Biologic Consequences of Obesity and Influences on the Development of Chronic Disease

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Obesity & Nutrition in a Changing World
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Learning Objectives

The learner will:

- Be able to give examples of obesity related co-morbidities
- Understand the primary functions of adipocytes
- Be able to describe key scientific points about how visceral adiposity and adipocyte dysfunction contribute to risk of chronic disease
- Discuss the significance of the metabolic syndrome for the health of children and adults
2010 Percent of Obese (BMI >30) in US Adults

2011 State Prevalence of Obesity among low-income children ages 2-4 years

CDC website accessed Sept 2012 – Obesity Trends
Overweight and Obesity

- Obesity is common
  - 35.7% of US adults are obese
  - 16.9% of youth are obese

- Obesity affects some groups more than others (JAMA 2012 307:491)
  - Age-adjusted rates by group:
    - Non-Hispanic black 49.5%
    - Mexican American 40.4%
    - All Hispanic 39.1%
    - Non-Hispanic white 34.3%
  - Effect of SES varies among groups

- Obesity-related medical conditions are among leading causes of preventable death; medical costs associated with obesity estimated to be $147 billion in 2008

CDC website accessed Sept 2012; 2009-2010 trend data
Understanding The Problem

- Obesity is multi-factorial

- Contributors to obesity:
  - Behavior and energy balance
  - Genetics
  - Environment
Overweight and Obesity

- Obesity: having an excess of adipose tissue (body fat), or a very high amount of body fat in relation to lean body mass
  - Obesity: Males >25% body fat, Females >33% body fat

- Indirectly Assessed by:
  - Waist circumference: high risk Men >102 cm (>40 inches), Women >88 cm (>35 inches)
  - Waist:hip ratio: high risk >1
  - Body Mass Index (BMI): high risk >30

\[
\text{BMI} = \frac{\text{weight in kg}}{\text{height in (m)}^2}
\]
## BMI-Associated Disease Risk

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk</th>
</tr>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese</td>
<td>I</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Very High</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

Body Fat Distribution

- Abdominal fat is a predictor of risk for obesity-related diseases
- BMI does not address body fat distribution

A. Central or upper body distribution
   - Android distribution
   - Visceral body fat
     - “Apple”

B. Lower body or gluteofemoral distribution
   - Gynoid distribution
     - “Pear”
Medical Complications of Obesity

- **Pulmonary disease**
  - abnormal function
  - obstructive sleep apnea
  - hypoventilation syndrome
- **Nonalcoholic fatty liver disease**
  - steatosis
  - steatohepatitis
  - cirrhosis
- **Gall bladder disease**
- **Gynecologic abnormalities**
  - abnormal menses
  - infertility
  - polycystic ovarian syndrome
- **Osteoarthritis**
- **Skin**
- **Gout**

- **Stroke**
- **Cataracts**

- **Coronary heart disease**
  - Dyslipidemia
  - Hypertension

- **Diabetes**
- **Severe pancreatitis**

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

- **Phlebitis**
  - venous stasis
Obesity related Co-Morbidities

- Central (visceral) adiposity is strongly and consistently related to metabolic risk of chronic disease.
- Lack of moderate to vigorous physical activity also related to metabolic risk…but visceral adiposity is more important.
- Risks of Diabetes and of Heart disease both are doubled in adults who are obese, compared with healthy weight.
- Children who are obese are also developing Diabetes & pre-Diabetes, as well as high blood pressure and high blood lipids – risk factors for Heart disease.
  - Approximately 1/3 of obese youth have these “adult” co-morbidities of obesity.
Biologic Consequences of Obesity in Children & Adults

- Understanding of metabolic and physiologic processes (and pathologic changes) that contribute to disease risk in adults continues to grow…but gaps exist in our understanding of their roles during childhood
  - It is unclear whether the metabolic and disease processes related to obesity are exactly the same in children as in adults
  - It is unclear to what extent the pediatric disease risk predicts adult disease risk (a strong relationship exists for childhood obesity, adult obesity and metabolic diseases…but unknowns are still present)

- The consequences of excess adiposity are related to development of disease, and the function of the adipose cell is central to the biologic effects…
Adipocytes: More than just Fat Droplets

- Adipocytes contribute to energy homeostatic mechanisms
- 2 main functions:
  - Lipid (TAG) storage & mobilization
    - Tightly regulated by hormones
  - Endocrine functions
    - Adipokines & cytokines are secreted (adiponectin, leptin, TNFa, IL-1, IL-6, etc.)
- Size & location matter
  - Visceral adipose
- Play a role in pathology of obesity-related chronic diseases
- Early environment (prenatal) can influence adipogenesis & impact adipocyte function in adulthood
Adipocyte Development

- **Hypertrophy** (enlargement) – overweight (BMI 25-29.9) and moderate obesity (BMI 30-34.9) characterized by adipocyte hypertrophy

- **Hyperplasia** (increase in number) – extreme obesity (BMI >40) characterized by hyperplasia as well as hypertrophy
Adipocyte Hypertrophy - When Inflammation Happens

Increased Nutrient influx

Adipose hypertrophy and hyperplasia allow adipose tissue to grow

Activated macrophages block preadipocyte recruitment and worsen insulin resistance in mature adipocytes, increasing FFA release and macrophage activation

Larger adipocytes secrete macrophage-attracting chemokines

Chemokines

Cytokines

FFA

Virtue S and Vidal-Puig A; Biochim Biophys Acta. 2010 Mar;1801(3):338-49.
Adipokines

Marra F and Bertolani C; Hepatology. 2009 Sep;50(3):957-69
Fig. 3. The adipocyte overflow hypothesis puts forward the notion that excess lipid accumulation within an adipocyte causes lipid "overflow" and ectopic fat deposition in surrounding tissue. This increases an individual's risk of developing metabolic diseases such as cardiovascular disease and Type 2 diabetes (Tsakos et al., 2007). Lipid "overflow" is often seen in obese individuals, while factors such as lifestyle may contribute to the onset of obesity, and thus lipid overflow. It is also now understood that the maternal environment encountered in utero can contribute to the development of adult-onset obesity. It is hypothesised that individuals with low adipocyte endowment or adipocytes with limited lipid storage capacity may be more susceptible to obesity-related diseases because they experience "overflow" at a lower level of body fat than individuals with more adipocytes.
COMMENTARY
Adipose tissue inflammation and insulin resistance: all obese humans are not created equal
Marie-Soleil GAUTHIER*† and Neil B. RUDERMAN‡

Figure 1  Link between abnormalities in WAT (white adipose tissue) and other organs and diseases associated with the metabolic syndrome
Bringing it all together…

Obesity: Adipocyte Dysfunction & Related Metabolic Consequences

- **Adipocyte dysfunction**
  - Macrophage infiltration, inflammation, ER stress, ↑FFA released leading to →↑lipoproteins circulating &↑ectopic fat deposition

- **Adipokines**
  - Changes in levels secreted, affecting appetite regulation, inflammation & insulin resistance

- **Mitochondrial dysfunction & oxidative stress**
  - ↑ oxidative stress, ↑redox intracellular signaling pathways, ↑insulin resistance

- **Inflammation**
  - ↑CRP, ↑cytokines, promoting atherosclerosis process

- **Hemostasis & thrombosis**
  - ↑inflammation linked to prothrombotic state

- **Insulin Resistance**
  - Influenced by multiple processes as above, evident in fat tissue, liver & muscle

- **Crosstalk at the molecular, cellular & organ levels**
  - Common gene transcriptional network influenced by all of above, lifestyle factors (diet) can affect gene expression
Visceral Adiposity, Insulin Resistance & Metabolic Dysregulation

Fig. 2 Relationships between twenty-first century lifestyle, non-alcoholic fatty liver disease (NAFLD), whole body insulin resistance and cardiovascular disease (CVD). A twenty-first century lifestyle is associated with physical inactivity and excess dietary carbohydrate and fat intake. In the presence of whole body insulin resistance, there is a predisposition towards storage of excess dietary calories as triglyceride in ectopic visceral sites, rather than peripheral subcutaneous adipose tissue depots. Accumulation of fat in ectopic visceral tissues such as the liver exacerbates insulin resistance in hepatic tissue, compounding the problem and creating a positive feedback loop driven by continuing physical inactivity and excess dietary carbohydrate and fat intake. The development of NAFLD may contribute to development of CVD through a variety of mechanisms that include increased inflammatory and metabolic stress, disturbances of triglyceride-rich lipoprotein metabolism (that causes decreased high-density lipoprotein cholesterol concentrations) and release of pro-coagulant factors.
Metabolic Syndrome (MetS)

A condition which is a constellation of several risk factors. All of the risk factors reflect similar underlying physiologic processes. Regardless of which risk factors are combined, the net result is that the MetS condition significantly increases the risk of the individual developing Diabetes and/or Cardiovascular disease.

- Current US population
  - ~66% overweight or obese (BMI ≥25+)
  - ~36% obese (BMI ≥30)

- NHANES 2003-2006
  - Using NCEP/ATP III criteria
    - Adults >20 years
    - Meet criteria for metabolic syndrome: ~34%

- MetS definition: 3 or more of the following:
  - Abdominal obesity:
    - men waist >40in (>102cm)
    - women waist >35in (>88cm)
  - Raised blood Triglycerides
    - TG ≥150 mg/dL
  - Low HDL (the good cholesterol)
    - low HDL cholesterol (M<40 mg/dL, W<50 mg/dL)
  - High blood pressure
    - ≥135 / ≥85 mg Hg
  - High blood glucose
    - Fasting glucose ≥100 mg/dL
The Metabolic Syndrome: Definition, Global Impact, and Pathophysiology

Matthew V. Potenza, MD¹; and Jeffrey I. Mechanick, MD²

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Table 1. Criteria for Diagnosis and Definitions of Risk Factors for the Metabolic Syndrome, According to the World Health Organization (WHO) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>WHO</th>
<th>NCEP ATP III</th>
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<tbody>
<tr>
<td>Criteria for diagnosis</td>
<td>T2DM or IGT¹ plus 2 or more risk factors</td>
<td>Any 3 risk factors</td>
</tr>
<tr>
<td>Obesity</td>
<td>Waist-hip ratio &gt;0.9 (male) or &gt;0.85 (female), and/or BMI &gt;30</td>
<td>Waist circumference &gt;40 in (male) or &gt;35 in (female)</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>≥150</td>
<td>≥150</td>
</tr>
<tr>
<td>Serum high-density lipoprotein (mg/dL)</td>
<td>&lt;35 (male), &lt;39 (female)</td>
<td>&lt;40 (male), ≤50 (female)</td>
</tr>
<tr>
<td>Hypertension (mm Hg)</td>
<td>≥140/90</td>
<td>≥130/85</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>No number given, use different measures of insulin resistance</td>
<td>≥100</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30 mg albumin/g creatinine</td>
<td>Not used</td>
</tr>
</tbody>
</table>

BMI, body mass index; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

*IGT = 75 g oral glucose tolerance test (2 h postload plasma glucose ≥140-199).

Figure 1. Worldwide prevalence of the metabolic syndrome.

*Obesity criteria adjusted to waist circumference appropriate for Indian population.
Risk Factors for MetS

- **Heredity**
  - Familial genetic influences $\uparrow$CVD risk & Insulin resistance

- **Ethnic Differences**
  - *Pima Indians* example, differences among White, Black and Hispanic populations

- **Lifestyle Behaviors**
  - Television watching habits –
    - *children* $\uparrow$TV $\rightarrow$ $\uparrow$risk overweight
  - Physical activity-
    - positive metabolic effects of PA, likely mediated in part through weight
  - Dietary intake-
    - diet patterns, whole grains, F/V, nutrients & other food components
Treatment for Metabolic Syndrome

- **Lifestyle change**
  - Emphasis on weight reduction
  - Increased physical activity

- **Drug therapy to target specific risk factors**
  - Such as statins for dyslipidemia, hypoglycemic agents to bring blood glucose (HgA1c) to guideline target, and medications to reduce hypertension

*Effective strategies for prevention of obesity & for health promotion are needed at all levels!!*
Summary

- Word Cloud for obesity & MetS
Thank You!