Body Fat is an Endocrine Organ that Modulates Appetite

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Summary

• Fat cells play a crucial role in the endocrine system
• Diet high in empty carbohydrates and low in fats and cholesterol leads to metabolic syndrome
• Fat cells extract cholesterol from damaged LDL and transport it to HDL
• Fat cells become dysfunctional over time
• Many bad consequences

Outline

• Fat Cells as an Endocrine Organ
• Why we are Unhealthy
• Cholesterol and Vitamin D are Vital Nutrients
• Lipoproteins (LDL, HDL, Chylomicron)
• Obesity Epidemic and Metabolic Syndrome
• How Excess Sugar Leads to Insulin Resistance
• How Fat Cells Become Damaged by Helping Out
• Roles of Pituitary Gland and Hypothalamus
• Relationship between Anorexia and Obesity
• Summary

Fat Cells are an Endocrine Organ

Endocrine Actions of Adipose Tissue

• Stores energy as triglycerides and releases it as free fatty acids
• Provides a buffer of cholesterol for lean times
• Secretes important peptides for regulating appetite:
  – Leptin: makes you feel full
  – Adiponectin: stimulates appetite
• Secretes regulatory proteins
  – Tumor necrosis factor-α (TNF-α)
  – Interleukin-6 (IL-6)
  – Angiotensin-II

What’s Missing from This Picture?

Endocrine System: Set of ductless glands that produce hormones regulating metabolism, growth, and development.
Endocrine Actions of Adipose Tissue (cont’d)

- Peptides released by fat cells influence other cell types:
  - Hypothalamus in the brain
  - Hepatocytes in the liver
  - Muscle cells in the skeletal muscles and heart
- Positive correlations exist between obesity, insulin resistance, chronic inflammation, and heart disease

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Why We Are Unhealthy!

- Too much sugar
- Less than 2% fat
- Too little vitamin D
- Too little fat

The Main Culprit: Empty Carbs

- A diet high in fructose and refined carbs leads over time to insulin resistance and obesity
- Deficiencies in four principle nutrients:
  - Fat, cholesterol, vitamin D, calcium
- Challenge is to assure adequate fuel supply at all times
  - Fat cells work overtime
  - Body fat mass increases

Scientific American, May, 2010

“If you reduce saturated fat and replace it with high glycemic index carbohydrates, you may not only not get benefit you might actually produce harm”

--- David Ludwig, director of the obesity program at Children’s hospital, Boston

- Sugared beverage industry is lobbying hard to keep this knowledge out of dietary guidelines

The French Paradox is No Paradox

- Caviar, crème brûlée, liver paté, brie, escargots
  - These foods contain lots of fat and cholesterol
- The Mediterranean sun
Cholesterol is Indeed the Problem

- But, it is a deep irony that ...

Too LITTLE rather than too MUCH cholesterol is a root cause of the metabolic syndrome

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These Crucial Nutrients Form a Tightly-Knit Support Group

- Cholesterol plays crucial role in fat digestion
  - Principal component of bile
- Vitamin D is fat soluble
  - Only found naturally in foods high in fat
- Vitamin D necessary for both:
  - Calcium absorption from the gut
  - Calcium-dependent metabolic processes
- Fats promote absorption of calcium and vitamin D
- Vitamin D is synthesized from cholesterol
- Cholesterol protects fats from oxidation

Cholesterol in the Brain

- Brain houses 25% of the body’s cholesterol with only 2% of the total mass
- Cholesterol enhances signal transport at synapse
- Cholesterol protects signal from leakage in myelin sheath
- Cholesterol protects cells from oxidative damage

Cholesterol and Vitamin D

- Cholesterol and Vitamin D are nearly identical in chemical structure
- Vitamin D is synthesized from cholesterol in the skin upon exposure to sunlight

Cholesterol is a Miracle Worker

- In the brain:
  - Synapse: promotes cell-cell communication
  - Myelin sheath: insulates channel from signal loss
- In the membranes of all cells
  - Protects from oxidative damage
  - Protects from pathogens (microbes)
- In the LDL
  - Essential for protecting fats and antioxidants in transport to cells
- Precursor to vital hormones
  - Vitamin D
  - All the sex hormones (testosterone, estrogen, etc.)
  - Cortisone: the stress hormone
- Aids in digestion of fats
Vitamin D is a Miracle Worker

- Vitamin D is necessary for proper utilization of calcium
  - Promotes absorption from gut
  - Promotes uptake by cells
- Vitamin D is essential for bone health
- Vitamin D plays important role in immunity
  - Helps fight infection
  - Protects against autoimmune diseases
- Vitamin D receptors are prevalent in the brain
- According to Michael Holick’s new book, vitamin D protects against:
  - Hypertension, diabetes, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, chronic pain, cancer, and inflammatory bowel disease
- Vitamin D deficiency is widespread in America, particularly among the obese

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Cholesterol Homeostasis

Sizes of Lipoprotein Particles in Blood Serum

Fats and cholesterol enter the bloodstream from the digestive system via the Chylomicron

GOOD

AWESOME

Chylomicron

BAD

VERY BAD: small dense LDL

Structure of LDL

The Life Cycle of the Chylomicron

- Triglyceride composition closely resembles dietary intake
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The Metabolic Syndrome

- Abdominal obesity
- Insulin resistance
- High blood pressure
- High serum triglycerides
- High LDL ("bad" cholesterol), especially "small dense LDL"
- Low HDL ("good" cholesterol)
- Increased risk to heart disease

The Big Picture

- Diet high in empty carbs
  - Liver overworked converting sugar to fat
  - Pancreas can’t release enough insulin
  - Brain doesn’t get enough cholesterol
  - Sugar piles up in blood and damages apoB in LDL (glycation damage)
- Fat cells to the rescue:
  - Work overtime to clean up damaged LDL
  - Work overtime to supply fat and cholesterol
  - Grow in number and size
  - Become damaged and die
- The consequences:
  - Obesity
  - Metabolic syndrome

The U.S. Obesity Epidemic*

- Source: CDC Behavioral Risk Factor Surveillance System

Two Recent Papers

- “Caloric Sweetener Consumption and Dyslipidemia Among US Adults” (JAMA, 2010)
  - HDL cholesterol levels inversely related to consumption of “added sugars” [in processed foods]
- “Saturated Fat, Carbohydrate, and Cardiovascular Disease” (Am. J. Clin Nutr, 2010)
  - Refined carbohydrates increase serum levels of small dense LDL
  - I hypothesize that this is due to glycation damage which interferes with fat and cholesterol uptake from LDL

Why Dietary Fat is Good

- Fat slows down digestion
  - Glucose enters blood stream more slowly
  - Insulin spike avoided
- Fat promotes absorption of calcium and vitamin D
- Fat digests more slowly than carbohydrates and provides buffer when glucose levels drop
- Fat is essential for healthy cell membranes
Type-II Diabetes, Heart Disease and Vitamin D*

- Cardiovascular disease is leading cause of death for diabetics
  - Low vitamin D levels nearly doubles relative risk
  - Vitamin D deficiency is 20% more prevalent in diabetics
- Vitamin D improves insulin signaling and therefore reduces glycation damage to LDL
- Vitamin D suppresses cholesterol uptake in atherosclerotic plaque


Feeding Hamsters Fructose*

- Hamsters resemble humans in lipoprotein metabolism
- Hamsters fed high-fructose diet for two weeks
- Liver synthesized substantially more LDL
- Liver hoarded cholesterol to encase fat stores
- Liver secreted much less cholesterol than controls
- Liver exhibited signs of insulin resistance


What Happens when you Feed Baboons a Zero-Cholesterol Diet?*

- Blood serum triglycerides and cholesterol go up
- They develop aortic fatty streaks
- They develop insulin resistance
- Their bile acids are depleted in cholesterol
- Four test conditions: fructose, glucose, sucrose, starch
  - Fructose-fed group had worst outcome (e.g., 65% increase in triglycerides)

* Kritchevsky et al., American Journal of Clinical Nutrition, 1974

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Insulin

- Insulin is essential for fat and muscle cells to consume glucose
- Insulin suppresses release of fats from liver and muscles
- Beta cells in pancreas can’t release insulin if conditions aren’t right

Regulation by Insulin and Glucagon

- Insulin and glucagon have opposite effects on liver, muscles, fat cells, and kidneys for controlling blood-glucose levels.
**Blood Sugar Levels after a Meal**

- **Steady State**
- **Prediabetic**
- **Diabetic**

**Beta Cells in Pancreas**
- Beta cells are very picky.
- They require:
  - Cholesterol
  - Fats
  - Vitamin D
  - Calcium
before they will release insulin
- Without these nutrients, they will become damaged and die

**Insulin is Very Potent**
- Fat cells can’t release fats
- Liver preoccupied with glucose uptake and storage
- Fat cells store glucose as fat

**Lipolysis Suppressed by Insulin**
- Adipose tissue
- Fat Cells
- Triglycerides
- Lipase
- Hormone-sensitive lipase
- Insulin
- Glucagon
- Enhance
- Suppress
- Insulin
- Lipolysis
- Suppressed
- UDL
- Insulin
- Lipogenesis
- Triglycerides

**Fat Cells Stay Up Late**
- Fat cells store reserve fats and cholesterol for protection against shortages
- Person on high-carb diet will be fat-deprived unless fat cells pitch in
  - Fat cells release high levels of triglycerides very early in the morning (after insulin levels have finally dropped)
  - These pre-released triglycerides must supply brain’s and body’s needs during entire day

**Fat Cells: Insulin Absent**
- Glucose
- Amino acids
- Fatty acids, glycerol
- Epihernine
- Growth hormone
- ACTH
- Glucagon
- Thyroid hormone
- Adipose cell
- Triglycerides
- Blood
Fat Cells: Insulin Present

- Membrane cholesterol depletion leads to...
- Defective glucose uptake
- Muscles switch over to fat metabolism
- Force liver to convert glucose to fats to be stored (fatty liver)

Condition Worsens over Time

- β cells must produce excess insulin
- β cells become damaged because of oxidation exposure due to excessive energy needs
- Eventually, β cells die and glucose can’t be metabolized by muscles and fat cells
- Fat cells must buffer up lots of fat for protection against starvation

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Fat Metabolism in Body

- How Cells Obtain Cholesterol
  - Most cells can’t make their own cholesterol: complicated 30 step process
**VLDL Remnants**
- Residue after fats have been delivered to tissues
- Damaged by exposure to oxygen, glucose, and fructose
- Fat cells scavenge them and break them down for recycling
- Exported as HDL if ApoE is abundant

**VLDL Clearance with High ApoE**
- After VLDL has delivered its contents, a "remnant VLDL particle" needs to be taken up and recycled
- Liver and fat cells accomplish this if they have sufficient ApoE

**VLDL Clearance with Low ApoE**
- ApoE is highly susceptible to damage by glucose and fructose

**Development of Atherosclerotic Plaque**
- Major purpose of macrophages in fatty streaks is to convert LDL to HDL

**Experiment on Cholesterol Depletion in Fat Cells**
- Normal fat cells from rats were exposed in vitro to MβCD
  - Depleted cholesterol from cell walls
  - Caused activation of cholesterol-acquiring proteins
  - Caused insulin resistance and increased synthesis of TNF-α, angiotensinogen, and IL-6
  - Related to hypertension, inflammation, and atherosclerosis

**Conclusion:**
- Fat cell membrane cholesterol depletion is key manifestation of metabolic syndrome
Endoplasmic Reticulum Becomes Sick
- Endoplasmic reticulum essential for protein folding and activation
- Absence of ApoE leads to internal cholesterol accumulation
- Excess cholesterol destroys cell’s ability to fold proteins
- This causes major dysfunction and eventually leads to cell disintegration

Fat Cells Become Dysfunctional
- Endoplasmic reticulum has too much cholesterol which inhibits calcium transport
- Plasma membrane has too little cholesterol, which causes sodium leaks

Fat Cells Launch Distress Cascade
- Release IL-6 and TNF-α
  - Calls in macrophages
- Release leptin
  - Decreases glucose uptake
- Release angiotensin-II
  - Suppresses synthesis of apoE
  - Increases thirst due to sodium leaks
  - Promotes uptake of cholesterol from HDL for plasma membrane

Widespread Effects of Angiotensin II
- Systolic hypertension
- Decreased systemic delivery
- Atherosclerosis
- Essential blood pressure
- Athero

Visceral Fat
- Damaged VLDL remnants leads to widespread cholesterol deficiency
- Major organs are especially susceptible (e.g., pancreas, liver, adrenal glands, reproductive organs, etc.)
- Proposal: Visceral fat deposits store reserve cholesterol supply

Visceral Fat Supplies Liver
- Both muscle and liver insulin sensitivity inversely related to amount of abdominal fat

Picture from Wan et al., The FASEB Journal, 2007

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Pituitary and Hypothalamus

Hypothalamus Controls Appetite

Obesity associated with:
- High leptin levels
- Low ghrelin levels

GI Neurons are Sick in Obesity

- “Glucose Inhibitory” cells = inhibited by glucose
- Fire to induce hunger when glucose is low
- They should stop firing when glucose is sufficient
- However, their metabolism is tied to that of the insulin-synthesizing β cells: they suffer from insulin resistance when β cells are defective
- They never stop firing; person is never full
- Fat and cholesterol accumulate in dysfunctional fat cells
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Anorexia and Obesity: Two Sides of a Coin

Anorexia:
- Insulin sensitivity
- Low leptin (not full)
- High adiponectin (hungry)
- Paradoxical reduced appetite

Obesity:
- Insulin resistance
- High leptin (full)
- Low adiponectin (not hungry)
- Paradoxical increased appetite

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Further Reading

- “Is the metabolic syndrome caused by a high fructose, and relatively low fat, low cholesterol diet?” Stephanie Seneff, Glyn Wainwright and Luca Mascitelli, Archives of Medical Science, In Press
- Good Calories Bad Calories, by Gary Taubes, New York Times journalist
- Fat and Cholesterol are Good for You, by Dr. Uffe Ravnskov
- Trick And Treat - how 'healthy eating' is making us ill, by Barry Groves
Thank You!