Emerging Concepts of Weight and Energy Regulation

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Disclosure of Multiplicity of Interests
(5 years)

Consultant to:
- ValenTx, Novo Nordisk, Piper Jaffray

Speaker with:
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Travel per diem and honorarium
- AACE/ACE
Objectives

- Review recent developments in our understanding of weight regulation
- Discuss non-hormonal contributors and novel mechanisms of energy balance
- Outline practical clinical considerations for your patient today

CASE
55 year old man

“My wife is successfully losing weight, and I want to do the same”

- Fatigue
- Snoring
- Low back pain
- Libido loss
Composition of Adipose Tissue

- 76-94 % lipid
- 1-4 % protein
- 5-20 % water

Factors Affecting Adipose Tissue Composition

- Cellularity and Age
- Anatomical location
- Species
- Sex
- Genetics
- Hormones
- Nutrition
- Environmental Temperature
Cell types in white adipose tissue

- adipocytes (lipid-filled cells) 30%
- preadipocytes and fibroblasts
- matrix of collagen fibres
- blood vessels (capillaries/endothelial cells)
- immune cells (monocytes/macrophages, lymphocytes)

Adipose tissue development

- ADIPOCYTE HYPERTROPHY & HYPERPLASIA
- ANGIOGENESIS
- INFLAMMATION
Cellular origin of the peptides secreted by human adipose tissue

Adipocytes ➔ Adipokines
- Leptin
- Adiponectin
- Serum amyloids
- Retinol binding protein 4 (RBP4)
- Apelin
- FIAF/PGAR

Stromavascular fraction cells ➔ cytokines & chemiokines
- Monocyte chemoattractant protein 1 (MCP1)
- Macrophage inflammatory protein (MIP)
- Tumor necrosis α (TNFα)
- Interleukins 1β, 6, 8, 10, ....
- Chemokines
- Resistin
- Apelin

CASE
55 year old man

BMI = 31.3 kg/m²

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Is the classification of overweight or obesity based on BMI the best predictor of health risk?

BMI does not always reflect adiposity

- Musculature
- Edema states
  - CHF
  - Nephrotic Syndrome
  - Cirrhosis
  - Lymphedema
- Dehydration
- Sarcopenia (especially the elderly)
- Pregnancy
What is the fat mass index?

DXA - BCA
Fat Mass Index

Fat weight (kg)
height (m²).

Fat Mass Index Classification

<table>
<thead>
<tr>
<th>Fat Mass Index (FMI) Class</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe fat deficit</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Moderate fat deficit</td>
<td>2 to &lt;2.3</td>
</tr>
<tr>
<td>Mild fat deficit</td>
<td>2.3 to &lt;3</td>
</tr>
<tr>
<td>Normal</td>
<td>3 to 6</td>
</tr>
<tr>
<td>Excess fat</td>
<td>&gt;6 to 9</td>
</tr>
<tr>
<td>Obese class I</td>
<td>&gt;9 to 12</td>
</tr>
<tr>
<td>Obese class II</td>
<td>&gt;12 to 15</td>
</tr>
<tr>
<td>Obese class III</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

Why, for patients with a BMI over 40, despite obvious adiposity:

- Do 1/3 not have dyslipidemia?
- Do 1/2 not have hypertension?
- Do 3/4 not have diabetes?
Not all patients who have overweight or obesity by BMI criteria have adiposopathy (sick fat)

BMI Among Patients With Metabolic Disease
NHANES 1999-2002

Diabetes Mellitus
Hypertension
Dyslipidemia

Body Mass Index (BMI)

Why, for patients with a BMI under 25 kg/m\(^2\), do so many have metabolic disorders?

Answer

Not all patients with metabolic disease have overweight or obesity by BMI criteria, but they may have adiposopathy (sick fat)
Adiposopathy

Harold Bays, MD

CASE
55 year old man

BMI = 31.3 kg/m²
WC = 44 inches
Adiposopathy is anatomically manifested by:

- Adipocyte hypertrophy
- Visceral adiposity
- Growth of adipose tissue beyond its vascular supply
- Increased number of adipose tissue immune cells
- Ectopic fat deposition (in other body tissues)


Waist Circumference

- Locate the superior iliac crests and the lower rib margins
- Place measuring tape around abdomen above iliac crests, keeping it parallel to the floor
- Ensure tape is snug but not compressing the skin

Waist Circumference

Visceral Adipose Tissue (VAT)
Visceral Tissue Area (VAT)

HR and 95% CIs for WC (5-cm increments) and all-cause mortality by BMI category (men and women). Adjusted for educational level, marital status, smoking, alcohol, physical activity, and BMI. WC cut points were <90.0, 90.0 to 94.9, 95.0 to 99.9, 100.0 to 104.9, 105.0 to 109.9, and ≥110.0 cm for men and <70.0, 70.0 to 74.9, 75.0 to 79.9, 80.0 to 84.9, 85.0 to 89.9, and ≥90.0 cm for women.

Cerhan. Mayo Clinic Proceedings 2014; 89:335-345
Adipose tissue infiltration by macrophages in adiposopathy

J. Intern. Med. 2007;262:422-430

Adiposopathy: Cellular changes in white adipose tissue
Adiposopathy is functionally manifested by:

- Impaired adipogenesis and adipocyte hypertrophy
- Heterogeneous distribution -- visceral adiposity
- Adipocyte lipolysis in excess of lipogenesis
  - Increased free fatty acids
- Pathogenic adipose tissue endocrine responses
  - i.e. Hypoadiponectinemia // Hyperleptinemia
- Pathogenic adipose tissue immune responses
- Pathogenic crosstalk between fat and other organs

Laboratory testing in bariatric endocrinology:

- C-reactive protein
- 11 pm salivary cortisol
- Gonadal axis evaluation
- Fasting insulin or c-peptide
- Leptin
- Adiponectin
- Leptin to adiponectin ratio

Gonzalez-Campoy et al. Int. J. Endocrinology, May, 2014
CASE
55 year old man

Total Testosterone = 253 ng/dL (348-1197)
CRP = 7.5 mg/L (< 5)
A1c = 6.6% (≤ 5.6)
Triglycerides = 300 mg/dL (≤ 150)
HDL = 36 mg/dL (≥ 40)

Lipid changes in adiposopathy

Lean  Adiposopathy

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CASE
55 year old man

- Adiponectin = 3.6 μg/mL (2.2 – 19.9)
- Leptin = 10.6 ng/mL
- Leptin to adiponectin ratio = 2.9

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Leptin levels rise with increasing BMI

Kazmi, JPMA, 63: 245; 2013
Adiponectin levels fall with increasing BMI

Leptin to Adiponectin Ratio Trending

CRP mg/L
| 7.48 (Abn) | 6.40 (Abn) | 4.10     |

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Human Microbiome Project

The Human Microbiome Project says the human body has 100 trillion microscopic life forms living in it.

You call this living?

More than 10,000 microbial species have been identified as living in human bodies thus far.
Microbial cells outnumber human cells in a human body 10 to 1.
Approximately 91% of the cells in our bodies are non-human microbial cells.
Microbes account for only 1-3% of human body weight.

The microbiome contributes 99.7% of the genetic material that encodes protein in our bodies.
The microbiome contributes 8 million protein-coding genes.
The gut microbiome
Some health conditions that have been found to be directly related to the balance of bacteria in the human body:

- obesity,
- type 1 diabetes,
- childhood asthma,
- inflammatory bowel disease,
- colorectal cancer,
- cardiovascular disease,
- human immunodeficiency,
- anxiety,
- respiratory infections.


Different gut microbial community in mice with obesity

**Effects of decreasing caloric intake**


**Microbiota fecal transplantation**

Turnbaugh et al., Nature 444: 1027-1031
Human migrations and metabolic adaptation to different environmental stressors: a new theory for ethnic obesity variation


Energy cost and food prices

Brimblecombe and O’Dea, MJA, 2009
Immobility (screen and car time) and sleep deprivation

Pathways linking sleep loss to insulin resistance and diabetes

McDermott R. Diabetes Management, 2012
Risks and Efficacy

Lower risk

- Meal Plans
- VLCD

Pharma

Devices*

Lap band
Sleeve
Roux-en-Y bypass
BPD-DS

Higher risk

Lower efficacy

- Orlistat

Sibutramine

Lap Band

Gastric Bypass

Higher efficacy

* Endoluminal gastric sleeve, gastric balloons, and vagal stimulator

VLCD = very low calorie diet.


Monotherapy vs Surgery for Obesity and Adiposopathy

Kg of absolute weight loss

Months of treatment

Baseline* 3 6 9 12 15 18 21 24

Orlistat
Sibutramine
Lap Band
Gastric Bypass

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Case Study #1

Before, BMI = 42, Weight = 313 lbs
After, BMI = 32, Weight = 235 lbs
Down 78 pounds

Case Study #2

Before, BMI = 57, Weight = 315 lbs
After, BMI = 40, Weight = 222 lbs
Down 93 pounds
Case Study #3

Before, BMI = 43,
Weight = 279 lbs

After, BMI = 27,
Weight = 176 lbs

Down 103 pounds

Combination therapy vs Surgery for
Obesity and Adiposopathy

Kg of absolute weight loss

Baseline* 3 6 9 12 15 18 21 24

Orlistat Sibutramine Lap Band Gastric Bypass

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Risks and Efficacy

* Endoluminal gastric sleeve, gastric balloons, and vagal stimulator

VLCD = very low calorie diet.

Principles of Bariatric Endocrinology

- Failure of monotherapy to achieve effective weight loss should not lead to discontinuation of treatment, but rather the institution of combination therapy


Gonzalez-Campoy et al. Int. J. Endocrinology, May, 2014
Pharmacotherapy to optimize metabolism and to reset the hypothalamic and CNS controls over energy balance and energy stores should be used indefinitely in the management of overweight, obesity, and adiposopathy (i.e. achieving a treatment goal is not a reason to stop treatment).

How does MNCOME do with extreme obesity?

July 10, 2004:
Weight = 629 pounds
BMI = 91.65

August 24, 2012:
Weight = 464 pounds
BMI = 69.7

Down 165 pounds in 8 years
Will extreme obesity respond to medical management?

September 13, 2006:
Weight = 513 pounds
BMI = 71.62

July 21, 2012:
Weight = 248 pounds
BMI = 34.6

Down 265 pounds in 6 years

How Does MNCOME do with BMI 30-35?

Down from 167 to 134 pounds with maintenance of weight loss over 5 years -- EASY!!!!
How Change Occurs in Organizations

Innovators | Early Adaptors | Late Adaptors | Non-adaptors

Leadership

High Receptiveness to Change

Low

Slide courtesy of Tim Herrington, MD