Pathophysiology of Obesity: Lipotoxicity

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Introduction

• Obesity is considered a disease
• Definition
  • Increased body weight caused by excessive fat
  • An amount sufficiently large to cause reduced health and longevity
• Obesity effects every organ system in the body
Medical Complications of Obesity

- **Pulmonary disease**
  - abnormal function
  - obstructive sleep apnea
  - hypoventilation syndrome

- **Nonalcoholic fatty liver disease**
  - steatosis
  - steatohepatitis
  - cirrhosis

- **Gall bladder disease**

- **Cancer**
  - breast, uterus, cervix, prostate, kidney
  - colon, esophagus, pancreas, liver

- **Stroke**

- **Coronary heart disease**

- **Diabetes**

- **Dyslipidemia**

- **Hypertension**

- **Idiopathic intracranial hypertension**

- **Gynecologic abnormalities**
  - abnormal menses
  - infertility
  - polycystic ovarian syndrome

- **Osteoarthritis**

- **Skin**

- **Gout**

- **Phlebitis**
  - venous stasis
Learning Objectives

• Define the pathological processes of obesity
  • Focus on lipotoxicity

• Discuss the importance of visceral fat and the metabolic effects of adipokines

• Describe the significance of ectopic fat with a focus on liver fat
Case Study

JW is a 52 year old male who is referred for MNT. He has a history of type 2 diabetes, hypertension, OSA, GERD, depression, knee arthritis, and obesity. He is having more shortness of breath with stair climbing and long distance walking.

Medications: metformin 1000 mg BID, glyburide 10 mg q d, metoprolol XL 200 mg q d, HCTZ 12.5 mg q d, ompeprazole 20 mg q d, paroxetine 40 mg q d, and Advil prn.

On exam, height is 70”, weight 244 lbs, BMI 35 kg/m², waist circumference 42”

Labs: glucose 125 mg/dl, HbA1c 7.0%, ALT 2x nl, AST nl
Why is obesity pathological?

- Lipotoxicity
- Increased mechanical burden
- Increased abdominal pressure
- Increased respiratory burden
- Fluid and hemodynamic changes/CV burden
- Dietary and physical activity changes associated with obesity
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Differentiating Fat Depots

Visceral fat

Subcutaneous fat
Waist Circumference Correlates With Visceral Adipose Tissue

The link between pathophysiology of obesity and associated comorbid conditions

**Ventral Adiposity**

- **Dyslipidemia**
  - Increased large VLDL
  - Increased small LDL
  - Increased LDL particles
  - Decreased large HDL

**Secreted Adipocyte Factors**

- **Dysfunction**
  - Vascular Reactivity
  - Dysfibrinolysis
  - Inflammation
  - Foam Cell

- **Insulin Resistance**
  - Glucose Intolerance

Lipotoxicity – Products of fat tissue

The link between pathophysiology of obesity and associated comorbid conditions

Inflammation

- TNFα
- TNF β
- IL6
- EGF

Arthritis

- Adiponectin

Asthma

- Adipose Tissue

Cancer

- Adipsin
- Resistin
- Leptin

Type 2 diabetes

- PAI-1

Stroke, Heart attack, PVD

- Angiotensinogen
- FFA
- Insulin
- prostataglandins

Hypertension

- Leptin

Dyslipidemia

- Estrogen

Thrombosis

Relationship between visceral adipose tissue and insulin action

![Graph showing the relationship between visceral adipose tissue volume per unit surface area (mL/m²) and glucose disposal (mg/kg LBM/min) for men and women. The graph indicates a negative correlation, with women generally having higher glucose disposal for a given visceral adipose tissue volume compared to men.](image)
Obese adipose tissue is characterized by macrophage infiltration and these macrophages are an important source of inflammation in this tissue.

**Illustration:** Wellen KE, Hotamisligil GS, *JCI* 2003 Dec;112(12):1785-8.

MCP-1 = monocyte chemoattractant protein-1

VEGF – vascular endothelial growth factor
Proof of concept that visceral adipose tissue (VAT) is the bad actor

Removal of subcutaneous fat had no effect on cardiovascular risk factors, inflammatory markers, and insulin resistance in obese women.

## Criteria for Metabolic Syndrome: 3 needed for diagnosis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>In US, men &gt;40 in, women &gt;35 in</td>
</tr>
<tr>
<td>Elevated TG (drug treatment for elevated TG is an alternate indicator)</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>Reduced HDL-C (drug treatment for reduced HDL–C is an alternate indicator)</td>
<td>&lt;40 mg/dL for men, &lt;50 mg/dL for women</td>
</tr>
<tr>
<td>Elevated BP (drug treatment for elevated BP is an alternate indicator)</td>
<td>Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg</td>
</tr>
<tr>
<td>Elevated fasting glucose (drug treatment for elevated fasting glucose is an alternate indicator)</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
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IDF, NHLBI, AHA, WHF, IAS, IASO Joint Statement on the Metabolic Syndrome
The lipid overflow ectopic fat model

- Normal adiposity
  - Energy-dense food (↑ fat + sugar content)
  - Lack of physical activity/exercise
  - Positive energy balance
    - Permissive neuroendocrine profile
      - Smoking
      - "Unfavorable" genotype
      - Maladaptive response to stress

- Subcutaneous obesity
  - "Healthy" adipose tissue
    - NO ECTOPIC FAT
      - Low liver fat and normal function
      - Low epicardial fat
      - Low muscle fat
    - Normal metabolic profile
      - Absence of metabolic syndrome clinical criteria

- Visceral obesity
  - Dysfunctional adipose tissue
    - LIPID OVERFLOW-ECTOPIC FAT
      - ↑ liver fat and altered function
      - ↑ epicardial fat
      - ↑ muscle fat (↑ intracellular lipids)
    - Altered metabolic profile
      - Presence of metabolic syndrome clinical criteria (including hypertriglyceridemic waist)
Fat topography:
“Overflow hypothesis of ectopic fat”
Ectopic liver fat

- Non-alcoholic fatty liver disease (NAFLD)
- When liver fat exceeds 5% of liver weight
- May present with increased liver function tests (ALT > AST)
- Clinically diagnosed by ultrasound

- Associated with increased risk of insulin resistance, type 2 diabetes and CVD
Subcutaneous adipose tissue

Visceral adipose tissue

~ 5-10% weight loss
~ 30% visceral adipose tissue loss (diet, physical activity, pharmacotherapy)

- Deteriorated
- Lipid profile

- Improved

- Impaired
- Insulin sensitivity
- Insulinaemia
- Glycaemia

- Improved

- Susceptibility to thrombosis

- Inflammation markers

- Improved

- Impaired
- Endothelial function

- Reduced obesity
- (low waist measurement)

Abnormally obese
(high waist measurement)

High
Risk of coronary heart disease

Low
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Summary of Key Learning Points

• Excess fat accumulation in ectopic depots (e.g., abdominal cavity, liver) leads to metabolic derangements throughout the body
• Visceral fat releases adipokines and other factors that are proinflammatory, prothrombotic and effect insulin sensitivity