Mechanisms and Effectiveness of Medical and Behavioral Obesity treatment
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University of Akron Nutrition & Dietetics Programs Advisory Board
8th Annual Nutrition Forum: Current Approaches to Weight Management

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Scope of the problem in the U.S.
1999-2010 data

- Prevalence of adult obesity is 36%
- Overweight and obesity prevalence is 69%
- Overweight + obesity prevalence is 77-80% for non-Hispanic blacks, Hispanics, and Mexican Americans
- Obesity rates highest in lowest socioeconomic levels and in women who self-identify a part of an ethnic minority - rates of obesity at 50% in some groups
- The prevalence of obesity in Children and adolescents as 16.9%

Obesity Risk Higher if:

- Female, black (women), Hispanic or and native American
- Maternal smoking or diabetes
- Lower socioeconomic status
- Sedentary lifestyle
- Higher fast-food intake
- Increased time-spent watching TV
- Pregnancy (2-3kg if age 18-30) – ? more in black women
- Sleep deprivation
- Smoking cessation – average 4-5kg
- Medications
- Injury/condition impairing ambulation/use of lower extremities
Obesity is a chronic disease

- There are many definitions of "chronic condition", some more expansive than others. We characterize it as any condition that requires ongoing adjustments by the affected person and interactions with the health care system.

© 2006-2011 Improving Chronic Illness Care
Obesity is often not reversible: Adipose tissue hyperplasia

- At normal BMI ranges usually very little visceral fat is present—largely subcutaneous

- With weight gain the adipocytes increase in size and then in number
  - both hypertrophy and hyperplasia. Hyperplasia may not be reversible

- Fat cell hyperplasia can be different depending on individual characteristics and the degree of weight gain. With more weight gain at least some hyperplasia occurs
Objectives:

- Introduce key pathways in energy intake (Eating) and expenditure (Living, Digesting, and Moving)
- Describe pathways affected by medications that reduce weight
- Define the role and effectiveness of behavioral interventions in obesity treatment
METABOLIC HOMEOSTASIS

Normal liver function:
- Hepatic glucose output
- Glucose uptake
  (conversion into glycogen)
- Fatty acid uptake
  (conversion into TGs)

Normal gastrointestinal activity:
- Dietary fats & sugar absorption
- Gut motility
- Healthy profile of gut microbiota

Normal visceral adipose tissue function:
- Glucose uptake
  (conversion into lipids & stored as fat)
- Lipid uptake
  (stored as fat)
- Lipolysis
  (release of fatty acids into the blood stream)

Normal muscle function:
- Glucose uptake
- Fatty acid uptake

Normal systemic immune function

Normal central regulation of systemic metabolism:
- Endocrine hormone axis (HPT)
- Efferent autonomic nervous system

Afferent autonomic nervous system

Pancreatic hormones:
- Glucagon
- Insulin

Dietary nutrients

Gut hormones:
- CCK
- GIP
- PP
- GLP-1
- GIP

Incretin action:
- Stimulates insulin release
- Inhibits glucagon release
- Increases insulin sensitivity
- Effects on gut motility

Anti-inflammatory & pro-inflammatory cytokines

Adipose tissue hormones:
- Leptin
  - Satiety
  - Energy expenditure
  - Immune regulation
  - Angiogenesis
  - Fertility
  - Bone homeostasis
- Adiponectin
  - Glucose homeostasis
  - Insulin sensitivity
  - Body weight
  - Endothelial function
**METABOLIC SYNDROME**

**Definition (IDF):**
- Central obesity (usually BMI > 30 kg/m²), plus 2 of the following:
  - TGs > 150 mg/dL
  - HDL < 40-50 mg/dL
  - ↑ blood pressure
  - ↑ hyperglycemia

**Complications of Chronic Diabetes:**
- chronic kidney disease
- cardiovascular disease
- peripheral nerve damage
- eye disease & blindness
- non-healing skin ulcers, usually leading to amputations
- non-alcoholic fatty liver disease, which can lead to cirrhosis

**Food intake >> energy needs**

- Abnormal hepatic glucose output ↑
- Glucose uptake ↑
- Fatty acid uptake ↑
- & conversion into TGs and VLDL and their release into the blood stream

- Abnormal liver function:
  - Hepatic glucose output ↑
  - Glucose uptake ↑
  - Fatty acid uptake ↑
  - & conversion into TGs and VLDL and their release into the blood stream

- Abnormal gastrointestional activity:
  - Dietary fats & sugar absorption ↑
  - Gut motility ↑
  - Alterations in gut microbiota, contributing to metabolic disease

- Pancreatic islet mass ↑, followed by exhaustion

- Pancreatic hormones:
  - Glucagon ↑
  - Insulin ↑ (but with resistance)

- Dietary nutrients ↑
  - CCK
  - Ghrelin
  - PYY
  - ECs
  - GLP-1

- Gut hormones:
  - GLP-1

- Incrletin action ↓
  - Stimulates insulin release
  - Inhibits glucagon release
  - Increases insulin sensitivity
  - Effects on gut motility

- Abnormal visceral adipose tissue function:
  - Glucose uptake ↓
  - Lipid uptake ↑
  - Lipid stored as lipids & stored as fat
  - Lipolysis ↑
  - Release of fatty acids into the blood stream

- Abnormal muscle function:
  - Glucose uptake ↓
  - Fatty acid uptake ↑

- Systemic low-grade inflammation

- Net result:
  - Increased fat storage & fat tissue hypertrophy

- Systemic glucotoxicity

- Fatty liver disease

- Heart disease

- Pre-diabetes, followed by overt diabetes

- Systemic lipotoxicity

- Abnormal central regulation of systemic metabolism:
  - Disrupted endocrine hormone axis (HPT)
  - Dysregulated efferent autonomic nervous system

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Fig. 1. Energy balance, body fat, and therapeutic options.
### Impact of Weight Loss on Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>~5% Weight Loss</th>
<th>5%-10% Weight Loss</th>
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</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Blood Pressure</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total Cholesterol</td>
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<td>3</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

Objectives:

- Introduce key pathways in energy intake (Eating) and expenditure (Living, Digesting, and Moving)
- Describe pathways affected by medications that reduce weight
- Define the role and effectiveness of behavioral interventions in obesity treatment
METABOLIC HOMEOSTASIS

Food intake = energy needs

Normal hedonic response
Normal homeostatic response
Normal satiety
Normal nutrient sensing
Normal central regulation of systemic metabolism:
  - Endocrine hormone axis (HPT)
  - Efferent autonomic nervous system
Afferent autonomic nervous system
Pancreatic hormones:
  - Glucagon
  - Insulin
Dietary nutrients
Gut hormones:
  - CCK
  - Ghrelin
  - PYY
  - ECs
  - GLP-1
  - GIP
Incretin action:
  - Stimulates insulin release
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  - Lipid uptake
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  - Conversion into glycogen & TGs

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  - Healthy profile of gut microbiota

Normal systemic immune function

Normal visceral adipose tissue function:
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Anti-inflammatory & pre-inflammatory cytokines
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  - Energy expenditure
  - Immune regulation
  - Angiogenesis
  - Fertility
  - Bone homeostasis
  - Adiponectin
  - Glucose uptake
  - Insulin sensitivity
  - Body weight
  - Endothelial function
Central and peripheral regulation of food intake and physical activity: pathways and genes. Lenard NR - Obesity (Silver Spring) - 01-DEC-2008; 16 Suppl 3: S11-22

Figure 4 Hypothalamic peptidergic circuitry related to feeding and energy balance. Highly simplified diagram showing the two known neuron populations in the arcuate nucleus sensitive to signals of fuel availability and their projections to other key neuron populations orchestrating the adaptive behavioral, autonomic, and endocrine responses. CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; GABA, \( \gamma \)-aminobutyric acid; MCH, melanin concentrating hormone; \( \alpha \)-MSH, \( \alpha \)-melanocyte-stimulating hormone; PVN, paraventricular nucleus.
Two key neuronal populations:

1. Orexigenic or appetite inducing through secretion of
   - neuropeptide Y (NPY)
   - agouti-related peptide (AgRP)

2. Anorexic or appetite suppressing through secretion of
   - Proopiomelanocortin (POMC).
   - Cocaine amphetamine related transcript (CART)
Sleep: Needed for normal appetite regulation and activity

- Obstructive sleep apnea (OSA) is a common chronic disorder. (25% men, 9% women in clinical populations)
  - Sleep studies show obstructive apneas, hypopneas, or respiratory effort related arousals. Daytime symptoms attributable to disrupted sleep, such as sleepiness, fatigue, or poor concentration.
  - OSA the severity and duration increase risk for cardiovascular mortality. Metabolic syndrome present in 75% or more of those who have OSA
  - Patients with OSA have a reduced upper airway size due to excess surrounding soft tissue or a highly compliant airway.

- Sleep deprivation (<6 hours nightly), particularly shift work, is associated with both obesity and higher cardiovascular and all-cause mortality
Sleep and Hypothalamic-pituitary-adrenal (HPA) axis

- Hypothalamic-pituitary-adrenal (HPA) axis mediates reaction to acute physical and psychological stress. HPA and sleep interact in multiple ways.
- Sleep, in particular deep sleep, has inhibits the HPA axis,
- Glucocorticoids activate the HPA axis—leads to arousal and sleepiness.
- The sequence of events in OSA—breathing cessation, nocturnal hypoxia, continuous brief arousals, and sleep fragmentation—activate:
  - Systemic sympathetic/adrenomedullary
  - HPA axis limbs of the stress system

Asphyxiation is bad; Sleep is good
CPAP helps

- CPAP is the main treatment and lowers blood pressure and sleepiness
- In an RCT (n=172) with sham CPAP, Sharma and colleagues showed CPAP treatment for 3 months in participants with moderate and severe OSA:
  - Reduced blood pressure - decreased 3.9/2.5mmHg
  - Decreased in Hemoglobin A1c by 0.2%, but did not improve insulin sensitivity or fasting glucose
  - Decreased total cholesterol (-13mg/dl), LDL (-9.5mg/dl)
  - Decreased waist circumference, visceral, and subcutaneous fat mass, and weight - 0.7kg
  - Decreased fatigue
  - Reduced carotid intima-media thickness (CIMT)
  - **Resolved metabolic syndrome in 11 intervention compared to 1 control participant**

Food and the Reward / Mood Stress systems

1. Endocannabinoids/GABA
2. Serotonin
3. Norepinephrine
4. Dopamine
Weight friendly medications NOT approved for Obesity treatment

- Anti-epileptics
  - Topiramate
  - Zonisamide

- Incretins
  - Exenatide
  - Liraglutide
  - Pramlintide and other amylin analogues
Neurotransmitters: GABA

- Induces food consumption
- Reduces energy expenditure

Two known receptors:

- $\text{GABA}_\text{A}$: over expression in rats linked to obesity and infusion of agonist in hypothalamus. Benzodiazepines bind to it
- $\text{GABA}_\text{A}$ knockout mice lean

Medications that affect GABA: valproic acid, topiramate, benzodiazepines
Topiramate

- Associated with weight loss, especially inpatients with highest initial weight
- Proposed mechanisms:
  - Inhibition of voltage gated Na/Ca channels
  - Activation of GABA A receptors
    - (decreases GABA levels)
  - *Inhibition of carbonic anhydrase
  - *Blockade of aminio-3-hydroxy-5-methylisoxazole-4propionic acid (AMPA glutamate receptors)
- Weight loss is maximal between 100 and 400mg/day, but usually tolerated at 100mg/day
Topiramate and weight maintenance

- 700 subjects with BMI of 30-50 enrolled in an 8-week low-calorie diet plan - those who lost at least 8% (n=557) enrolled in a placebo-controlled trial of low-calorie diet + behavior modification with placebo or topiramate max at either 96 mg or 192 mg/day.

- At 44 weeks, the placebo group had maintained 8.9% loss, and the topiramate group maintained a 15.4% and 16.5% loss respectively.

Astrup, Caterson, et al. 2004
Topiramate – abbreviated side effect summary

- Common side effects: Weight loss, renal stones, paresthesias, menorrhagia, GERD, interference with BCP
- Less common side effects: Fatigue, nervousness, difficulty concentrating, confusion, depression, anorexia, language problems, anxiety, mood problems, tremor
- Serious side effects: Acute myopia and glaucoma; oligohydrosis and hyperthermia which primarily occur in children
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names</th>
<th>DEA Schedule</th>
<th>Approved Use</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical</td>
<td>None</td>
<td>Long-term</td>
<td>1999</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Meridia</td>
<td>IV</td>
<td>Long-term</td>
<td>1997</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Tenulate</td>
<td>IV</td>
<td>Short-term</td>
<td>1973</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Adipex, Ionamin</td>
<td>IV</td>
<td>Short-term</td>
<td>1973</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Bontril, Prelu-2</td>
<td>III</td>
<td>Short-term</td>
<td>1961</td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>Didrex</td>
<td>III</td>
<td>Short-term</td>
<td>1960</td>
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</table>
Effect of Continuous and Intermittent Phentermine Therapy on Body Weight
(Short-term only approved)


NAASO Slide Library
Controlled-Release Phentermine/Topiramate in Severely Obese Adults

Controlled-Release Phentermine/Topiramate in Severely Obese Adults

Regulation of Food Intake

**Brain**

**Central Signals**

<table>
<thead>
<tr>
<th>Stimulate</th>
<th>Inhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY</td>
<td>α-MSH</td>
</tr>
<tr>
<td>Orexin-A</td>
<td>CART</td>
</tr>
<tr>
<td>AGRP</td>
<td>CRH/UCN</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>NE</td>
</tr>
<tr>
<td>Galanin</td>
<td>GLP-I</td>
</tr>
<tr>
<td></td>
<td>5-HT</td>
</tr>
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</table>

**Peripheral signals**

- Glucose
- CCK, GLP-1, Apo-A-IV
- Vagal afferents
- Insulin
- Ghrelin
- Leptin
- Cortisol

**Peripheral organs**

- Gastrointestinal tract
- Adipose tissue
- Adrenal glands

**External factors**

- Emotions
- Food characteristics
- Lifestyle behaviors
- Environmental cues

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*NAASO Slide Library*
Food and the Incretins:
Glucagon-like-peptide (GLP-1)

- **Site of Synthesis:** secreted of the L-cells distal small intestine, Also made in the NTS, hypothalamus and amygdala

- **Site(s) of action:** Inhibits NPY neurons and stimulates the POMC system, PYY decreases ghrelin levels, activates neurons in the area postrema of the PVN

- **Factors affecting production:** secreted in response to rapid passage of food to hindgut with contact with chyme

- **Major known effects:** increases insulin secretion and increases insulin sensitivity. It leads to decreased food ingestion and weight.
GLP-1 receptor agonists (i.e. exenatide, liraglutide)

- **Mechanism:** long-acting synthetic peptide that is a GLP-1 receptor agonist
  - Currently twice daily or daily subcutaneous dosing
  - Weekly dosing in release

- **Side effects:**
  - Most common is nausea
  - Hypoglycemia as discussed prior
  - Weight loss
  - ?increase in INR in patients on coumadin
  - Local reaction/allergy
  - ?rare pancreatitis
Figure 2 Comparison of weight change between EXE + LMP and PBO + LMP Groups and Subgroups. (A) Change in body weight from baseline over time in ITT participants with type 2 diabetes treated with EXE + LMP (black squares) or PBO + LMP (white squares) plus oral agents. Data are LS mean ± SE. *P < 0.0001 compared with baseline, †P < 0.01 compared with PBO + LMP. (B) Change in body weight from baseline at 24 weeks with EXE + LMP (black bars) and PBO + LMP (white bars) divided into subgroups by oral agent. Data are LS mean ± SE. *P < 0.05 compared with baseline. (C) Percentage of participants achieving clinically meaningful weight loss >5% at endpoint with EXE + LMP (black bars) and PBO + LMP (white bars) divided into subgroups by oral agent. (D) Percentage of participants achieving clinically meaningful weight loss >10% at endpoint with EXE + LMP (black bars) and PBO + LMP (white bars) divided into subgroups by oral agent. Abbreviations: EXE = exenatide; ITT = intent to treat; LMP = lifestyle modification program; LS = least squares; MET = metformin; PBO = placebo; SE = standard error; SU = sulfonylurea.
Figure 3  Comparison of glycemic control between EXE + LMP and PBO + LMP Groups and Subgroups. (A) Change in HbA1c from baseline over time in ITT patients with type 2 diabetes treated with EXE + LMP (black squares) or PBO + LMP (white squares) plus oral agents. Data are LS mean ± SE. *P < .0001 compared with baseline. †P < .0001 compared with PBO + LMP. (B) Change in HbA1c at 24 weeks with EXE + LMP (black bars) and PBO + LMP (white bars) divided into subgroups by oral agent. Data are LS mean ± SE. *P = .0009 compared with baseline. (C) Percentage of participants achieving HbA1c goal =6.5% at endpoint with EXE + LMP (black bars) and PBO + LMP (white bars) divided into subgroups by oral agent. (D) LS mean ± SE 6-point SMBG profiles at baseline and 24 weeks for EXE + LMP (black squares with solid line, baseline; black squares with broken line, 24 weeks) and PBO + LMP (white squares with solid line, baseline; white squares with broken line, 24 weeks). All 24-week glucose measurements were significantly reduced compared with baseline for both treatment groups (all P < .0001). *P < .01, †P < .05 compared with PBO + LMP. Abbreviations: EXE = exenatide; HbA1c = hemoglobin A1c; ITT = intent to treat; LMP = lifestyle modification program; LS = least squares; MET = metformin; PBO = placebo; SE = standard error; SMBG = self-monitored blood glucose; SU = sulfonylurea.
<table>
<thead>
<tr>
<th>DRUGS THAT MAY PROMOTE WEIGHT GAIN</th>
<th>ALTERNATIVE TREATMENTS—WEIGHT NEUTRAL OR WEIGHT LOSS</th>
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<tbody>
<tr>
<td><strong>PSYCHIATRIC AND NEUROLOGIC MEDICATIONS</strong></td>
<td><strong>ALTERNATIVE PSYCHIATRIC AND NEUROLOGIC MEDICATIONS</strong></td>
</tr>
<tr>
<td>Antipsychotics: olanzapine, clozapine, risperidone,quetiapine, aripiprazole</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Nortriptyline, bupropion, nefazodone, fluvoxamine, sertraline, duloxetine</td>
</tr>
<tr>
<td>Tricyclics: imipramine, amitriptyline</td>
<td>Topiramate, zonisamide (weight loss), lamotrigine (less weight gain)</td>
</tr>
<tr>
<td>Triazolopyridines: trazodone</td>
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</tr>
<tr>
<td>Serotonin reuptake inhibitors: paroxetine, fluoxetine, citalopram</td>
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<tr>
<td>Tetracyclics: mirtazapine</td>
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<tr>
<td>Monamine oxidase inhibitors</td>
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<tr>
<td>Antiepileptic drugs: gabapentin (higher doses), valproic acid, carbamazepine, divalproex</td>
<td></td>
</tr>
<tr>
<td>Mood stabilizers: lithium, carbamazepine, lamotrigine, gabapentin (higher doses)</td>
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<td><strong>STEROID HORMONES</strong></td>
<td><strong>ALTERNATIVES TO STEROID HORMONES</strong></td>
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<tr>
<td>Progestational steroids</td>
<td>Barrier methods, IUD</td>
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<tr>
<td>Corticosteroids</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<td>Hormonal contraceptives</td>
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<td><strong>ANTIDIABETES AGENTS</strong></td>
<td><strong>ALTERNATIVE ANTIDIABETES AGENTS</strong></td>
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<tr>
<td>Insulin (most forms)</td>
<td>Metformin</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Acarbose, miglitol</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Exenatide</td>
</tr>
<tr>
<td><strong>ANTIHISTAMINES</strong></td>
<td><strong>DECONGESTANTS, MAST CELL STABILIZERS, ANTAGONISTS OF ENDogenous MEDIATORS OF INFLAMMATION</strong></td>
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<tr>
<td>Commonly reported with older agents; also oxatomide, loratadine and azelastine</td>
<td>DPP-4 inhibitors</td>
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<tr>
<td><strong>ANTIHYPERTENSIVE AGENTS</strong></td>
<td><strong>ALTERNATIVE ANTIHYPERTENSIVE AGENTS</strong></td>
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<tr>
<td>α-Adrenergic and β-adrenergic receptor blockers</td>
<td>Angiotensin–converting enzyme inhibitors,</td>
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<td>Calcium channel blockers: nisoldipine</td>
<td>Calcium channel blockers—most other agents</td>
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<td><strong>HIGHLY ACTIVE ANTIRETROVIRAL THERAPY</strong></td>
<td>Angiotensin receptor blockers</td>
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<td>Diuretics</td>
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### TABLE 1 -- Potential targets for new obesity treatments

<table>
<thead>
<tr>
<th>Agonists/stimulators</th>
<th>Antagonists/inhibitors</th>
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<tbody>
<tr>
<td>☐ Adiponectin</td>
<td>☐ Acetyl CoA carboxylase Agouti-related protein 11βHSD1</td>
</tr>
<tr>
<td>☐ 2αMSH/MC4R</td>
<td>☐ Central CPT1</td>
</tr>
<tr>
<td>☐ Apolipoprotein A-IV</td>
<td>☐ CRH receptor</td>
</tr>
<tr>
<td>☐ Brain-derived neurotrophic factor/TrkB receptor</td>
<td>☐ DP-IV</td>
</tr>
<tr>
<td>☐ CCK/CCK-A receptor CNTF/axokine</td>
<td>☐ Endocannabinoid receptor (rimonabant/SR141716A)</td>
</tr>
<tr>
<td>☐ Cocaine- and amphetamine-regulated transcript</td>
<td>☐ Fatty acid synthase (cerulenin; C75)</td>
</tr>
<tr>
<td>☐ GLP-1/exendin-4 Human GH fragment (AOD9604)</td>
<td>☐ Galanin</td>
</tr>
<tr>
<td>☐ Insulin mimetics</td>
<td>☐ GIP</td>
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<tr>
<td>☐ Leptin; leptin receptor Oxyntomodulin</td>
<td>☐ Ghrelin</td>
</tr>
<tr>
<td>☐ PYY</td>
<td>☐ Histamine receptor</td>
</tr>
<tr>
<td>☐ Phosphatidylinositol 3-kinase</td>
<td>☐ MCH</td>
</tr>
<tr>
<td>☐ Somatostatin</td>
<td>☐ NPY</td>
</tr>
<tr>
<td>☐ β3, serotonin, norepinephrine, dopamine receptors</td>
<td>☐ Orexin A and B</td>
</tr>
<tr>
<td></td>
<td>☐ Suppressor of cytokine signaling-3</td>
</tr>
<tr>
<td></td>
<td>☐ Tyrosine phosphatase IB</td>
</tr>
</tbody>
</table>

*Korner J - J Clin Endocrinol Metab* - 01-JUN-2004; 89(6): 2616-21
Fig. 2. Mean percent weight change during a 15-year period in the control group and surgery group, according to the method of bariatric surgery as reported in SOS (error bars = 95% C.I.). (From Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357(8):747; with permission.)
Objectives:

- Introduce key pathways in energy intake (Eating) and expenditure (Living, Digesting, and Moving)
- Describe pathways affected by medications that reduce weight
- Define the role and effectiveness of behavioral interventions in obesity treatment
Figure 2 Highly schematic diagram showing major components and flow of information of the peripheral and central systems involved in energy balance, regulation, and control of food intake. CNS, central nervous system.
Defining Lifestyle Treatment

- Non-drug treatment in which an individual opts to engage and persist in regular activities to prevent, improve, or control a medical condition.

- For obesity treatments may include activities affecting:
  - Dietary patterns and content
  - Activity level
  - Sleep quantity and quality
  - Other behavioral habits
Eating and Activity Assessment and counseling are necessary for good primary care

- Physicians are required to let a patients know the most effective preventive and treatment tools for chronic disease

- A person’s activity and diet are two of their most important medications

- Patients want our help to discern where their efforts are best spent
Lifestyle counseling for obesity treatment and prevention

Necessary for best treatment for:
- Hypertension, diabetes mellitus, dyslipidemia, obstructive sleep apnea, GERD, asthma, dyslipidemia, degenerative disease of weight-bearing joints
- Prevention of stroke, myocardial infarction, and several cancers
- Providers must have some comfort with assessing and guiding the most important medications all patients take daily
Obesity treatment: Both healthier eating and active living for life

- The goal is to reduce fat mass and preserve or increased lean mass
  - Diet changes drive weight loss
  - Exercise preserves weight loss and lean mass
  - Pregnancy, menopause, injury, aging, and sedentary life are particular times weight gain is likely
Rationale for Primary Care Providers to guide Lifestyle Treatment for Obesity

- Patients who improve dietary, activity, and other behavioral recommendations have: better health outcomes, better social outcomes, and reduced mortality
Non-Pharmacologic Treatments

Weight loss goals of 5-15% considered achievable and sustainable, and improve health

Components of Basic Program

- Diet Recommendations
- Exercise Recommendations
- Behavior Therapy
- Monitoring and/or follow-up life-long

All 4 components needed!
Diet Recommendations

- Low-calorie (1000kcal or more)
- Can be achieved with plans – do not need to count - few people can count accurately
- Use office guidelines for starting ranges and adjust as needed
Evidence for Lifestyle Improving Chronic Conditions

- Weight loss, lower fat and lower glycemic index diets, aerobic and resistance exercise have been shown to reduce progression to diabetes, improve diabetes control and outcome.

- Weight loss, lower salt, DASH diet, regular aerobic exercise has been shown to lower blood pressure and reduce morbidity and mortality.

- Lifestyle interventions when followed are much more effective than any single medication that treats diabetes, hypertension, and lipid.
Key Lifestyle Trial Results

Diabetes Prevention Program:

- progression to DM reduced by 58%
- 7% average weight loss through dietary changes and supervised exercise – walking

ENCORE\textsuperscript{2,3}: unmedicated, obese or overweight adults with hypertension were treated with DASH (Dietary Approaches to Stop Hypertension) low-calorie, low salt diet and exercise

- 16.1/9.9 reduction in blood pressure
- 19pound average weight loss
- Improved insulin sensitivity

Results from Non-pharmacologic Programs

- Patient overwhelmingly regain the weight.
- Behavior therapy and exercise key to weight loss maintenance
- High intensity interventions most effective
Long-term Weight Loss is Improved with Long-term Maintenance Therapy

Panel B shows the change in weight for each of the dietary Groups during the weight-maintenance intervention, adjusted for body-mass index at randomization, Weight loss during the low-calorie-diet phase, sex, family Type (single-parent family, two-parent family with one parent as participant, or two-parent family with both parents as participants), center, and age at screening, on the basis of an intention-to-treat mixed-model analysis.

The changes in body weight from randomization to week 26 among participants who completed the intervention are also shown (boxes). HGI denotes high glycemic index, HP high protein, LGI low glycemic index, and LP low protein.
MetroHealth's Healthy Plate for Everyone

Fill 1/2 plate with non-starchy foods
These foods include:
- Spinach, carrots, lettuce, greens, cabbage, bok choy, green beans, broccoli, cauliflower, tomatoes, vegetable juice, salsa, onions, cucumbers, beets, okra, mushrooms, peppers, turnips

Add an 8 oz. glass of non-fat or low-fat milk. If you don’t drink milk, you can add another small serving of a carbohydrate such as a 6 oz. container of light yogurt or a small roll.

Fill 1/4 plate with starchy foods
- A piece of fruit
- A 1/2 cup fruit salad (fresh, frozen or canned in juice or frozen in light syrup)
- Whole-grain bread (whole wheat or rye)
- Whole-grain, high-fiber cereal
- Cooked cereal (oatmeal, grits, hominy, cream of wheat)
- Brown rice, whole-grain pasta, tortillas
- Cooked beans and peas (pinto beans, black-eyed peas)
- Potatoes, corn, lima beans, sweet potatoes, winter squash
- Low-fat crackers and snack chips, pretzels and fat-free popcorn - best if high-fiber

Fill 1/4 plate with meat or substitutes
- Chicken or turkey without the skin
- Fish (tuna, salmon, cod, catfish)
- Other seafood (shrimp, clams, oysters, crab, mussels)
- Lean cuts of beef and pork (sirloin or port loin)
- Tofu, eggs, low-fat cheese

Breakfast
Your plate will look different at breakfast, but the idea is the same. Keep your portions small. Use half your plate for high-fiber foods. You can add fruit in one quarter and a protein like lean meat, dairy or eggs in the other. Having 12 or more grams of protein helps keep you full all day.

Brought to you by the Weight Management Clinic at MetroHealth Medical Center, 216-779-7423
Adapted from www.diabetes.org
Dietary Recommendations

- Low-calorie diet better than very-low calorie diet for maintaining weight loss.
- Meal replacements (e.g. South Beach, Atkins, Slimfast or Glucerna) often helpful in improving success with dietary caloric adherence – best if >10g protein, >5gm fiber, <7grams sugar.
- Portion-controlled servings also useful for weight loss adherence.
Dietary Recommendations

- For many, a low calorie diet that is low in fat and refined carbohydrates is best for long-term adherence
- Breakfast with 12-18 grams protein – and more than 35 grams daily
- High proportion of produce (5-7 cups vegetable, 2-3 fruit)
- Limit/eliminate fast food and liquid calories (except skim milk)
Dietary Recommendations

- Avoid or limit refined carbohydrates
- Avoid or limit foods with 7 grams of sugar or more
- Avoid high salt food – over 450 mg/serving
- Avoid liquid calories except skim milk
- Identify and avoid trigger foods
Quick Diet wins

- Meal replacement
- Healthy plate approach
- Routinization of meals
- DASH/low salt
- Breakfast
- Eggs/protein at breakfast – 12g or more
- Elimination of sugary beverages
- Sugarless gum chewing can decrease grazing and increase alertness
Commercial Programs

Limited studies show:

- They can work, are often expensive, none proven superior.
- More improvements in lipid profile and fasting sugar results known in low carbohydrate diets, the new Weight Watchers, and Mediterranean diets

Fig. 1. Energy balance, body fat, and therapeutic options.
What modifies the REE over time?

- Aerobic exercise from 40-60 minutes can raise REE the following day for 19-24 hours
- Caffeine mildly raises REE
- Resistance work over time will increase lean mass and raise REE for that weight
- Calorie restriction lowers REE
- Weight loss of 10-20% reduces REE – (lasts at least 3-5 years)
Why Exercise Regularly?

Benefits:

- Cardiovascular benefit: – delays or prevents development of high blood pressure, reduces the risk of MI and CVA
- Cancer – decreased risk of colon cancer, improved survival in breast cancer patients,
- Endocrine– lowers the risk of DM2
- MS – maintains muscle strength, joint structure and joint function
- Bone – resistance or endurance exercises reduce bone loss in post-menopausal women
Benefits, contd:

- GU – associated with improved urine control and erectile dysfunction
- Function – improves global functioning, reduces risk of falls in the elderly – improves cognitive functioning in elderly and may reduce dementia
- BMI – reduces development and progression of obesity and maintains loss in those who have lost weight
- Mental health – improves anxiety and depression
Effect of exercise on body composition and energy expenditure

- Moderate to vigorous aerobic activity of 35 minutes or more increases RMR the following day.

- Regular resistance exercise slows or prevents the loss of lean mass, preserving a higher RMR and insulin sensitivity.

- All activity has calorie output.
How much is enough?

- A study of Amish men and women in Canada was done in 2002.

- How many steps a day do you think they walked?

- How many steps a day do you think the average American adult walks?

- How many steps a day do you think you walk?
How much is enough?

- The Canadian Amish pedometer study showed the men walked 20-24,000 steps a day and the women 16,000-20,000 steps.

- Only 1 in 20 was obese
  (1 in 3 Americans are obese)
How much is enough?

- The average American adult walks 5,000-7,000 steps a day

- 10,000 steps a day is the minimum recommendation for normal activity – this is about 5 miles
Figure. BMI at Each CARDIA Visit by Habitual Activity Category

Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. Data are adjusted for age and race. CARDIA (Coronary Artery Risk Development in Young Adults) study examination years are baseline, 2, 5, 7, 10, 15, and 20.
What exercise is Recommended?

- CDC/ACSM - 1993: 30 min. of moderate activity most/all days of the week
- AHA – 2003: 30-60 min. of activity 4-6x weekly and resistance training 2-3 x weekly
- IOM - 2003: 60 minutes of physical activity daily
General Exercise Goal Recommendations

- Aerobic Activity: 30-60 minutes of moderate to vigorous activity most days of the week (e.g. brisk walking, stationary bike, swimming)

- Strengthening/Resistance 3 days a week
When do I prescribe Exercise?

- Research shows effective counseling can be done in about 5 minutes
- Research shows patients who are counseled to exercise by physicians have higher activity levels in the year following the counseling


Where does a patient begin

- Reducing TV time is a free way for a patient to reduce sedentary activity and possibly reduce calories
- Activities should include safe, weather independent, and cost neutral options
- Activities should be chosen in part on patients personal preference
- Scheduling time or making daily weekly goals help patients maintain routines (step/day or minute/week goals)
- Small bouts at work / home
Assessing Weight Loss Readiness

- **Motivation:** Patient is ready to make long-term changes in activity AND diet to lead to a lower weight
- **Stress level:** Patient is free of major life crises
- **Psychiatric issues:** Patient does not have untreated or under treated depression, substance abuse, bulimia nervosa
- **Medical issues:** Patient medical problems are stable
- **Time availability:** Patient can devote 15-30 min/d to weight control for next 26 weeks

**Patient Ready?**

- **YES** Initiate weight loss therapy
- **NO** Prevent weight gain and explore barriers to weight reduction

*Clinical Guidelines on the Identification, Evaluation and Treatment of overweight and Obesity in Adults, NIH – NHLBI 1998*
Assess values and motivators

- The effort of lifestyle change is great
- Motivations vary
- Persistence is linked to how connected a person is to his or her motivator
- Values like responsibility, self-concern, and honesty may be key to making and adapting plans
Build in Monitoring - Success and persistence linked to keeping records or high structure

- Journal
- Reflect on data
- Daily to weekly weights
- Goal setting
Lifestyle management: Processes to be tended and amended

Sustainable Choices fit

- Values
- Plans to reduce barriers
- Preferences – convenience, type
- Resources – time, money, place
- Finances
- Ability
Lifestyle management: Connect patients to local resources

- Refer to programs – nutritionists, Weight management clinic, behaviorists, appropriate commercial diets, self-help groups, local recreation centers, local produce programs
- Encourage investigation and experimentation
- Encourage persistence, flexibility, and hope
Document the plan

- Type of goal: dietary, activity, other
- Tools to achieve: stuff, time, people, places, skills, knowledge
- Date for start
- Resources needed: people, places, things
- Anticipated barriers
- Strategies
- Assess and redesign
How do I follow-up with clients/patients?

- Research shows that appointments 1-2 times a month for at least 16 weeks are most effective in establishing behavior changes. Long-term frequent follow-up needed for maintenance.

- Follow-up can be in person, group visit, on-line or by phone
Pick your counseling tool

- PACE+
- 5 As
- Motivational interviewing
- Personal improvement
- Diet and activity prescriptions

Make your approach:
- Non-judgmental
- Patient-centered
- Focused
- Documentation friendly
Key Knowledge about obesity that change treatment approach

- Obesity is not fair
- Other diseases promote obesity and impede its treatment
- How much and how well we sleep matters
- It really is unfair for women – pregnancy, motherhood, and menopause provide additional challenges and opportunities
- Obesity is not always reversible, and its control with treatment is variable
- Average activity levels currently lead to decreased lean mass quantity and quality. This decrease has profound implications for obesity and chronic disease prevention and treatment
- Exercise cannot over-come high calorie-dense foods for many people
Key Knowledge about obesity that changes treatment approach

- It is not just calories – protein, fiber, fat composition, sugar, and other factors affect: satiety and satiation, blood pressure, lipids, insulin sensitivity
- Some foods make you hungry
- When we eat matters
- The goal is to teach people basic concepts to assess, adjust and adapt as change is relentless
- Healthcare providers have more impact when they are engaged, not perfect, in making healthy lifestyle choices
- The environment matters
- While everyone does not get “sick” in high risk environments, fewer can stay well, get better, improve optimally
- We all work harder to make good choices in less healthy environments – do we really want to work that hard?
Conclusion

- Obesity is a chronic disease influenced by multiple endocrine pathways that influence eating behaviors and activity levels.
- Neuroendocrine substances that are made in the brain, the gastrointestinal system, and the adipose tissue are just being elucidated.
- Obesity treatment requires behavioral treatment and may require pharmacologic and sometimes invasive treatment to produce optimal disease control.
Weight Management Clinic

- Currently 4 physicians and two nurse practitioners

- This clinic is for obese patients (BMI>30) who are READY to commit to lifestyle changes to maintain weight loss.

- Currently can only accommodate patients with MetroHealth primary care provider
Weight Management Clinic

- Medical management of co-morbid problems through behavior management to produce weight loss
- Evaluation for pharmacologic treatment
- Meal replacement products appropriate for people with hypertension, diabetes, and bariatric patients
- Evaluation for gastric bypass appropriateness and readiness
- Post-operative gastric bypass follow-up for medical problems, nutritional assessment, and adherence to diet and exercise recommendations
- STRIDES 11 week behavioral class
Obesity Treatment Guidelines

The Practical Guide can be found at:

NHLBI web site: www.nhlbi.nih.gov

The Obesity Society web site: www.obesity.org
## Obesity-Related Resources

### Professional Associations

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<tr>
<th>Association</th>
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<tr>
<td>The Obesity Society</td>
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<td>American Academy of Family Physicians (AAFP)</td>
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<td>American College of Sports Medicine (ACSM)</td>
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<td><a href="http://www.eatright.org">www.eatright.org</a></td>
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<td>American Gastroenterological Association (AGA)</td>
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<td>American Society for Bariatric Surgery (ASBS)</td>
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<td>Government Organizations</td>
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<tr>
<td>Centers for Disease Control (CDC):</td>
<td><a href="http://www.cdc.gov/nccdphp/dnpa/obesity/index.htm">www.cdc.gov/nccdphp/dnpa/obesity/index.htm</a></td>
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<td>Centers for Disease Control (CDC):</td>
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<td><em>Prevalence data and growth charts</em></td>
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<td>National Institutes of Health (NIH)</td>
<td><a href="http://www.nih.gov">www.nih.gov</a></td>
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<td>Digestive &amp; Kidney Diseases (NIDDK)</td>
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<td><em>Weight-Control Information Network (WIN)</em></td>
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Weight Management Clinic

- Currently 3 physicians and two nurse practitioners
- This clinic is for obese patients (BMI>30) who are READY to commit to lifestyle changes to maintain weight loss.
Weight Management Clinic

- Evaluation for gastric bypass: appropriateness/readiness
- Medical management of co-morbid problems through behavior management to produce weight loss
- Evaluation for pharmacologic treatment
- Pre-operative gastric bypass evaluation
- Post-operative gastric bypass follow-up for medical problems, nutritional assessment and adherence to diet and exercise recommendations
mice acutely exposed to a high fat diet in the third postnatal week

As adults, the early-exposed mice displayed a significant preference for a diet high in fat compared to controls.

increased intake of high fat diet in early exposed mice was specific to dietary preferences as no changes were detected for total caloric intake or caloric efficiency.

Mechanistically, mice exposed to a high fat diet during early life exhibited significant alterations in biochemical markers of dopamine signaling in the nucleus accumbens, including changes in levels of phospho-dopamine and cyclic AMP-regulated phosphoprotein, molecular weight 32 kDa (DARPP-32) threonine-75, DeltaFosB, and cyclin-dependent kinase 5.

results support our hypothesis that even brief early life exposure to calorically-dense palatable diets alters long-term programming of central mechanisms important in dietary preferences and reward.

Changes may underlie the passive overconsumption of high fat foods contributing to the increasing body mass in the western world.
Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance
Tong Q - *Nat Neurosci* - 01-SEP-2008; 11(9): 998-1000

The physiologic importance of GABAergic neurotransmission in hypothalamic neurocircuits is unknown. To examine the importance of GABA release from agouti-related protein (AgRP) neurons (which also release AgRP and neuropeptide Y), we generated mice with an AgRP neuron-specific deletion of vesicular GABA transporter. These mice are lean, resistant to obesity and have an attenuated hyperphagic response to ghrelin. Thus, GABA release from AgRP neurons is important in regulating energy balance.
Direct and indirect effects of cannabinoids on in vitro GABA release in the rat arcuate nucleus.


The pivotal role of these neuropeptides in energy homeostasis is well-known, although GABA may also be an important signal because targeted knockout of the GABA transporter in NPY/AgRP/GABA neurones results in a lean, obesity-resistant phenotype. In the present study, we describe an in vitro model of K(+) evoked GABA release from the hypothalamus and determine the effects of cannabinoid receptor activation. K(+) evoked GABA release was sensitive to leptin, insulin and PYY(3-36), indicating that GABA was released by arcuate NPY/AgRP/GABA neurones. In the presence of tetrodotoxin (TTX), the cannabinoid CB1 receptor agonist WIN 55,212-2 inhibited K(+) evoked GABA release. This was prevented by the CB1 receptor inverse agonist rimonabant. Rimonabant had no effect when applied alone. In the absence of TTX, however, the opposite effects were observed: WIN 55,212-2 had no effect while rimonabant inhibited GABA release. This indicates that GABA release can involve an indirect, TTX-sensitive mechanism. The most parsimonious explanation for the inhibition of GABA release by a CB receptor inverse agonist is via the disinhibition of an cannabinoid-sensitive inhibitory input onto GABAergic neurones. One local source of an inhibitory neurotransmitter is the opioidergic arcuate neurones. In our in vitro model, K(+) evoked GABA release was inhibited by the endogenous opioid peptide beta-endorphin in a naloxone-sensitive manner. The inhibitory effect of rimonabant was also prevented by naloxone and a kappa-opioid receptor selective antagonist, suggesting that GABA release from arcuate NPY/AgRP/GABA neurones can be inhibited by endogenous opioid peptides, and that the release of opioid peptides is sensitive to cannabinoids.
Physical activity can be divided into three categories: (1) exercise (fitness-and sports-related activities); (2) work-related physical activity; and (3) nonexercise, nonemployment (spontaneous) activity. Tables are widely available that allow one to calculate energy expenditure based on an individual's weight as well as the type and duration of exercise. Only a fraction of Americans engage in exercise at the recommended frequency, intensity, or duration that could be expected to have a protective effect on the development of obesity and other health problems. The portion of Americans who exercise regularly is about 30%, and this does not appear to be changing; therefore, it seems unlikely that a change in exercise habits over the past several decades is causing the increase in obesity. Recent data suggest that the amount of time spent in sedentary activities (e.g., watching television, computer) is an independent predictor of metabolic abnormalities associated with obesity over and above the effects of exercise per se. Thus, to the extent reduced physical activity is contributing to the epidemic of obesity, it is likely that it is reduced employment-related and spontaneous physical activity that is changing.

It is difficult to measure the energy expended in nonexercise activity. Although it seems obvious that employment physical activity has decreased with the advent of more automated systems in the workplace, there are few data in this regard. One estimate suggests that between 1982 and 1992, energy expenditure at work decreased by about 50 kcal/day. The additional changes in the workplace since that time have likely further reduced employment physical activity.

The other component of nonexercise physical activity, the activities of daily living, is equally difficult to measure. A plethora of labor-saving conveniences (e.g., drive-through food and banking, escalators, remote controls, e-mail, online shopping) have been introduced into the modern environment. Each of these further reduces the energy humans must expend to get through the day. Again, there are few hard data to assess how much of a change has actually occurred, although a reduction in daily walking trips and an increase in daily automobile trips has been documented.

Perhaps because it is easier to assess, information on how differences in sedentary activity (television watching, video games, and computer use) relate to obesity is more readily available. There is compelling evidence that more time spent in sedentary pursuits is associated with an increased risk of
Visceral or splanchnic bed tissues account for about 25% of resting metabolic rate but a much smaller proportion of body weight. The brain, which is only a few percent of body weight, accounts for almost 15% of RMR. Likewise, the heart (~7%) and kidneys (~5 to 10%) account for greater portions of resting energy needs than their relative contribution to body mass. In contrast, resting muscle makes up 40 to 50% of lean tissue mass but accounts for only 25% of RMR. This contribution changes dramatically with exercise, however, at which time muscle can account for 80 to 90% of energy expenditure. Adipose tissue is a minor contributor to daily energy expenditure, consuming only approximately 3 kcal/kg of body fat per day. Brown fat is adipose tissue that expresses large amounts of uncoupling protein-1, a protein that allows a mitochondrial membrane proton leak, resulting in heat release as opposed to chemical work from adenosine triphosphate—“uncoupling” of substrate oxidation from chemical or mechanical work. This thermogenic tissue was thought to be present only in human infants but has recently been shown to exist in adults, albeit in amounts insufficient to have measurable thermogenic properties.

Although most of the RMR can be accounted for by the mass of lean tissue, there are also other, more subtle influences on RMR. Age, sex (women have slightly lower BMR even corrected for fat-free mass), and fat mass affect RMR. Small changes in BMR occur during the menstrual cycle (luteal phase > follicular phase). There is also evidence that heritable or family factors influence BMR, accounting for as much as 10% of the interindividual differences.

There are both obligatory and facultative components to resting metabolic rate. With an energy-restricted diet, significant reductions in BMR relative to the amount of fat-free mass occur. Reductions in the production of triiodothyronine from thyroxine and the sympathetic nervous system drive are thought to contribute to this phenomenon. Likewise, during brief periods of overfeeding, resting metabolic rate increases above what would be expected for the amount of lean tissue present.

It has been proposed that individuals with basal metabolic rates lower than predicted are at increased risk of future weight gain. Published data suggest that the relative risk is small, and clinical effort to identify such patients is not warranted. Measurement of BMR is sometimes helpful in the evaluation of patients who insist they are unable to lose weight while following diets containing less than 1000 kcal/day. Almost without fail, their BMR is substantially greater than their reported food intake. This underscores the fact that most adults are unreliable in assessing their own food intake.
Approximately 10% of the energy content of food is expended in the process of digestion, absorption, and metabolism of nutrients. There is a significant interindividual variability in this value, however, ranging from a low of about 5% to a high of about 15% of meal calories that are “wasted” in the postprandial interval. The thermic effect of a meal is related to its carbohydrate and protein caloric content; the fat content has little stimulatory effect. Both obligatory (60 to 70%) and facultative (30 to 40%) components of the thermic effect of food have been identified. The obligatory components no doubt reflect the energy costs of digestion, absorption, and storage of nutrients. The two factors thought to play a role in the facultative component of the thermic effect of food are the postprandial insulin response and activation of the sympathetic nervous system. The thermic effect of food is somewhat lower in insulin-resistant and obese humans, but this has not been linked to future obesity.
The more we store the more fat cells we make

- The excess energy consumed by adults is generally stored as triglycerides in adipocytes. Humans continuously recruit new adipocytes from a large preadipocyte pool, to replace dying adipocytes. Although the primary means by which adipose tissue mass expands is through increased fat cell size (adipocyte hypertrophy), this process can only store a limited amount of fat. If sufficient fat is deposited, eventually there will be a net increase in adipocyte number as more new adipocytes are created than needed to replace dying cells. Some adults recruit new adipocytes more readily than others and thus gain weight more so from adipocyte hyperplasia than from hypertrophy. Those who gain fat with large adipocytes, especially if associated with an adipose tissue inflammatory response (greater numbers of macrophages and other immune cells), are more likely to be insulin resistant and have signs of low-grade systemic inflammation (increased C-reactive protein, mildly elevated interleukin-6 and tumor necrosis factor-α).
From: Diabetes and Coronary Heart Disease

**Metabolic Rate**

Although there is a profound increase in energy expenditure during an actual episode of exercise, the addition of regular exercise to a weight-loss program has negligible effects on REE. In a meta-analysis of prospective RCTs that assigned obese subjects to treatment with diet alone or diet plus exercise, the addition of exercise did circumvent the expected decline in REE when REE was adjusted for body mass.316

**Body Composition**

The composition of weight loss can be influenced by the addition of exercise to a diet program. Pooled data from two meta-analyses found that exercise can reduce the loss of FFM that occurs with weight loss.317 When diet-induced weight loss was approximately 10 kg, regular exercise of low or moderate intensity reduced the percentage of weight lost as FFM from approximately 25% to 12%. Although the difference in weight lost as FFM was large on a percentage basis, it nonetheless represented only a small (approximately 1 kg) difference in the absolute amount of FFM lost. This preservation of FFM with exercise might not necessarily reflect preservation of muscle protein; instead, it may involve increased retention of body water and muscle glycogen. Indeed, nitrogen balance studies have not been able to detect any nitrogen-sparing effect of exercise during diet-induced weight loss in women.318 Whether there is a difference between the effects of endurance and those of resistance exercise on FFM conservation is not clear because the available data are limited and conflicting.
Energy Gap:

Peripheral metabolic responses occur, including preferential lipid accumulation in adipose tissue via hyperplasia and the presence of two humoral adiposity factors that underestimate peripheral adiposity.122 This underestimation of peripheral adiposity likely signals the central nervous system to positively skew the energy balance. These findings support the existence of a compensatory metabolic response to weight loss that opposes weight-loss maintenance and instead encourages the body to regain lost weight. Moreover, this homeostatic feedback system does not appear to readjust over time as a function of weight-loss maintenance.

Consequences of the Energy Gap
These studies indicate that the issues surrounding weight loss maintenance may be much broader than that of individual motivation and self-control. Because RMR decreases after significant weight loss, the resulting energy gap shifts the balance between energy intake and expenditure requirements. With lower energy expenditure, it becomes more difficult for individuals to achieve the energy balance necessary for weight-loss maintenance. According to Hill, a weight loss of 40 pounds would result in an energy gap of 300 kcal to 350 kcal.125 Thus, to maintain weight loss, an individual would have to either permanently reduce their energy intake by an additional 300 kcal to 350 kcal per day or increase their energy expenditure by 300 kcal to 350 kcal per day. This would roughly equate to taking an additional 6,000 steps or 3 miles per day. Although possible, both of these options pose difficult life-long challenges to weight maintenance. This highlights the challenge caused by the energy gap in weight maintenance and the importance of viewing weight loss and weight maintenance as two separate issues with separate underlying processes.
Fig. 2. Scatterplot of weight change and initial BMI for black adolescents. OCP = oral contraceptive pill; DMPA = depot medroxyprogesterone acetate; BMI = body mass index.

Mangan, Larsen, and Hudson: Weight Gain in Adolescents Using DMPA
**Fig. 1.** Scatterplot of weight change and initial BMI for white adolescents. OCP = oral contraceptive pill; DMPA = depot medroxyprogesterone acetate; BMI = body mass index.
Increased Risks in Pregnancy associated with Obesity

- Gestational Diabetes
- Hypertension
- Disordered breathing/Obstructive Sleep Apnea
- Cesarean section rate (RR 1.5-1.8)
- Congenital heart defects (OR 1.4-2.0)
- Spina Bifida (OR 3.5)
- Omphalocele (OR 3.3)
- Increased levels of leptin, crp and tnf-alpha
Adipose Tissue

- Cell differentiation from pre-adipocytes is also stimulated by cortisol which bonds with the cytosolic nuclear hormone receptor.
- Visceral adipose tissue has very high lipolytic activity and releases nonesterified fatty acids (NEFA) into the blood. The NEFA inhibit glucose metabolism.
- Cortisol is synthesized locally in an unregulated manner and acts to increase hepatic gluconeogenesis and glucose release as well as lypolysis – up 15 times higher than serum concentration.
Visceral Adipose Tissue as a Cause of Insulin Resistance

- HPA theory: In obesity increased hypothalamic pituitary axis activation causes preferential adipose deposition in the trunk
- Glucocorticoids inhibit growth hormone, gonadal steroid production - leads to less lipolysis, bone and muscle catabolism – leads to more adiposity and decreased lean mass
- Slow wave Sleep supports HPA inhibition with minimized cortisol, increased GH and TSH diurnal peaks
Visceral Adipose Tissue as a Cause of Insulin Resistance

Overflow theory: Visceral tissue represents the limited storage capacity of subcutaneous adipose tissue. After the compartment is filled, it overflows to ectopic sites – liver / muscle – and excessive ectopic fat causes metabolic dysfunction

- Hepatic fat is associated with dyslipidemia and hepatic insulin resistance
- Myocellular fat is associated with skeletal muscle insulin resistance
Visceral Adipose Tissue as a Cause of Insulin Resistance

- Direct effect of omental and mesenteric adipose tissue depots on the insulin resistance, lipoprotein metabolism, and blood pressure. Metabolic products of omental and mesenteric adipose tissue depots are released into the portal vein which provide direct delivery to the liver and provide substrate for lipoprotein synthesis.

- Ectopic lipids in the pancreatic islets can cause lipotoxic destruction of beta cells.
Obesity is often not reversible: Adipose tissue hyperplasia

Examples in human research:

- Obese women with more fat cell hyperplasia regained more weight than those with hypertrophy only, and those with mixed hypertrophy and hyperplasia.

- In women who lost weight to non-obese levels through low calorie diets, adipose tissue hyperplasia (too many small fat cells) and low leptin production resulting in relative hypoleptinemia in the fasting (basal) state are common features.

- Body-weight-reduced obese women had low basal and catecholamine-stimulated adipocyte lipolysis, presumably due to adipose tissue hyperplasia - may contribute weight regain.

- After the more extreme no longer performed jejunal-ileal bypass, fat cell size was much smaller, fat cell number unchanged. This is true for gastric bypass as well.

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Figure 1 A screen capture from the American Medical Association’s video “Is Obesity a Disease?” (44).
Endocannabinoids

- Endogenous lipophilic substances made centrally and peripherally in vertebrates that activate G protein receptors
- Best characterized are:
  - N-arachidonoylethanolamine (anandamide)
  - 2-arachidonoylglycerol (2-AG)
- Centrally endocannabinoids activate CB1 receptors
- Peripherally endocannabinoids activate CB2 receptors
Endocannabinoids, contd.

FROM RODENT STUDIES:

- CB1 ligands highest during fasting (High ghrelin, low leptin state) and lowest after feeding) in hypothalamic and limbic areas

- Enzymes that hydrolyze endocannabinoids:
  - Leptin decreased endocannabinoid levels centrally and peripherally through the upregulation of a hydrolytic enzyme (FAAH)
  - Ghrelin may upregulate endocannabinoids and CB1 blockers may down-regulate ghrelin

FROM RODENT STUDIES:

- CB1 deficient rodents are lean and resistant to high fat diets
- Cannabinoids modulate fatty acid synthesis and β-oxidation in the liver and hypothalamus through the AMP activated protein kinase system which is the sensor for cellular energy status. It is activated by an increased AMP:ATP ratio. A decline in ATP lead to increased food intake
Change from Baseline in Body Weight and Waist Circumference: RIO-Europe

Proportion of Patients Who Lost ≥5% & ≥10% of Baseline Weight at 1 Year: RIO-Europe

**Weight Loss ≥5%**

**A. ITT Population**

- Placebo: 19-2%
- Rimonabant 5 mg: 33-2%*
- Rimonabant 20 mg: 50-9%*

**B. Completers**

- Placebo: 30-5%
- Rimonabant 5 mg: 44-2%†
- Rimonabant 20 mg: 67-4%*

**Weight Loss ≥10%**

* p<0.001 vs. placebo
† P=0.002 vs placebo

Mean Percent Change from Baseline in HDL-C and TG: RIO-Europe

Sibutramine Blocks Neuronal Monoamine (Serotonin, Norepinephrine, Dopamine) Reuptake

= Monoamine  S = Sibutramine
Effect of Continuous vs Intermittent Sibutramine Therapy on Body Weight

Sibutramine dose=15 mg/d.

Zonisamide – proposed mechanisms of action

- Serotonergic and dopaminergic activity
- Inhibits Na/Ca channels
- Carbonic anhydrase inhibitor
Zonisamide evidence

- 16 week trial in 60 obese subjects on a low calorie diet tx with 400-600mg/day zonisamide or placebo. Treated group with 6.6% weight loss compared to 1% weight loss in placebo group.

- 37 completed a second 16 weeks. Weight loss 9.6% in zonisamide compared to 1.6% in placebo (Gadde et al., Zonisamide for weight loss in obese adults: a randomized controlled trial. JAMA 2003; 289:1820).

- Also effective in a small 12-week open label trial for the treatment of BED in combination with bupropion (Gadde et al – J Clin Psychiatry 8, 2007).
Summary of Zonisamide side effects

- Common: Nausea, anorexia
- Less common: Somnolence, dizziness, ataxia, confusion, difficulty concentrating
- Serious: Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, agranulocytosis, nephrolithiasis; renal insufficiency; in children, fever and hyperhidrosis
National Weight Loss Registry

Original Cohort: 784 in initial cohort (629 female)
Eligible subjects had maintained 13.6kg loss for over a year
(avg. loss 28kg)
Now over 2900 members who have lost an average of 32.4kg
and maintained the loss for 5.5 years

FINDINGS:

- Low calorie diet (1296kcal/day for women and 1724kcal/day for men)
- High levels of physical exercise (equivalent of about 28miles of walking/week)
- Weight maintenance method (77% weigh at least weekly)
- Later study found maintenance less difficult with time

### TABLE 1. 
*Estimated Nutrient Composition of Popular Diets and National Dietary Recommendations*

<table>
<thead>
<tr>
<th>Popular Diet Program</th>
<th>Kcal from Carbohydrate (%)</th>
<th>Kcal from Protein (%)</th>
<th>Kcal from Fat (%)</th>
<th>Kcal from Saturated Fat (%)</th>
<th>Cholesterol (mg)</th>
<th>Fiber (gm)</th>
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<tbody>
<tr>
<td>Atkins [82]</td>
<td>5</td>
<td>35</td>
<td>59</td>
<td>26</td>
<td>924</td>
<td>4</td>
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<td>“Protein Power”</td>
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<td>35</td>
<td>53</td>
<td>19</td>
<td>657</td>
<td>11</td>
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<td>“Sugar Busters”</td>
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<td>32</td>
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<td>24</td>
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<tr>
<td>“The Zone”</td>
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<td>28</td>
<td>32</td>
<td>7</td>
<td>264</td>
<td>18</td>
</tr>
<tr>
<td>Ornish [83]</td>
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<td>7</td>
<td>2</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>National dietary recommendations</td>
<td>55–58</td>
<td>12–15</td>
<td>30–35</td>
<td>&lt;10</td>
<td>&lt;300</td>
<td>20–30</td>
</tr>
</tbody>
</table>

*Based on 1600 kcal/d. 
Figure 1. Mean (±SE) Percent Change in Weight among Subjects on the Low-Carbohydrate Diet and Those on the Conventional (Low-Calorie, High-Carbohydrate) Diet, According to an Analysis in Which Base-Line Values Were Carried Forward in the Case of Missing Values (Panel A) or an Analysis That Included Data on Subjects Who Completed the Study and Data Obtained at the Time of the Last Follow-up Visit for Those Who Did Not Complete the Study (Panel B). In Panel B, the low-carbohydrate group had 28 subjects at 3 months, 24 subjects at 6 months, and 20 subjects at 12 months, and the conventional-diet group had 21 subjects at 3 months, 18 subjects at 6 months, and 17 subjects at 12 months. Asterisks indicate a significant difference (P<0.05) between the groups.
Meal Replacements Enhance Initial and Long-term Weight Loss

1200–1500 kcal/d diet prescription.
CF=conventional foods.
MR-2=replacements for 2 meals, 2 snacks daily.
MR-1=replacements for 1 meal, 1 snack daily.

Providing Prepackaged Meals Enhances Weight Loss

![Graph showing weight change over time for different treatment groups.]

- **Weekly Treatment**
  - Control: Weight remains stable.
  - Behavior Therapy + Self-selected diet: Significant weight loss.
  - Behavior Therapy + Food Provision: Moderate weight loss.

*P* = 0.0001 treatment vs control.
*P* = 0.0002 behavior therapy + self-selected diet vs behavior therapy + food provision.