ABDOMINAL OBESITY AND METABOLIC RISK

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Evolution of Man

+ =

[Image of human evolution from ape to modern man with a burger symbolizing the end result.]
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

2006

2008 U.S. Election Results
McCain

Obama
Increased Caloric Intake
Decreased physical activity

Other causes (?)
- Food environment
- Exercise environment
- Temperature regulation
- Medicines
- Associative sorting
- Infective agent
- Intrauterine environment
- Maternal age
- Sleep debt

Obesity, Nocturnal FFA

Insulin Resistance

Type 2 Diabetes

Beta-Cell Defect
# Animal models of obesity

<table>
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<tr>
<th>Model</th>
<th>Genetic Homology</th>
<th>Advantages</th>
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<tr>
<td>Mouse</td>
<td>~75%</td>
<td>Genetics</td>
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<tr>
<td>Rat</td>
<td>~85%</td>
<td>Physiological measures</td>
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<tr>
<td>Dog</td>
<td>~90%</td>
<td>Longitudinal studies</td>
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<td>Portal access</td>
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<tr>
<td>Monkey</td>
<td>~95%</td>
<td>Primate model</td>
</tr>
<tr>
<td>Human</td>
<td>100%</td>
<td>The real deal</td>
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</tbody>
</table>
Baseline Adiposity is Highly Variable

Unpublished data from the Bergman lab

n=82 dogs studied at baseline
High fat diet

Body Weight (kg)

Weeks on diet

Body Fat (cm³)

Obesity during Fat Feeding

Unpublished data from the Bergman lab

**Body Fat (cm³)**

- **Baseline**
  - Subcutaneous
  - Visceral

- **Fat Fed**
  - Subcutaneous
  - Visceral

**BW (kg)**

- **Dog #**

n=50 dogs pre/post 6 g/kg fat-supplemented diet for 6 wks
In SQ depot there was one major population with a lower mean size compared to VIS fat.

After 6 weeks of fat feeding, mean values of the major population increased and a minor population became evident.

Conclusion: Additional 16 weeks of fat feeding introduced another large adipocyte population. RIM prevent the occurrence of the large cell population, returning to pre-fat conditions.
In VIS depot at w-6 (pre-fat) there was one major and two minor populations.

3 distinct fat cell populations become evident, 2 major and one minor after 6 weeks of fat feeding.

Conclusion: After an additional 16 weeks of fat feeding 4 populations were still evident, but with higher mean sizes compared to w0. RIM completely eliminated multiple populations of cells, restoring adipocyte distribution to pre-fat conditions.
INFLAMMATION IN OBESITY

Gene Expressions of Inflammatory Factors
Visceral Adipose Tissue

- IL-6
- TNF-α
- IL-1β
- MCP-1
- CD68
- IL-10
- IL-1RA
- Adiponectin

Macrophage Infiltration - Immunostaining CD68

Subcutaneous Adipose Tissue
- Fat + PL

Visceral Adipose Tissue
- Fat + PL

Kabir et al., Diabetes. (in review)
Body Habitus and Metabolic Changes Associated with 6 Weeks of High Fat Feeding

Fasting Insulin
- Increase: 28%

Insulin Sensitivity
- Decrease: 32%

Insulin Clearance
- Decrease: 17%

Acute Insulin Response
- Increase: 40%

n=58 dogs for all except AIRg (n=36 dogs)
Changes with Fat Feeding – **HOMA-IR**

*(n = 36 dogs)*

**HOMA-IR**

[mU/mM]

![Graph showing changes with Fat Feeding](image)

- **Baseline** vs. **Fat Fed**
- **HOMA-IR** changes with Fat Feeding: **13%**
- **p=0.117**

Updated 9/16/10
Does Clearance Predict Insulin Sensitivity?

*(Clamp-based MCR and SI)*

**BASELINE**

(n=90 dogs)

**EFFECT OF FAT FEEDING**

(n=58 pre/post diet)

\[ y = 1.5826x + 1.0903 \]

\[ r = 0.51 \quad p < 0.0001 \]

\[ y = 2.0083x - 3.7364 \]

\[ r = 0.58; \quad p < 0.0001 \]

\[ y = 1.038x + 7.4451 \]

\[ r = 0.42; \quad p = 0.001 \]
Hypothetical Sequence of Events in Insulin Resistance with Fat Feeding (Nondiabetic)

- **Insulin Clearance**
- **FFA FLUX TO LIVER**
- **VISCERAL FAT**
- **FAT IN LIVER**
- **FAT DIET**
- **Insulin Resistance**
- **Hyperinsulinemia**
- **B-cell response**
- ↑**Nocturnal FFA**
Are FFA elevated in patients at risk for cardiometabolic disease?

Adapted from Succurro et al., *Obesity*. 2008

Adapted from Golay et al., *JCEM*. 1986
Role of FFA in Obesity-induced Insulin Resistance

*Basal FFA may not change, but Nocturnal FFA may increase!*
Following a high fat diet, overnight FFA are elevated

Kim et al., Am J Physiol Endocrinol Metab. 292:E1581, 2007
2-3 fold increase in FFA at night in Normal Individuals!
Enhanced by sleep deprivation

Broussard, Tasari and VanCauter, 2009 (ADA)
Hypothesis:

Nocturnal surge in FFA is responsible for insulin resistance in fat-fed obesity
HYPOTHESIS: THAT NIGHTTIME RELEASE OF FFA UNDER SYMPATHETIC CONTROL CAUSES HEPATIC INSULIN RESISTANCE
Effect of beta$_3$-blockade (bupranolol) on bursts of FFA release:

Saline control

beta$_3$-blockade

Plasma FFA levels with constant, or pulsatile FFA infusion

- **Saline**
- **Constant FFA**
- **Pulse FFA**

A.U.C., 0-60 MIN

Hsu et al., *Am J Physiol Endocrinol Metab.* 299:E131, 2010
Pulsatile FFA causes hepatic insulin resistance

Liver glucose output

Hsu et al., Am J Physiol Endocrinol Metab. 299:E131, 2010
Pulsatile FFA do exacerbate liver insulin resistance

Omentectomy reduces insulin resistance
Omectomy

Sham

0 2 4 6 8 10
Pre-Surgery Post-Surgery

*INSULIN SENSITIVITY

Change in Insulin Sensitivity by Individual
(*10^4 dL per min*kg*pM )

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<td>(+) 5.16</td>
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<td>Dog 5</td>
<td>(+) 2.47</td>
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<td>Dog 6</td>
<td>(+) 5.33</td>
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<td>Dog 5</td>
<td>(+) 6.09</td>
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<tr>
<td>Dog 6</td>
<td>(-) 3.08</td>
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</table>

Lottati et al., Obesity (Silver Spring). 17:674, 2009

OMENTECTOMY IN THE DOG INCREASES INSULIN SENSITIVITY
HYPOTHESIS: THAT NIGHTTIME RELEASE OF FFA UNDER SYMPATHETIC CONTROL CAUSES HEPATIC INSULIN RESISTANCE

“SNS Nocturnal Pulsatile Lipolysis”

GH
TSH, PTH
ANP
Glucocorticoids
“intrinsic lipolysis”

HEPATIC INSULIN RESISTANCE


**“SNS Nocturnal Pulsatile Lipolysis”**

- **HEPATIC INSULIN RESISTANCE:** Visceral Lipolysis
- **SKELETAL MUSCLE INSULIN RESISTANCE:** Inhibition of TET

- GH
- TSH, PTH
- ANP
- Glucocorticoids
  - “intrinsic lipolysis”
Increased Caloric Intake
Decreased physical activity
Other causes (?)
- Food environment
- Exercise environment
- Temperature regulation
- Medicines
- Associative sorting
- Infective agent
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- Maternal age
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Obesity, Nocturnal FFA

Insulin Resistance

Type 2 Diabetes

Beta-Cell Defect
Hyperbolic Law of Glucose Tolerance

Insulin Secretion $\times$ Insulin Sensitivity = Constant = Disposition Index (DI)

Bergman et al, JCI 1981
Reduction in the Disposition Index in Pimas destined to Type 2 diabetes

From Weyer, et al. JCI 104 1999
Effect of a Combination of Risk Alleles on Changes in Insulin Secretion and Sensitivity in the Botnia Prospective Study

A. Body-Mass Index
- Baseline vs. Follow-up
- Comparing ≥12 Risk alleles vs. ≤8 Risk alleles

B. Insulin Sensitivity
- Baseline vs. Follow-up
- Comparing ≥12 Risk alleles vs. ≤8 Risk alleles

C. Insulin Secretion
- Baseline vs. Follow-up
- Comparing ≤8 Risk alleles vs. ≥12 Risk alleles

D. Disposition Index
- Baseline vs. Follow-up
- Comparing ≤8 Risk alleles vs. ≥12 Risk alleles
Type2 diabetes prediction: DI compared to commonly used risk assessment tools

Clinical model trained on Inter99 uses age, waist, fasting glucose, triglycerides, HDL and total cholesterol
Bariatric surgery

RYGB (Roux-en-Y gastric bypass)

DJB (duodeno-jejunal bypass)

Bariatric surgery OGTT (n=2)
RESULTS – OGTT (insulin)
RYGB Improves Glucose Tolerance beyond weight loss

Does RYGB remove a gut factor which reduces glucose tolerance?

Does this factor normally prevent postprandial hypoglycemia?

Does it causes insulin resistance?

Does it reduce b-cell response (direct, or incretin)?

Does this factor act via portal receptors?
Effect of jejunal bypass on glucose tolerance in Type 2 diabetic dog model.

- FPG (mg/dl)
- FPI (pM)

Glucose (mg/dl) vs time (min)
Pathogenesis of Type 2 diabetes

Genetic Predisposition

Environmental Factors

Mystery Gut Factor

Genes

Insulin Resistance

Obesity

Normal \( \beta \)-cells

Hyperinsulinemia with Normal Glucose Tolerance

Impaired Glucose Tolerance

\( \geq 65\% \) \( \beta \)-cell defect

TYPE 2 DIABETES
Increased Caloric Intake
Decreased physical activity
Other causes (?)
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Obesity, Nocturnal FFA

Insulin Resistance

Type 2 Diabetes

Beta-Cell Defect
Inventor of the BMI index, 1830

Lambert Adolphe Jacques Quételet

\[ \text{BMI} = \frac{70 \text{ kg}}{(1.75 \text{ m})^2} = \frac{70}{3.0625} = 22. \]

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<th>Classification</th>
<th>Principal cut-off points</th>
<th>Additional cut-off points</th>
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<td>Obese class III</td>
<td>≥40.00</td>
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Men

R = 0.717
P < 0.001
\[ y = 0.91 \times -1.27 \]

Women

R = 0.763
P < 0.001
\[ y = 0.7 \times +17.51 \]

Bergman et al., *Obesity (Silver Spring)*. (under review)
<table>
<thead>
<tr>
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<th>pfat</th>
<th>hip</th>
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</table>

**Hip circumference and height had strongest correlations with percent fat**

Bergman et al., *Obesity (Silver Spring).* (under review)
\[ SBAI = \frac{\text{Hip}}{\text{Height}^\text{Power}} \]

Maxima: Power = 1.479399

Bergman et al., *Obesity (Silver Spring)*. (under review)
BODY ADIPOSITY INDEX

\[ BAI = \frac{\text{height}}{\text{hip} \sqrt{\text{hip}}} \]
Bergman et al., *Obesity (Silver Spring)*. (under review)
Bergman et al., *Obesity (Silver Spring)*. (under review)
Darko Stefanovski, Viorica Ionut, Marilyn Ader, Stella Kim, Morvarid Kabir, Edgardo Paredes, Rita Thomas, Joyce Richey, Yours Truly, Josiane Broussard, Cathryn Kolka, Ana Valeria Castro, (Malini Iyer)

Macedonia, Romania, New Yorkia, Los Angeles, Los Angeles, Paris, Syria, Detroit, Chicago, Maine, Tasmania, Brazil, Mumbai