Why Obese People are Unable to Keep Weight Off After Losing It

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Chief Scientific and Medical Officer
American Diabetes Association
I have no Pertinent Financial Disclosures
DPPOS Results

Weight Loss

Change in weight (kg)

Placebo

Metformin

Years since DPP Randomization
LookAHEAD
Weight Loss in Diabetes

![Graph showing weight loss over time for DSE and ILI groups. The main effect is -4 (-5, -3), p<0.05.](image)
Why is body weight (fat mass) regulated?

UP
• Reproduction

• Environmental vicissitudes

DOWN
• Predator evasion

WAGES OF EVOLUTION
• Defense against loss of fat mass >> gain
RESEARCH SYMPOSIUM

Biologic Responses to Weight Loss and Weight Regain

April 26-28, 2013
Omni Shoreham Hotel
Washington, D.C.

The Mission of the American Diabetes Association is to prevent and cure diabetes and to improve the lives of all people affected by diabetes.
## Maternal Anthropometrics in Relation to % Body Fat in Children at Age 8

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1 (n=21)</th>
<th>Tertile 2 (n=21)</th>
<th>Tertile 3 (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child’s % Body fat (DXA)</strong></td>
<td>19.7±2.6</td>
<td>28.2±2.6</td>
<td>39.3±4.3</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Maternal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-gravid weight (kg)</td>
<td>64.8±15</td>
<td>66.2±13</td>
<td>84.4±26</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-gravid BMI (kg/m²)</td>
<td>23.5±6.1</td>
<td>23.9±4.0</td>
<td>30.8±9.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight Gain (kg)</td>
<td>14.2±6.9</td>
<td>14.3±5.7</td>
<td>11.6±7.6</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>13</td>
<td>15</td>
<td>10</td>
<td>ns</td>
</tr>
<tr>
<td>GDM</td>
<td>8</td>
<td>6</td>
<td>11</td>
<td></td>
</tr>
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</table>

Catalano; AJCN, 2009
## Metabolic Dysregulation in Children at Age 8

<table>
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<th>Tertile 3 (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child body fat by DXA (%)</td>
<td>19.7±2.6</td>
<td>28.2±2.6</td>
<td>39.3±4.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>55.3±5.0</td>
<td>62.0±6.8</td>
<td>72.0±8.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>105±8</td>
<td>109±5</td>
<td>114±13</td>
<td>0.01</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.5±0.5</td>
<td>2.2±1.1</td>
<td>3.4±1.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0.62±0.3</td>
<td>0.72±0.32</td>
<td>1.23±0.77</td>
<td>0.009</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>2.5±0.6</td>
<td>7.6±4.7</td>
<td>15.9±7.0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Catalano; AJCN, 2009
Adiposity at Birth Predicts Adiposity in Children at Age 8

Catalano; AJCN, 2009
In utero Programming of Obesity and Metabolic Dysfunction

- Insulin Resistance in pregnancy
- Obesity/GDM
- Metabolic Inflammation

Adult Metabolic syndrome
T2DM and Obesity

Fetal-Neonatal programming of Obesity

childhood obesity
? Pre-metabolic syndrome

Catalano, JCEM; 2003
An epigenetic basis for obesity and insulin resistance?

- Preconception stress
  - Demethylation and remethylation of the genome
  - Organogenesis
  - Heart development
  - Nephron number established
  - Rapid fetal growth and fat deposition

- Preimplantation period

- Early gestation
  - Heart
  - Risk of adult coronary heart disease

- Mid-gestation
  - Kidney
  - Greater incidence of renal disease

- Late gestation
  - Adipose tissue
  - Reduced weight at birth and altered intermediary metabolism

- Postnatal stress

- Obesity
  - Impaired glucose tolerance

optimizing preconception care for the overweight-obese woman

Contraception
Planned pregnancy

Diabetes
Hypertension
Dyslipidemia

Screening and/or control

Micronutrient/vitamins supplements

Diet

Optimizing weight

Regular exercise

Transdisciplinary - multi-specialty strategy
Metabolic Effects of Weight Reduction

Obese
50 kCal/kg LBM

Formerly-Obese
42 kCal/kg LBM

Never-Obese
50 kCal/kg LBM

- Hunger
- Cold intolerance
- Amenorrhea
- Leukopenia
Leptin Threshold Determines Response to Wt Loss

Signal Threshold Resistance: LEPR, MC4R, POMC, CPE, CB1R, AGRP, FTO/FTM, etc.
Wt-10% Decline in NREE is Reversed by Leptin

*P<0.05 compared to Wtinitial and Wt-10%lep
Bioenergetics of Reduced Body Weight

Calories per Day Needed to Maintain Weight

<table>
<thead>
<tr>
<th>Fat-Free Mass (kg)</th>
<th>Thin</th>
<th>Average</th>
<th>Heavy</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>500</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
</tr>
</tbody>
</table>

Leptin and weight loss markers indicated on graph.
Weight change during a 15-Year period in control group and surgery group

Weight Loss in RYGB-R Mice Despite Increased Food Intake

Liou et al., Science Transl Med 2013
Understanding Mechanisms of Weight Loss and Diabetes Resolution after Bariatric Surgery

Changes in brain function

Changes in signaling
GLP-1/2, PYY, CCK, ghrelin, metabolites, bacterial proteins, cytokines, bile acids, FGFs vagal & spinal afferents

Changes in food intake and choice

Changes in autonomic outflow

Dynamic adaptive changes in the gut
hypertrophy & hyperplasia motility, absorption, microbiome

Altered Gut

Surgery

Circulating & Neural Signals

Other Organs
Liver, Pancreas Adipose, Muscle

Medulla & Neural Signals

GLP-1/2, PYY, CCK, ghrelin, metabolites, bacterial proteins, cytokines, bile acids, FGFs vagal & spinal afferents

Energy Metabolism & Expenditure

Food Intake

Behavior

Weight Loss

Diabetes Resolution

Brain

Limbic

Hypothalamus

Brainstem

Physiol Behav 2011
ADA 2013
Central blockade of GLP-1 signaling increases body weight in both RYGB and sham-operated rats.

**Graph:**
- **Y-axis:** Bodyweight Gain (g)
- **X-axis:** Time from start of infusion (days)
- **Lines:**
  - Sham/Sal (n = 7)
  - RYGB/Sal (n = 8)
  - Sham/Ex9 (n = 8)
  - RYGB/Ex9 (n = 8)
- **Markers:**
  - + 5.9%
  - + 7.3%
- **Notes:**
  - Continuous infusion of Exendin-9 or saline
  - ADA 2013
Central blockade of GLP-1 signaling increases food intake and feed efficiency in both RYGB and sham-operated rats

- 24h food intake (kcal): +25% (+28%)
- Feed efficiency (weight gain/kcal): [Graph showing differences between conditions and statistical significance]
PYY-KO mice do not significantly decrease body weight after a modified bypass surgery

Chandarana et al. *Diabetes*, 2011
Conclusions

There is a contribution of GLP-1 (or combined GLP-1/GLP-2) signaling to the food intake and weight-reducing effects of RYGB, but it is not the critical factor.

We found no evidence for a role of central PYY/Y2R signaling.

So far we found no evidence for a role of vagal afferent signaling (selectivity).

Ghrelin is not required for VSG to be effective in mice (Chambers...Seeley, Gastroent 2012).

Thus:

None of the major hypothesized hormonal and neural mechanisms has so far received much support.

Given the complexity of gut-brain and other organ-signaling, it is perhaps naïve to think that one single mechanism is responsible for the beneficial effects of RYGB.
A Molecular Target for VSG: Bile Acids
14 Days Post Surgery

No Surgery, Sham, Sham PF, VSG

Bile Acid Concentration (μmol/L)

***=P<0.0001

Kohli et al., in preparation
Microbiome changes after VSG

Ryan et al., in review

Relative abundance of Roseburia in different groups:
- WT-sham
- WT-vsg
- KO-sham
- KO-vsg

Blood glucose (mg/dL)

Graph showing box plots with significance markers (*) and (**).
Mice colonized with microbiota from a **lean** donor

Mice colonized with microbiota from an **obese** donor

No significant difference in chow consumption, initial body fat, or initial weight

# Fecal Microbial Changes Relative to Obese Mice

<table>
<thead>
<tr>
<th>Microbial Changes</th>
<th>Diet-induced weight loss</th>
<th>RYGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firmicutes – Clostridiales</td>
<td>↓</td>
<td>↓ ↓ ↓</td>
</tr>
<tr>
<td>Firmicutes – Lactobacillus</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Firmicutes – Erysipelotrichales</td>
<td>No Δ</td>
<td>↓ ↓ ↓</td>
</tr>
<tr>
<td>Verrucomicrobiales</td>
<td>↑</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>Enterobacteriales</td>
<td>No Δ</td>
<td>↑ ↑ ↑ ↑</td>
</tr>
</tbody>
</table>

*Microbial changes after RYGBG differ from microbial changes after dietary weight loss*
Several Metabolic Outcomes of RYGB Appear Mediated by the Intestinal Microbiota

<table>
<thead>
<tr>
<th></th>
<th>RYGB</th>
<th>RYGB-Microbiota</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiposity</td>
<td></td>
<td></td>
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<tr>
<td>Food Intake</td>
<td></td>
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<tr>
<td>Blood insulin</td>
<td></td>
<td></td>
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<tr>
<td>Blood TGs</td>
<td></td>
<td></td>
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<tr>
<td>Energy Expenditure</td>
<td></td>
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</table>
Why is it so hard to keep weight off?

• Biology!
  – Genetics/Epigenetics
  – Leptin resistance/deficiency
  – Energy efficiency
  – ?Microbiota?

• Environment
ADA/J DRF RESEARCH SYMPOSIUM

Diabetes and the Microbiome

October 27-29, 2014 – Chicago, Illinois