Obesity I: Overview and Molecular and Biochemical Mechanisms

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Adjunct Faculty, UC Hastings College of the Law
“Exclusive” view of obesity and metabolic dysfunction

260 million adults in U.S.

110 million
Obese (42.4%)

150 million
Normal weight (57.6%)

Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm
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260 million adults in U.S.

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Obese and sick (80% of 42.4%)

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“Exclusive” view of obesity and metabolic dysfunction

260 million adults in U.S.

110 million
Obese (42.4%)

150 million
Normal weight (57.6%)

86 million
Obese and sick (80% of 42.4%)

90 million
NL weight and sick (60% of 57.6%)

Total: 176 million sick

Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm
Relation between visceral and subcutaneous obesity: **TOFI** (thin on the outside, fat on the inside)

THE LITTLE WOMEN OF LOJA — GROWTH HORMONE–RECEPTOR DEFICIENCY IN AN INBRED POPULATION OF SOUTHERN ECUADOR

ARLAN L. ROSENBLOOM, M.D., JAIME GUEVARA AGUIRRE, M.D., RON G. ROSENFELD, M.D., AND PAUL J. FIELDER, PH.D.

The Little Women of Loja are obese yet insulin sensitive

Table 1. Anthropometric Data, Lipid Metabolism, Carbohydrate Metabolism, and Insulin Sensitivity Measures for 35 Controls and 27 GHRD Subjects

<table>
<thead>
<tr>
<th>Carbohydrate metabolism, adipocytokines</th>
<th>Controls</th>
<th>GHRD</th>
<th>P</th>
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<tbody>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>93.2 (22.4)</td>
<td>88.6 (10.6)</td>
<td>.34</td>
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<td>Postprandial glucose, mg/dL</td>
<td>94.1 (35.4)</td>
<td>77.1 (13.4)</td>
<td>.027</td>
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<td>Fasting insulin, μU/mL</td>
<td>13.6 (15.5)</td>
<td>4.29 (0.74)</td>
<td>.0034</td>
</tr>
<tr>
<td>HOMA2%B</td>
<td>141 (103)</td>
<td>90 (48)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HOMA2%IR</td>
<td>108 (87)</td>
<td>261 (133)</td>
<td>.0255</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>10.36 (5.24)</td>
<td>7.32 (4.7)</td>
<td>.0212</td>
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<td>Adiponectin, mg/L</td>
<td>6.92 (4.41)</td>
<td>9.94 (4.84)</td>
<td>.0128</td>
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<td>HMW adiponectin, mg/L</td>
<td>4.29 (2.89)</td>
<td>7.59 (4.07)</td>
<td>.0004</td>
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</table>

Abbreviations: SDS ht, SD score for height; C, cholesterol. Data are shown as mean (SD). Conversion factors: glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; LDL and VLDL to mmol/L, multiply by 0.0259; TGs to mmol/L, multiply by 0.0113.
The Little Women of Loja are obese yet insulin sensitive

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<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>39.8 (13)</td>
<td>34.5 (11)</td>
<td>.09</td>
</tr>
<tr>
<td>SDS ht</td>
<td>-1.7 (1.2)</td>
<td>-7.4 (1.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4 (4.4)</td>
<td>27.6 (5.6)</td>
<td>.16</td>
</tr>
<tr>
<td>AV Fat</td>
<td>1.08 (0.18)</td>
<td>1.97 (0.09)</td>
<td>.79</td>
</tr>
<tr>
<td>% Fat</td>
<td>41.1 (6.6)</td>
<td>47.7 (8.9)</td>
<td>.0014</td>
</tr>
<tr>
<td>LF</td>
<td>1.48 (0.47)</td>
<td>1.18 (0.48)</td>
<td>.016</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total C, mg/dL</td>
<td>199 (43.9)</td>
<td>229 (47.3)</td>
<td>.0124</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>43.5 (13.7)</td>
<td>50.9 (12.8)</td>
<td>.034</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>4.87 (1.33)</td>
<td>4.65 (1.10)</td>
<td>.49</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>123.1 (37.5)</td>
<td>157.6 (37.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Apo A, g/L</td>
<td>1.24 (0.23)</td>
<td>1.34 (0.23)</td>
<td>.0007</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>0.95 (0.24)</td>
<td>1.085 (0.23)</td>
<td>.029</td>
</tr>
<tr>
<td>VLDL, mg/dL</td>
<td>31.5 (18.7)</td>
<td>20.2 (7.6)</td>
<td>.0044</td>
</tr>
<tr>
<td>TGs, mg/dL</td>
<td>158.3 (95.3)</td>
<td>100.7 (37.8)</td>
<td>.0001</td>
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**Carbohydrate metabolism, adipocytokines**

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<td>0.59 (0.51)</td>
<td>.0025</td>
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<td>Leptin, mg/mL</td>
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Familial Partial Lipodystrophy,
Dunningan or Type 2

- X-linked or autosomal dominant
- Absence of limb fat
  - Easily visible veins
  - Defined musculature
- Normal or excess facial fat
- Cushingoid facies (moon facies)
- Dorsocervical fat pad
- Acanthosis nigricans
- Severe metabolic syndrome
Three fat depots
Three fat depots

1. Subcutaneous fat
The standard model of insulin resistance
The standard model of insulin resistance
The standard model of insulin resistance

- Decreased Insulin Sensitivity
- Increased Portal FFA
- Cytokines
- Islet Cells
- Decreased Glucose Uptake
- Hyperinsulinemia
- Increased Hepatic Gluconeogenesis
- Liver
- Decreased Hepatic Insulin Uptake
- Hyperinsulinemia
- Increased Peripheral Insulin Resistance
- Skeletal Muscle
- Fat
- Further Hyperinsulinemia

Source: Clin Endocrinol © 2005 Blackwell Publishing
Relationship between BMI and insulin sensitivity (N=220)

Insulin sensitivity/resistance is more determinant of morbidity and mortality than obesity/normal weight

Meigs et al. J Clin Endocrinol Metab 97:2906, 2006
Calgori et al. Diab Care 34:210, 2011
Three fat depots

1. Subcutaneous fat
2. Visceral fat
Visceral fat is due to chronic stress.

Acute stress (norepi): Brown adipocytes, Lipolysis, NE, β-ADR, thermogenesis, Burn fat, loose weight.


Zukowska, Science 2008
Three fat depots

1. Subcutaneous fat
2. Visceral fat
3. Ectopic (liver, and to some extent muscle) fat
Histology of (N)AFLD

Normal

(N)AFLD
NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances

Mazen Noureddin MD, MHSc, Aarshi Vipani MD, Catherine Bresee MS, Tsuyoshi Todo MD, Irene K. Kim MD, Naim Alkhouri MD, Veronica Wendy Setiawan PhD, Tram Tran MD, Walid S. Ayoub MD, Shelly C. Lu MD, Andrew S. Klein MD, Vinay Sundaram MD & Nicholas N. Nissen MD

The American Journal of Gastroenterology (2018) | Download Citation
NAFLD is a worldwide problem, even in normal weight people

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Mode of diagnosis</th>
<th>NAFLD prevalence BMI &lt;25</th>
<th>NAFLD prevalence BMI &gt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younossi et al.2012</td>
<td>United States</td>
<td>11,613</td>
<td>Ultrasound</td>
<td>9.6%</td>
<td>28.8%</td>
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<tr>
<td>Xu et al.2013</td>
<td>China</td>
<td>6,905</td>
<td>Ultrasound</td>
<td>7.2%</td>
<td>Not studied</td>
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<tr>
<td>Das et al.2010</td>
<td>India</td>
<td>1,911</td>
<td>Ultrasound/CT</td>
<td>5.1%</td>
<td>31.7%</td>
</tr>
<tr>
<td>Kwon et al.2012</td>
<td>Korea</td>
<td>29,994</td>
<td>Ultrasound</td>
<td>12.6%</td>
<td>50.1%</td>
</tr>
<tr>
<td>Bellentani et al.2000</td>
<td>Italy</td>
<td>257</td>
<td>Ultrasound</td>
<td>16.4%</td>
<td>75.8%</td>
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<tr>
<td>Sinn et al.2012</td>
<td>Korea</td>
<td>5,878</td>
<td>Ultrasound</td>
<td>27% (BMI 20-25)</td>
<td>Not studied</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16% (BMI &lt;20)</td>
<td></td>
</tr>
<tr>
<td>Wei et al.2015</td>
<td>Hong Kong</td>
<td>911</td>
<td>Magnetic Resonance</td>
<td>19.3%</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

Kumar and Mohan, J Clin Trans Hepat 5:216, 2017
Liver fat is a driver of diabetes, even in normal weight people

Adolescent NAFLD and future risk for diabetes
\[ RR = 2.59 \]

Bardugo et al. J Clin Endocrinol Metab. 109:e34, 2021
Obese
Low Liver Fat = 2.6%
Obese
Low Liver Fat = 2.6%
Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%
Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%

Normal Weight
High Liver Fat = 23%
Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%

Normal Weight
High Liver Fat = 23%
MRI Fat Fraction Maps

Obese
Low Liver Fat = 2.6%
Fat Healthy

Obese
High Liver Fat = 24%
Fat Sick

Normal Weight
High Liver Fat = 23%
Thin Sick
A different model of insulin resistance

The liver is the primary fat depot
A different model of insulin resistance

The liver is the primary fat depot
A different model of insulin resistance

The liver is the primary fat depot
Both adipose tissue and liver transcription factors promote fat cell differentiation.

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<th>Adipose Tissue Transcription Factors</th>
<th>Abbreviation</th>
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<tr>
<td>Peroxisome proliferator-activated receptor gamma (heterodimer with RXR)</td>
<td>PPARγ</td>
</tr>
<tr>
<td>Peroxisome proliferator-activated receptor alpha</td>
<td>PPARα</td>
</tr>
<tr>
<td>Peroxisome proliferator-activated receptor beta/delta</td>
<td>PPARβ/δ</td>
</tr>
<tr>
<td>Retinoid X receptor (heterodimer with PPARγ)</td>
<td>RXR</td>
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<td>Liver X receptor</td>
<td>LXR</td>
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<tr>
<td>Pregnane X receptor</td>
<td>PXR</td>
</tr>
<tr>
<td>Constitutive androstan receptor</td>
<td>CAR</td>
</tr>
<tr>
<td>Farnesoid X receptor</td>
<td>FXR</td>
</tr>
<tr>
<td>Aryl hydrocarbon receptor</td>
<td>AhR</td>
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# Endocrine hormone receptors promote energy deposition and fat cell growth

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<tr>
<td>Insulin receptor</td>
<td>IR</td>
</tr>
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<td>Estrogen receptors</td>
<td>ER (α, β)</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>AR</td>
</tr>
<tr>
<td>Glucocorticoid receptor</td>
<td>GR</td>
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<tr>
<td>Thyroid hormone receptors</td>
<td>TR (α, β)</td>
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Endocrine control of metabolism
Insulin blocks leptin signaling – “brain starvation”
Fetal origins of obesity

1. Small for gestational age and developmental programming
2. Large for gestational age and epigenetics
3. Prenatal stress and glucocorticoids
4. Environmental exposures (e.g. DDE, BPA, PFAS, fructose)