Obesity and Fat Metabolism in HIV-infected Individuals Workshop

Fat types, distribution, sex differences, age differences, racial and ethnic differences

Aaron M. Cypess, MD, PhD, MMSc

Investigator and Acting Chief, Translational Physiology Section Diabetes, Endocrinology, and Obesity Branch, NIDDK, NIH

May 22, 2018
Too Much Fat is Highly Morbid

Obesity (BMI ≥30 kg/m²)

1994

2000

2007

Diabetes

1994

2000

2007

At Least Two Types of Fat

White (WAT)
- Energy storage
  - 50g contains 300-500 kcal

Brown (BAT)
- Energy expenditure
  - 50g consumes 5 → 750 kcal/day

❖ Cold-induced [NST]
❖ Diet-induced [DIT]

Uncoupling Protein-1 [UCP1]
Thermogenesis

Brown and Beige/Brite Fat

**Structure**

➢ Predominantly in specific regions of the body.

➢ We can measure it non-invasively via PET/CT.

**Function**

➢ Protects against cold acutely [NST].

➢ People with detectable brown fat are more frequently female, younger, leaner [DIT?], and not taking beta-blockers.

➢ Nearly every adult human has brown fat.

References:

WAT as an Endocrine Organ

- Lipid metabolism and energy storage
  - lipoprotein lipase
  - acylation stimulating protein
  - angiopoietin like protein 4

- Hematopoiesis
  - leptin

- Modulation of immune system
  - interleukin 6 and 8
  - monocyte chemoattractant protein-1
  - migration inhibitory factor
  - leptin
  - resistin
  - adiponectin

- Angiogenesis
  - vascular endothelial growth factor
  - leptin
  - angiopoietin-2
  - adiponectin

- Energy homeostasis and metabolism
  - leptin
  - adiponectin
  - visfatin
  - interleukin 6
  - tumour necrosis factor-α

- Bone metabolism
  - leptin
  - adiponectin
  - interleukin 1 and 6
  - tumour necrosis factor-α

- Steroid hormones conversion
  - 11β-hydroxysteroid dehydrogenase type 1

- Coagulation and fibrinolysis
  - plasminogen activator inhibitor-1
  - leptin

- Vasoconstriction/vasorelaxation
  - nitric oxide
  - prostaglandin E₂
  - angiotensin II
  - asymmetric dimethylarginine
  - adrenomedullin
  - adiponectin
  - hydrogen sulfide
  - angiotensin 1-7
  - omentin
  - visfatin
  - leptin
  - resistin

- Kidney function
  - leptin
  - adiponectin

- Sexual maturation
  - leptin

Adamczak M, Wiecek A. Semin Nephrol. 2013;33:2
WAT Pathophysiology

Lake JE...Erlandson KM. Clin Infect Dis. 2017;64:1422
Potential Endocrine Roles for BAT

- **De novo lipogenesis** decreases
- **Hepatic steatosis** decreases
- **Insulin sensitivity** increases

**Adipose tissue**
- Inguinal
- Epididymal
- BAT

**Circulation**
- Exosomal miRNAs
- miR-99b
- Others
- Liver
- FGF21
- Muscle
- Other

**Target tissues**
- Liver
- FGF21
- Muscle
- Other

**Acute**
- Lipolysis & Ephx1/2 activity
- 12,13-diHOME
- Cold/Norepinephrine

**Chronic**
- Ephx1/2 transcription
- CD36c FATP1c
- CD36m FATP1m
- Fatty acid uptake

**Brown adipocyte**

**References**
- Thomou T...Kahn CR Nature 2017;542:450
- Stanford KL...Goodyear LJ Cell Metab 2018;27:1111
Human WAT Distribution

- **Subcutaneous adipose tissue (SAT)** = (a) abdominal, (g) gluteofemoral, (h) intramuscular
- **WAT is also found in the visceral adipose tissue (VAT)** = (b) omental, (c) mesenteric, (d) retroperitoneal, (e) gonadal, (f) pericardial

Chusyd DE...Nagy TR. Front Nutr. 2016;3:10
1. *Cervical* C3 → C7
2. *Supraclavicular* C7 → T3
3. *Axillary* T3 → T7
4. *Anterior Mediastinal* T1 → T10
5. *Paraspinal* T1 → T12
6. *Abdominal* T12 → L4 (perirenal, retroperitoneal)
Theoretical “Browning/Beiging/Britening” Potential

n = 20 men

*Total Fat = 1,080 g
*Total BAT = 240 g
= 20-25%

But “brownable” is only 4% of total body fat mass!

Leitner BP…Cypess AM Chen KY PNAS 2017;114:8649
Pharmacological Stimulation Could Achieve that Browning Potential

64yW, BMI = 18.0 kg/m², bladder PGL → norepinephrine 13,238 pg/mL
(112-750 pg/mL)

WAT+BAT = 460 g
Active BAT = 300 g = 65%

Total fat = 175 g
BAT = 158 g = 90% !!!
Sexual Dimorphism in Fat Distribution

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>32.0</td>
<td>37.8</td>
</tr>
<tr>
<td>Mexico</td>
<td>20.3</td>
<td>31.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>6.9</td>
<td>15.0</td>
</tr>
<tr>
<td>India</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>China</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>World</td>
<td>5.7</td>
<td>9.4</td>
</tr>
</tbody>
</table>

- Women (33%) have more total body fat than men (23%).
- Women have more subcutaneous fat, and men have more visceral fat.

Kershaw EE, Filer JS (2004) JCEM 89:2548
Yet a Paradoxical Physiological Dimorphism


• Meal fatty acids are stored in women to a greater extent in sc adipose tissue, whereas in men a greater proportion is stored in visceral fat. Romanski SA et al. (2000) Am J Physiol Endocrinol Metab 279:E455.

• Available evidence points to intrinsic, cell autonomous differences in preadipocytes and adipocytes, as well as modulatory roles for sex steroids, the microenvironment, and embryonic development and patterning factors. Karastergiou et al. Biology of Sex Differences 2012, 3:13
Age Differences in WAT

- Aging is associated with increases in waist circ. (0.7 cm/y)
- Seen in both cross-sectional and longitudinal studies
- Women show a greater increase than men of the same age and race/ethnicity


- Older people have more visceral fat despite having the same body weight or waist circumference
- Clinically significant age-related changes may not be apparent through anthropometric markers such as body weight and waist circumference.
Pediatric BAT is More Frequently Active, but there is no Sexual Dimorphism

Cypess AM et al. (2009), NEJM 360:1509; Drubach LA et al. (2011) J Pediatr 159:939
BAT Activity Appears to *Increase* Through Adolescence, Then Declines

Drubach LA et al. (2011) J Pediatr 159:939
Pediatric BAT Activity Correlates Inversely with BMI%

$P = 0.01$, Kruskal-Wallis test

Drubach LA et al. (2011) J Pediatr 159:939
Racial and Ethnic Differences – SAT v VAT

- AA and women have more age-adjusted total body fat than Whites and men.
- While SAT did not differ among ethnic or sex groups, VAT was higher in Whites and men.
- These ethnic and sex differences are important confounders in the prevalence of obesity and in the assignment of disease risk in children and adolescents.
Higher Risk in East Asians for Intra-Abdominal Fat Accumulation

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org


Higher Risk in East Asians for Intra-Abdominal

• Asian, Hispanic, and White populations are particularly prone to intra-abdominal obesity and its associated health risks.

• For example, compared to Whites, Blacks with the same abdominal adiposity generally have a better lipoprotein-lipid profile, including lower fasting triglyceride and apolipoprotein B levels as well as higher HDL cholesterol concentrations.

Lipodystrophy Syndromes

- Heterogeneous group of disorders
- Selective deficiency of adipose tissue
Classification of Lipodystrophies

- **Etiology**
  - Genetic
  - Acquired (e.g. HIV, autoimmune)

- **Distribution of Body Fat Deficiency**
  - Partial
  - Generalized

- Congenital Generalized
- Acquired Generalized
- Familial Partial
- Acquired Partial
Pathophysiology of Lipodystrophy

Hyperphagia

Starvation signal

Low leptin

Low fat mass

Excess calories cannot be stored in adipocytes

Ectopic lipid storage:
- Muscle
- Liver

Insulin resistance

Diabetes

Hypertriglyceridemia

Non-Alcoholic Fatty Liver Disease

Rebecca Brown
WAT has a pervasive sexual dimorphism in which there are intrinsic, cell autonomous differences among adipocytes, but also roles for sex steroids, the microenvironment, and patterning genes.

Clinically significant age-related changes in adiposity may not be apparent through anthropometric markers such as body weight and waist circumference.

Ethnic and sex differences are important confounders in the prevalence of obesity and in the assignment of disease risk.

WAT and BAT are both functional and endocrine organs found in all adult humans. The anatomical features and physiological roles of both tissues require much more study.
Thank You

**NIH**

**DEOB**
- Marc Reitman
- Kong Chen
- Suzanne McGehee
- Rob Brychta
- Shan Huang
- Brooks Leitner
- Courtney Duckworth

**Nutrition**
- Amber Courville
- Shanna Bernstein

**Mass Spectrometry Core**
- Peter Walter
- Martin Garraffo
- Hongyi Cai

**Laboratory Core**
- Mary Walter
- Karel Pacak
- Lee Weinstein

**CRC PET Department**
- Peter Herscovitch
- Corina Millo

**CRC Radiology and Imaging Sciences**
- Brad Wood
- Elliot Levy
- Sheng Xu
- Ahmed Gharib
- Ron Ouwerkerk

**Harvard University**

**Joslin Diabetes Center**
- Lauren Weiner
- Carla Roberts-Toler
- Christie Sass
- Peter Kahn
- Skyler Kessler
- C. Ronald Kahn
- Yu-Hua Tseng
- Alessandro Doria

**Beth Israel Deaconess Medical Center**
- Gerald M. Kolodny
- Andrew White
- Madhu Misra

**Massachusetts General Hospital**
- Sunia Trauger
- Steve Grinspoon
- Martin Torriani

Grant support: NIH DK087317, DK070722, DK46200, DK33201, DK55545, DK46200, RR25758, DK81604, DK36836, CITP, the Eli Lilly Foundation, Chugai Pharma, Ltd., Molecular Metabolism LLC.