Apple Shape or Pear Shape:
Bad Fat Good Fat

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What is the Problem?

- Obesity
- Diabetes
- Kidney Disease
- Depression
- Sleep Apnea
- Heart Disease
- High Blood Pressure
- Nerve Damage
- Fatty Liver
- Cancer
What is the Problem?

- Adipose tissue distribution is an important determinant of obesity-related comorbidities.
Four Types of Fat Distribution

- Lower Body Subcutaneous
- Abdominal Subcutaneous
- General Coverage
- Visceral
Abdominal Fat Deposition: Subcutaneous vs. Visceral

Estimation of abdominal fat compartments by bioelectrical impedance: the validity of the ViScan measurement system in comparison with MRI.
Thomas El, Collins AL, McCarthy J, Fitzpatrick J, Durighel G, Goldstone AP, Bell JD
Why is the apple bad?
Why is Visceral Fat Bad?

Location

Adipocyte Characteristics
Visceral Adipose Tissue Effluent

- Adipokines – adipose derived hormones
- Cytokines – immunomodulating agent
Adipokines and Adipose Derived Cytokines

• Adipokines
  – Leptin
  – Adiponectin
  – Resistin
  – Visfatin

• Cytokines
  – TNF-alpha
  – IL-6
  – monocyte chemoattractant protein 1
Visceral Adipose Tissue Effluent

- Adipokines – adipose derived hormones
- Cytokines – immunomodulating agent
- Free Fatty Acids, there is a constant flux of FFA entering and leaving the cells
  - Obesity induced decline in adipocyte function can interrupt the flux balance
Fatty Acid Trafficking

• Chronic exposure of the liver to elevated fatty acids (FA):
  – promotes liver gluconeogenesis
  – reduces enzymes of FA oxidation
  – increases hepatic lipogenesis
  – leads to increased liver triglyceride content (i.e., fatty liver)
  – insulin resistance develops

• Dysregulation of FA storage within adipose tissue provides a fundamental link among obesity and metabolic disease
Potential Consequences of Visceral Obesity

- Glucose Intolerance
- Inflammatory Responses
- Visceral Obesity
- Insulin Resistance
- NAFLD
- Dyslipidemia
Glucose Intolerance

- A state of hyperglycemia (elevated glucose)
  - High fasting glucose
- Associated with insulin resistance
- Measured with a glucose tolerance test
GLUCOSE TOLERANCE TEST (GTT)

1.) After an overnight fast the rodents tail is clipped.
2.) 0 minute baseline glucose measurement is collected.
3.) Rodent is injected with dextrose solution 2g/kg body weight
4.) Glucose is measured 15, 30, 45, 60 and 120 minutes after injection.
Insulin Resistance

- Cells fail to respond to the normal action of insulin
- Body produces insulin, cells become insulin resistant
- The hyperglycemia caused by impaired glucose uptake causes the pancreas to increase insulin release

Measure by
- Insulin tolerance test
- Liver pAKT/AKT
INSULIN TOLERANCE TEST (ITT)

1.) After an overnight fast the rodents tail is clipped.
2.) 0 minute baseline glucose measurement is collected.
3.) Rodent is injected with insulin 0.1mU/g body weight
4.) Glucose is measured 15, 30, 45 and 60 minutes after injection.
Measurement Of Tissue Specific Insulin Sensitivity
= Phosphorylated Akt (PKB)
Dyslipidemia

• Too high lipids in the bloodstream
  – Cholesterol
  – Triglyceride
  – Free Fatty Acids

• Lipid concentration is determined in portal plasma
Non-Alcoholic Fatty Liver Disease

• Multiple stages
  – 1.) Fat accumulation in the liver (steatosis)

• Measure triglyceride concentration in the liver

Normal Rodent Liver

High Fat Fed Rodent Liver
Inflammatory Responses

• Obesity is associated with a state of chronic low grade inflammation
• Obesity induces abnormal cytokine (immunomodulating agent) production
• Inflammatory factors are measured in the liver and portal plasma
Procedures to Answer My Experiment Questions

- Adipose Tissue Manipulation
  - Removal/Excision
  - Transplantation
    - Heterologous – Fat from a donor
    - Autologous – Fat Relocation
Adipose Tissue Manipulation via Transplantation and/or Removal

Intra-Abdominal Adipose Depots
Adipose Tissue Manipulation via Transplantation and/or Removal

Subcutaneous Adipose Depots
Game Of Operation

• Meet the patient
  — Cavity Sam
Is Visceral Adipose Tissue Bad Because of location?

- Three Groups
  - Visceral Adipose Tissue Removed
  - Non-visceral Adipose Tissue Removed
  - Sham Control

Portal Draining Adipose Tissue

Systemic Draining Adipose Tissue Removed
Portal Located Adipose Removal Induced Greatest Improvements
What was improved?

- Removal of intra-abdominal adipose tissue:
  - Glucose Tolerance
  - Liver inflammation
  - Dyslipidemia - Decreases hepatic lipid deposition

**All these improvements were greater following removal of portal draining adipose tissue**

Foster, Shi, Seeley, Woods Physiology and Behavior, 2011
Summary for Location Studies

- Nutrient release (effluent) from visceral adipose tissue has greater consequences on metabolic regulation
  - Due, in part, to the location of the depot
- Decreases in hepatic lipids may be due to decrease visceral lipid flux
- Reduction in Adipo/Cytokine release may also play a role
- Decreases in hepatic lipid likely plays a role glucose improvement
Is Visceral Adipose Tissue Bad Because of Intrinsic Characteristics?

• Two surgical models are used to investigate this experimental question:
  – Heterotransplantation – Removal of adipose tissue from a donor subject with subsequent transplantation to a recipient
  – Autotransplantation – Removal of adipose tissue from one location within a subject with subsequent relocation to another area
Is Visceral Adipose Tissue Bad Because of Intrinsic Characteristics?

Visceral Tissue Transplant

Donor

Non-Visceral Transplant
How do we verify that adipose transplants revascularize?
Blunt Dissection
Transgenic Mice Expressing GFP
Fluorescent Transplant Verification

GFP Transgenic Control

Mesenteric Transplant

Omental Transplant

Foster et al.,
Adipose Tissue Histology

Control

Transplant

Epididymal

Omental

Mesenteric

Foster et al.
Is Visceral Adipose Tissue Bad Because of Intrinsic Characteristic

- Hetero-transplantation of adipose tissue to the visceral cavity:
  - Surprisingly, increasing visceral adipose mass did not induce metabolic dysregulation
  - Non-visceral, not visceral, transplant improves glucose tolerance
  - Visceral transplant increases hepatic lipid deposition
Is Visceral Adipose Tissue Bad Because of Intrinsic Characteristics?

- Auto-transplantation of adipose tissue to the visceral cavity:
  - Improved glucose tolerance
  - Decreased insulin concentration
  - Decreased hepatic lipid deposition
  - Increased hepatic insulin sensitivity
  - Decreased hepatic lipoprotein lipase, fatty acid oxidation and cytokines
  - Inguinal relocation decreased adiposity
Adipose Depot Characteristics

Adipose Tissue as an Endocrine Organ

- Energy Balance
- Lipid Metabolism
- Insulin Sensitivity and Glucose Regulation
- Inflammation and Immunity
Cell-Autonomous Characteristics

- Lipid Regulation
  - Adipocyte Growth
  - Vasculature/Blood Flow
  - Triglyceride Uptake Rate
  - Triglyceride Hydrolysis/Release Rates
- Adipokine Secretion
- Cytokine Release
Subcutaneous

Circulating pool
Of substrates

Visceral

Cell-Autonomous Characteristics
Lipid Regulation

↓ vasculature
↓ Blood Flow

↑ α receptor
β receptor

HSL
TG

↑ SNS drive

Subcutaneous

Adipocyte

Visceral

TG Intake
LPL activity

VLDL

FFA

50% ↑

2 fold more

2-3 times higher

↑↑ FFA to portal circulation

↑↑ vasculature
↑ Blood Flow

↑ SNS drive

VLDL

Visceral

↑ SNS drive

HSL
TG

 α receptor

VLDL

50% ↑

TG Intake
LPL activity

VLDL

↑↑ FFA to portal circulation
Cell-Autonomous Characteristics
Adipokines

**Energy Homeostasis**

<table>
<thead>
<tr>
<th>Subcutaneous</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Leptin</td>
<td>166%</td>
</tr>
<tr>
<td>-Resistin</td>
<td>156%</td>
</tr>
<tr>
<td>-Visfatin</td>
<td>300%</td>
</tr>
<tr>
<td>-Adiponectin</td>
<td>113.32%</td>
</tr>
</tbody>
</table>

**Inflammatory Mediators**

<table>
<thead>
<tr>
<th>Subcutaneous</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>-TNF-α</td>
<td>50%</td>
</tr>
<tr>
<td>-IL-6</td>
<td>60%</td>
</tr>
<tr>
<td>-MCP-1</td>
<td>206%</td>
</tr>
</tbody>
</table>

Adapted From - Romero, MD. et al. Cardiovascular Diabetology 8:42,2009
Summary for Transplantation Studies

- Metabolic consequences resulting from diet-induced visceral obesity do not occur with transplantation of additional fat.
- An increase in intra-abdominal fat is not solely a risk factor for metabolic syndrome.
- Inherent cellular characteristics of non-visceral and visceral fat are dissimilar.
- Quality of adipose tissue is a bigger factor than quantity.
Why is the pear good?

Peripheral/subcutaneous adipose tissue is a “metabolic sink” storing lipids that could lead to disturbances in non-adipose tissue.

There, however, is a lack of direct evidence.
**Decreases in Subcutaneous Adipose Tissue**

- Previous Experiment - Removal of inguinal adipose tissue in HFD glucose intolerant mice
  - No alterations in glucose tolerance
  - No lipid or hepatic alterations
  - Portal plasma leptin increased
  - Portal plasma insulin increased
DeCREASES in Subcutaneous Adipose Tissue PART 2

- Removal of inguinal adipose tissue in lean mice maintained of chow or given HFD post-surgery
Decreases in Subcutaneous Adipose Tissue **PART 2**

- Removal of inguinal adipose tissue in lean mice maintained of chow or given HFD post-surgery
Decreases in Subcutaneous Adipose Tissue PART 2

- Removal of inguinal adipose tissue in lean mice maintained of chow or given HFD post-surgery

![Graph showing liver and muscle triglyceride levels](image)
Decreases in Subcutaneous Adipose Tissue \textit{PART 2}

- Removal of inguinal adipose tissue in lean mice maintained of chow or given HFD post-surgery
Summary for Peripheral Adipose Tissue Studies

• Studies support to the notion that peripheral adipose tissue functions as a “metabolic sink”

• Compensatory skeletal muscle triglyceride accumulation may not, in and of itself, have negative consequences on glucose homeostasis.
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