyltransferase ↓ Triglyceride synthesis ↓ Re-esterification

Growth factors

Preadipocyte recruitment ↑ Adipocyte number

Others

Williams Textbook of Endocrinology, 11th ed
Cushing’s or Pseudo-Cushing’s

- Central adiposity
- Supraclavicular fat pad
- Proximal muscle weakness
- Fatigue
- Hypertension
- Glucose intolerance
- Acne
- Hirsutism
- Menstrual irregularity

Williams Textbook of Endocrinology, 11th ed
Cushing’s or Pseudo-Cushing’s

Amy is a 32 year old female.

CC: weight gain
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PMHx: Major Depression

SocHx: no exercise, no specific diet, works 9 hours a day, single mother
Drinks 6 beers per week (report)—actual is 17

FMHx: Autoimmune hypothyroidism

Twin sister

Meds: health food store stuff (when asked directly)
Normal ACTH and cortisol dynamics

Increased pulse frequency and pulse amplitude in Cushing’s disease

Non-suppressability of cortisol

Williams Textbook of Endocrinology, 11th ed
Cortisol Metabolism in Obesity

Cortisone (inactive)

11 β hydroxysteroid dehydrogenase type 1

Cortisol (active)

• Cortisol levels are normal or reduced in obesity
• Cortisol levels determine fat distribution, especially visceral fat

• 11 b HSD-1 is impaired in obesity
• No known interaction with thyroid hormone or insulin function

Assumption: with increased cortisol activity, to maintain normal levels, then cortisol should have an increased net metabolic clearance rate

Stewart, JCEM, 1999
Tomlinson, JCEM, 2004
Yaniv, Intern J Obesity 2003
**HPA Axis: Alcohol**

- Alcohol influence on HPA axis based upon duration of intake with exact mechanism unknown

- Malnutrition and associated depression stimulate HPA axis simultaneously

- No direct stimulus to adrenal glands

- Appears to be related to hypersecretion of CRF with pituitary non-responsiveness

HPA Axis: Depression

Belmaker, NEJM 2008
HPA Axis: Depression

- Mild elevations of cortisol and ACTH are present

- ACTH and cortisol levels are significantly higher in those depressed patients who have not lost weight

- DST is not diagnostic, but non-suppression of cortisol post therapy for depression predicts poor prognosis
  - Suppression of neurogenesis
  - Hippocampal atrophy

Pfohl, et al. Biol Psychiatry 1985
Ribeiro, Am J Psychiatry. 1993
Cushing’s Screening

• Screening
  – 1 mg or 3 mg overnight dexamethasone suppression test
    • Cutoff >5 mcg/dl is positive (91% specificity)
    • Anticonvulsants can cause false positive (accelerate hepatic metabolism of dexamethasone)
    • Testing measures suppression of autonomous adrenal function

JCEM 93:1525-1540, 2008
Cushing’s Screening/Confirmatory Testing

• Confirmatory
  – 24 hour urinary free cortisol
  – Midnight salivary cortisol measurement
  – Serum ACTH and cortisol
  – 2 day 2mg dexamethasone suppression
  – Dexamethasone-CRH testing

  – Rec: 3.9: Repeat if needed . . .

JCEM 93:1525-1540, 2008
Diagnosis: Cushing’s Disease

*******NOTE********

Case is not typical, but illustrates complexity of clinical obesity:

• Genetics
• Endocrine impact
• Lifestyle
• Medications/Alcohol
• Psychiatric Health
• Diagnosis
• Therapy
Clinical Take Home Points

• Continue to leverage therapeutic lifestyle changes – We don’t get paid for it, but we are paying for it!

• Optimize thyroid hormone therapy – TSH (0.5-2.5 OR 1-2.5 mU/L based on age) – Use with empty stomach, water only – Am use or HS 2 hours post meal

• Consider concerns of potential MTF

• Be aware of your limitations clinically—avoid inappropriate “over-therapy”
Clinical Take Home Points

• Obesity phenotypes are difficult to distinguish from Cushing’s disease and Pseudo-Cushing’s
  – Muscular atrophy
  – Purple striae

• Correction of underlying confounders and patience with biochemical investigation, though extensive, can potentially be clinically rewarding (but slow)
Conclusions

• Weight gain is a greatly endocrine mediated condition, but not thyroid exclusively

• Complex milieu of interactions influencing the energy metabolism equation that exceed most clinical tools we have currently

• Thyroid hormone therapy is not the panacea of energy metabolism, but . . . an important part of it (and increasingly investigated)
Conclusions

• Our clinical understanding of obesity is constantly challenged by our molecular/in vivo understanding of endocrinology

  – Endocrine and paracrine signaling of endocrine hormones /energy signaling

  – Integrated sensors of metabolism require further understanding

  – Adapted/maladapted counterregulatory responses re-define a broader perspective of endocrine mediated weight gain