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Biochemistry 2

Doctor 2018 | Medicine | JU

Sheet Slides

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Hormones and Metabolism

I) Metabolic effects of insulin

See the dimerization in insulin "tyrosine kinase" receptors.

Insulin is a peptide hormone release by the β cells of the islet of Langerhans in response to rising glucose in your bloodstream (after eating a carbohydrate- rich meal).

Its metabolic effects are anabolic, favoring, for example, synthesis of glycogen, TAG, and protein.

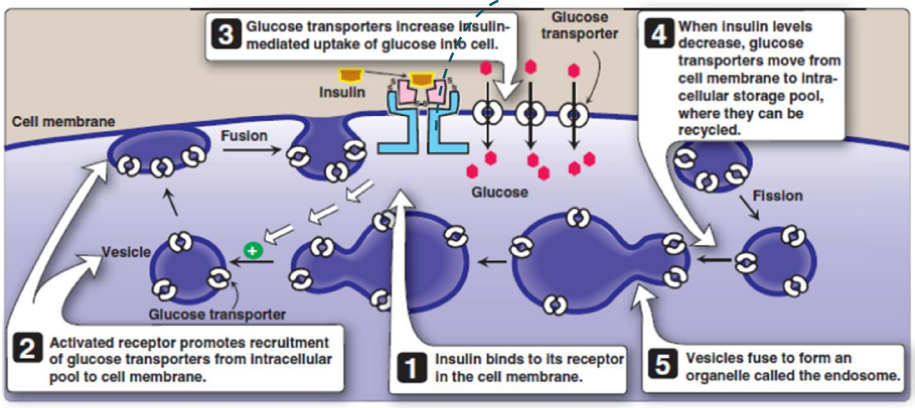


Figure 23.8
Insulin causes the recruitment of glucose transporters (GLUTs) from intracellular stores in skeletal and cardiac muscle and adipose tissue.

Effects on carbohydrate metabolism

Glucose is **stored** mostly in three tissues: liver, muscle, and adipose.

- In the liver and muscle (glycogen storages): insulin **increases↑** glycogen **synthesis**.

-In the muscle and adipose, insulin **increases↑** glucose **uptake** by increasing the number of glucose transporters (GLUT-4) in the cell membrane.

- In the liver, insulin **decreases↓** the production of glucose through the **inhibition↓** of **glycogenolysis** and **gluconeogenesis**.

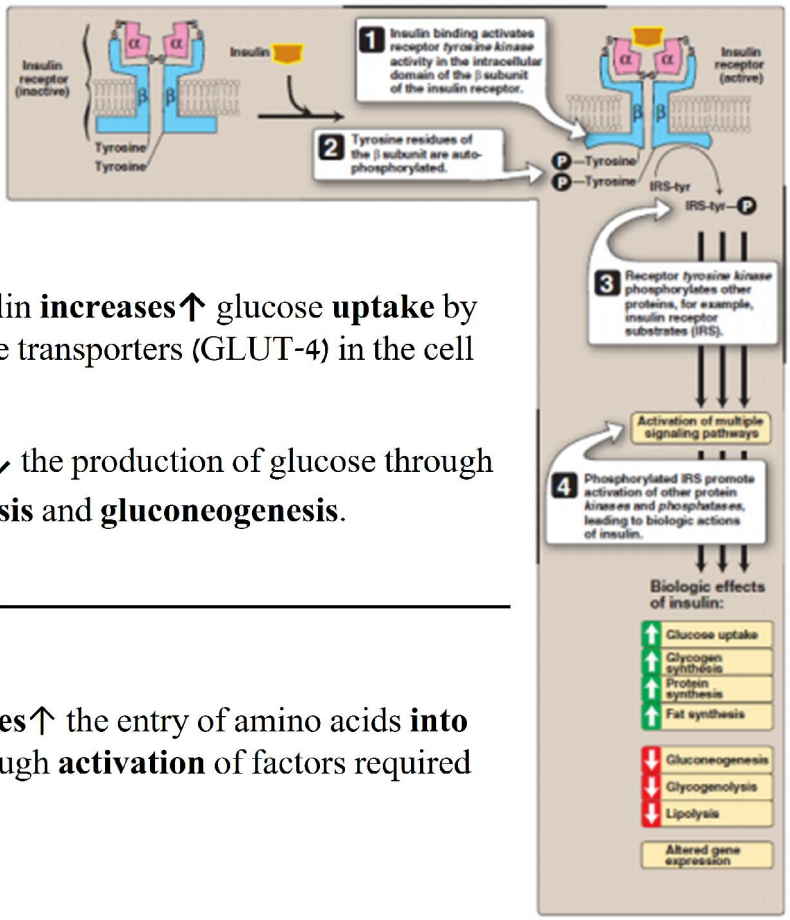


Figure 23.7
Insulin receptor. IRS = Insulin receptor substrate.

Effects on protein synthesis

In most tissues, insulin **stimulates↑** the entry of amino acids **into** cells, and **protein** synthesis through **activation** of factors required for translation.

Effects on lipid metabolism

Adipose tissue (very sensitive to insulin) responds within minutes to insulin causing a significant **reduction↓** in the release of fatty acids. This happens by two mechanisms:

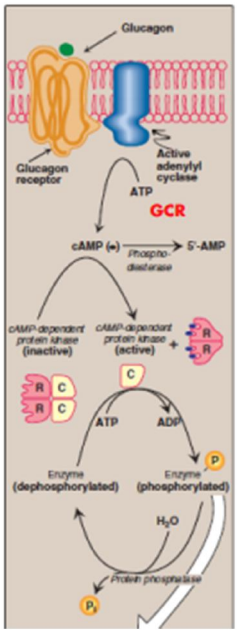
1. **Decreased↓** TAG degradation: Insulin **decreases↓** circulating free fatty acids by **inhibiting↓** the activity of *hormone sensitive lipase* that degrades triacylglycerol in adipose tissue (**inhibiting↓** lipolysis). It acts by promoting the **de**phosphorylation and, hence, **in**activation of the enzyme.

2. **Increased↑** TAG synthesis: Insulin **increases↑** the transport and metabolism (DHAP reduction to glycerol 3-P) of glucose **into** adipocytes, providing **glycerol 3-phosphate (from the liver)** for TAG synthesis.

Insulin also **increases** the lipoprotein lipase activity of adipose tissue by **increasing↑** the enzyme's **synthesis**, thus providing fatty acids for esterification (within adipocytes).

In **liver**, insulin promotes the conversion of glucose to TAG.

II) Metabolic effects of glucagon



Glucagon is a polypeptide (29 amino acids) hormone secreted by the α cells of the pancreatic islets of Langerhans when the concentration of insulin (and indirectly glucose) in the bloodstream falls too low.

Glucagon is synthesized as a large precursor molecule that is converted through a series of cleavages.

Glucagon, along with **epinephrine** (fight or flight neurotransmitter / hormone), **cortisol**, and **growth hormone** (the "counter-regulatory hormones") opposes many of the actions of insulin.

Glucagon receptors (**G-protein coupled receptors**) are found in **hepatocytes** but not on skeletal muscle.

Glucagon **secretion** is increased in response to:

1. **Low↓** blood glucose.

2. **Amino acids↑** derived from a meal containing **protein (in order to be utilized in gluconeogensis)**.

3. Epinephrine or norepinephrine (fight or flight).

Glucagon secretion is **inhibited** by **elevated↑** blood glucose and by insulin.

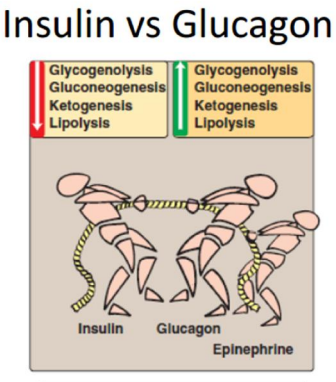
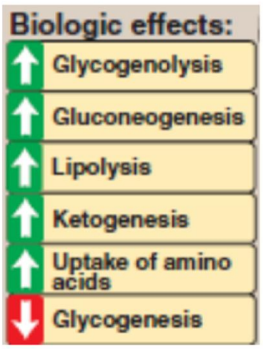


Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

It acts to maintain blood glucose levels by **activation**↑ of hepatic **glycogenolysis** and **gluconeogenesis**.

Effects on carbohydrate metabolism

Glucagon **increases**↑ the **breakdown** of liver (not muscle) **glycogen** and **activates**↑ gluconeogenesis.



Effects on lipid metabolism

Glucagon **activates**↑ **lipolysis** in adipose tissue and the free fatty acids released are taken up by **liver** and **oxidized** to acetyl coenzyme A, which is used in **ketone body synthesis**.

Effects on protein synthesis

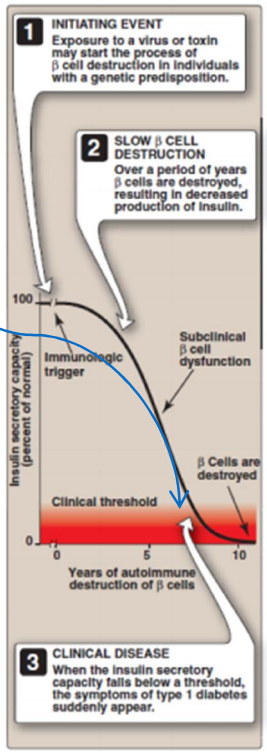
Glucagon **increases**↑ uptake of amino acids by the **liver**, resulting in **increased**↑ availability of carbon skeletons for **gluconeogenesis**, thus, plasma levels of amino acids are **decreased**↓.

The citric acid cycle is unable to oxidize all the acetyl units generated by the degradation of fatty acids. Gluconeogenesis depletes the supply of oxaloacetate, which is essential for the entry of acetyl CoA into the citric acid cycle. Consequently, the liver produces large quantities of ketone bodies (insufficient oxaloacetate for the condensation step).

Diabetes and Metabolism

Type I Diabetes Mellitus (DM)

This disease is characterized by an absolute deficiency of insulin caused by an autoimmune / toxins/ infections attacks on the β cells of the pancreas. However, the disease doesn't appear immediately after the cells distruction.



It affects metabolism in three tissues: liver, muscle, and adipose tissue.

Elevated levels of blood **glucose**↑ and **ketones**↑ are the hallmarks of untreated disease.

Hyperglycemia is caused by **increased**↑ hepatic production (gluconeogenesis↑, glycogenolysis↑) of **glucose (no insulin to dephosphorylate the enzymes)**, combined with **diminished**↓ peripheral **utilization** (muscle and adipose have the **insulin-sensitive** GLUT-4). ←cells are starving when blood glucose is **high**! (Insulin is absent) ☹

Ketosis results from **increased**↑ mobilization of fatty acids from adipose tissue (lipolysis↑), combined with **accelerated** hepatic fatty acid β-oxidation↑ and synthesis of 3-hydroxybutyrate and acetoacetate.

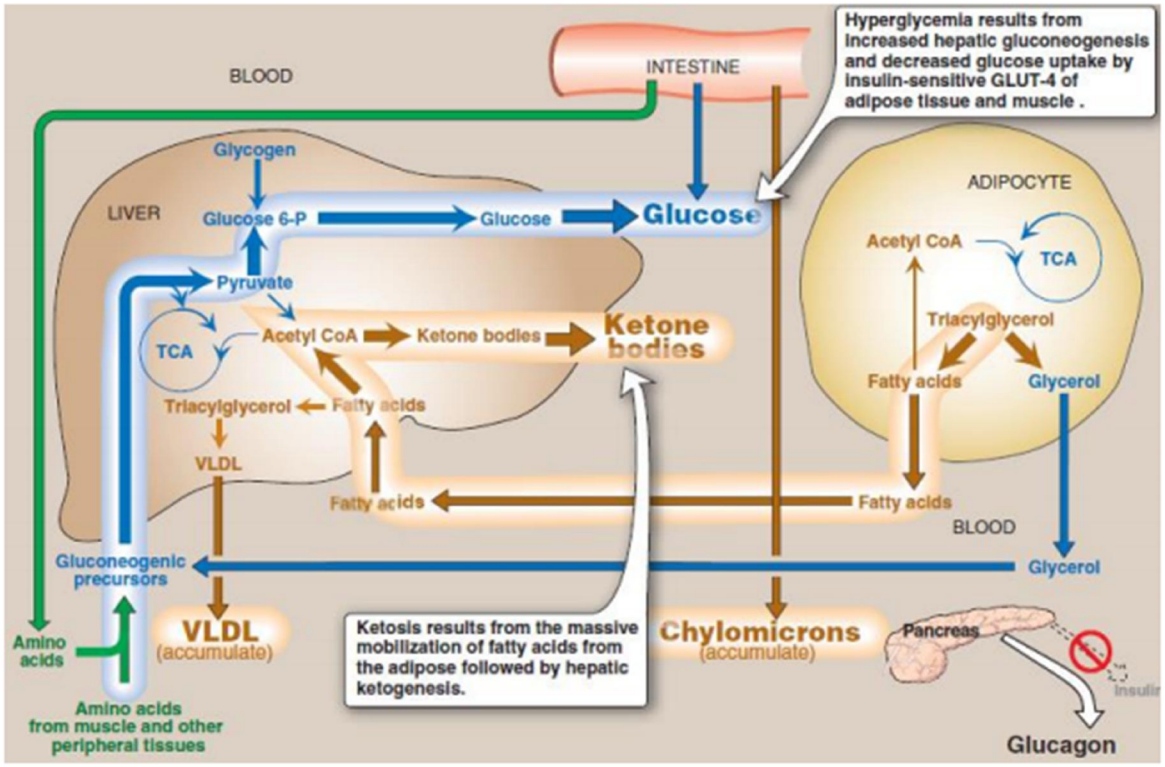
Hyper-triacylglycerolemia

Not all the fatty acids flooding the **liver** can be disposed of through **oxidation** or **ketone** body synthesis.

These excess fatty acids are **converted** to TAG, which is packaged and secreted in very-low-density lipoproteins (**VLDL**).

Chylomicrons are synthesized from **dietary** lipids by the intestinal mucosal cells following a meal.

Now because lipoprotein degradation catalyzed by **lipoprotein lipase** in the capillary beds of muscle and adipose tissue is low↓ in diabetics (**synthesis of the enzyme is decreased** when insulin levels are **low**), the plasma **chylomicron and VLDL** levels are elevated↑, resulting in "hyper-triacylglycerolemia" or "dyslipidemia".



Type II Diabetes Mellitus (DM) (more common (90%)

It develops gradually without obvious symptoms.

Polyuria, polydipsia and polyphagia. (This is not mentioned by the doctor)

A combination of **insulin resistance** and dysfunctional β cells (the doctor mentioned insulin resistance only).

The metabolic alterations are **milder** than those for type 1, because insulin secretion in type 2, **does restrain ketogenesis and blunts the development of diabetic ketoacidosis** (DKA).

Pathogenesis **does not** involve viruses or autoimmune antibodies.

So what does "insulin resistance" mean?

IR is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal (or elevated) circulating concentrations of insulin.

It is characterized by **uncontrolled** hepatic glucose production↑ (the liver is not responding to insulin which tells it to stop glucose production) and **decreased**↓ glucose **uptake** by muscle and adipose tissue (the same idea, these cells resist insulin).

Obesity is the most common cause of IR.

Type 2 diabetes develops in insulin-resistant individuals who also show impaired β-cell function.

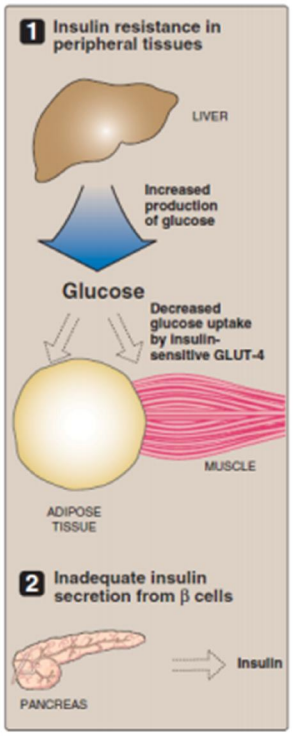


Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes.

Insulin Resistance (IR)

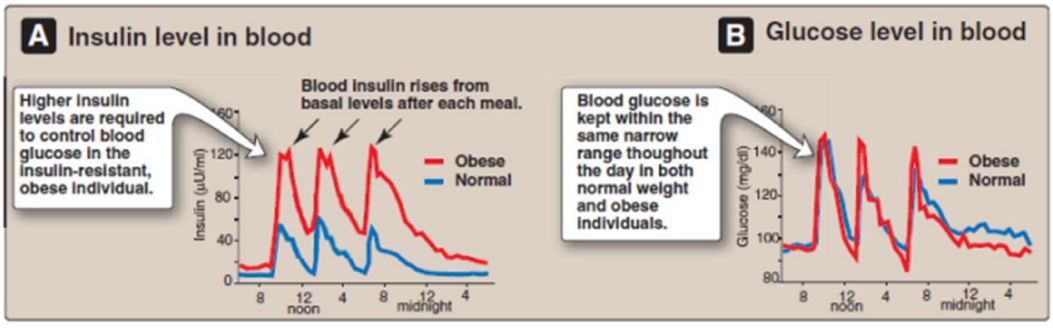


Figure 25.7
Blood insulin and glucose levels in normal weight and obese subjects.

In DMT2 hyperglycemia is caused by increased hepatic production of glucose, combined with diminished peripheral use. Cells are **starving** when blood glucose is **high**! (Cells are not responding) ☹

Ketosis is usually minimal or absent in type 2 DM because the **presence of insulin** -even in the presence of IR- **diminishes** hepatic ketogenesis.

Dyslipidemia; in the liver, fatty acids are converted to triacylglycerols, which are packaged and secreted in VLDL. Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal.

Now because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is **low** in diabetics, the plasma chylomicron and VLDL levels are elevated↑, resulting in hyper-triacylglycerolemia.

Low↓ HDL (the good one) levels are also associated with type 2 diabetes.

IR alone will not lead to type 2 diabetes.

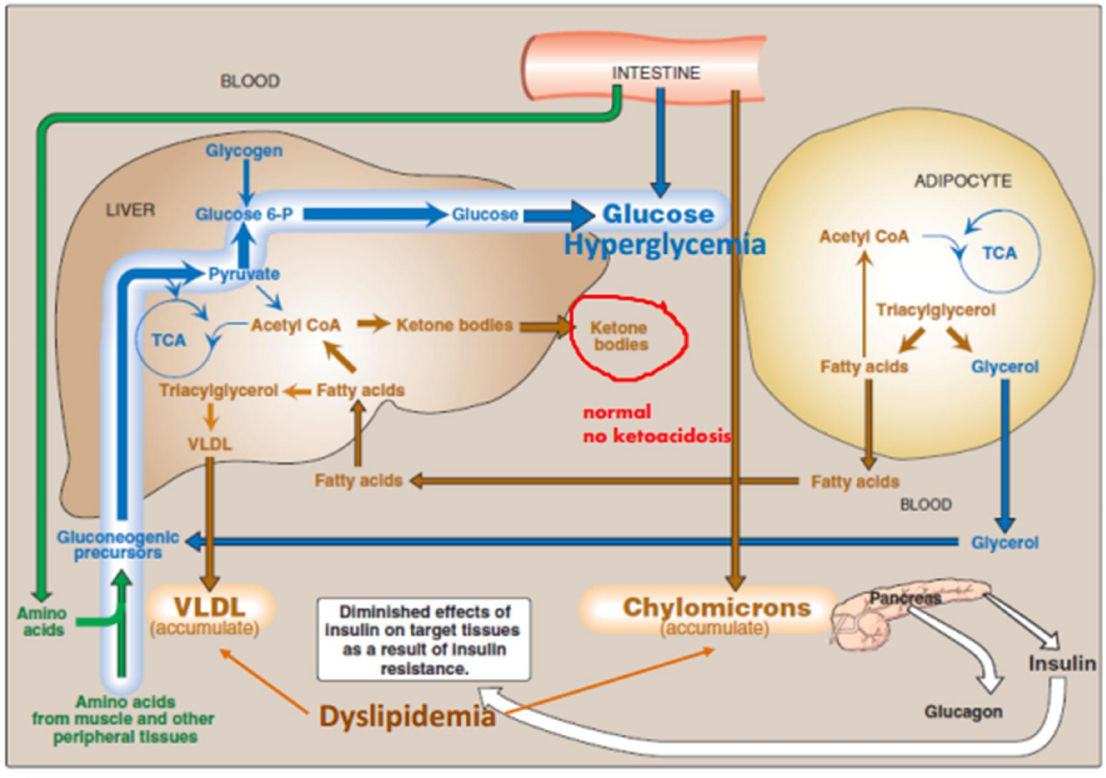


Figure 25.10
Intertissue relationships in type 2 diabetes.

Fasting and Metabolism

Fasting begins if no food is ingested after the absorptive period.

It results from an inability to obtain food, the desire to lose weight rapidly, or clinical situations in which an individual cannot eat, for example, because of trauma, surgery, cancer, or burns.

In the absence of food, plasma levels of glucose, amino acids, and TAG **fall**↓, triggering a decline in **insulin** ↓secretion and an increase in **glucagon**↑ release.

The nutrient deprivation is a catabolic (anabolism↓)period characterized by degradation of TAG, glycogen, and protein in order to:

1) Maintain adequate plasma levels of **glucose** to sustain energy metabolism of the **brain**, **red blood cells**, and other glucose-requiring tissues.

2) Supply the need to mobilize **fatty** acids from adipose tissue, and the synthesis and release of **ketone** bodies from the liver, to supply energy to **all** other tissues.

Although protein is an energy source, protein also has another function, therefore, only ~1/3 of the body's protein can be used for energy production without fatally compromising vital functions.

Also, glycogen degradation supplies energy that is sufficient for the next 8-12 hours only.

Therefore, fat is the major energy reserve of the body.

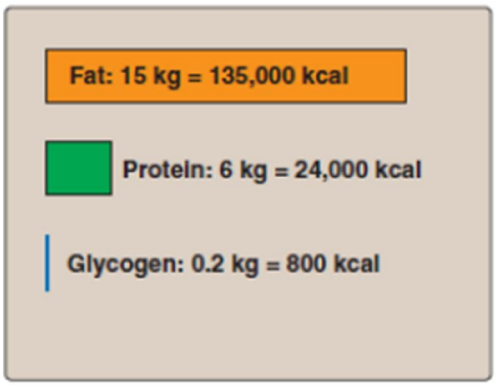
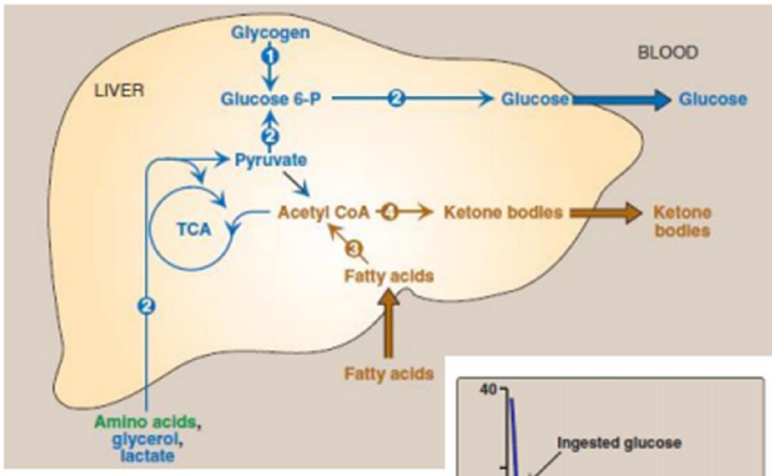


Figure 24.9
Metabolic fuels present in a 70-kg man at the beginning of a fast. Fat stores are sufficient to meet energy needs for about 3 months.

Enzymatic changes in fasting

The flow of intermediates through the pathways of energy metabolism is controlled by four mechanisms: 1) the availability of **substrates** 2) **allosteric** regulation of enzymes 3) **covalent** modification of enzymes 4) induction-repression of enzyme **synthesis**.

Most of the enzymes regulated by covalent modification are **dephosphorylated** and **active** in the fed state, whereas in the fasted state, they are **phosphorylated** and **inactive**. *Three exceptions are **glycogen phosphorylase**, glycogen **phosphorylase kinase**, and **hormone -sensitive lipase** of adipose tissue which are **inactive** in their **dephosphorylated** states.



In fasting, substrates are not provided by the diet, but are available from the breakdown of stores and/or tissues.

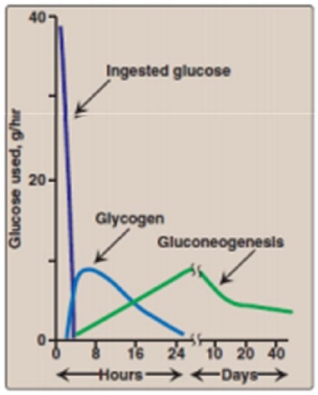


Figure 24.10
Sources of blood glucose after ingestion of 100 g of glucose.

In the liver

• The primary role of the **liver** during fasting is to maintain **blood** glucose through the synthesis and to distribute fuel molecules for use by other organs.

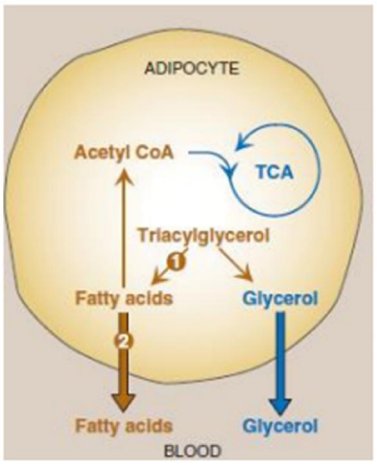
• The liver first uses **glycogen degradation** and then **gluconeogenesis** to maintain blood glucose levels to sustain energy metabolism of the brain and other glucose-requiring tissues in the fasted (post-absorptive) state.

• **Increased↑** fatty acid oxidation as a major source of energy for **liver**.

• **Increased↑** synthesis of **ketone bodies** especially **3-hydroxybutyrate for use by the brain.**

In adipocytes

• Glucose transport by insulin-sensitive GLUT-4 into the adipocyte and its subsequent metabolism are **depressed↓** due to **low↓** insulin levels. This leads to a **decrease↓** in fatty acid and TAG synthesis.



• **Increased ↑** degradation of TAG by **hormone sensitive lipase.**

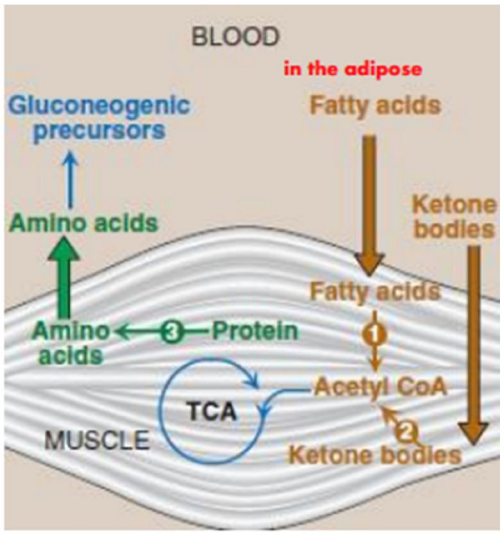
• **Increased↑** release of hydrolyzed fatty acids from stored TAG into the blood as albumin bound FA to be transported to a variety of tissues for use as fuel.

• The glycerol produced from TAG degradation is used as a gluconeogenic precursor by the liver.

• **Decreased**↓ uptake of fatty acids since lipoprotein lipase activity of adipose tissue is **low**↓ during fasting. Consequently, circulating TAG of lipoproteins is **not available** to adipose tissue.

In muscles

• **Resting** muscle uses **fatty acids** as its major fuel source, whereas exercising muscle initially uses its **glycogen** stores as a source of energy (more rapid).



• During intense exercise, glucose 6-phosphate derived from glycogen is converted to **lactate** by **anaerobic** glycolysis.

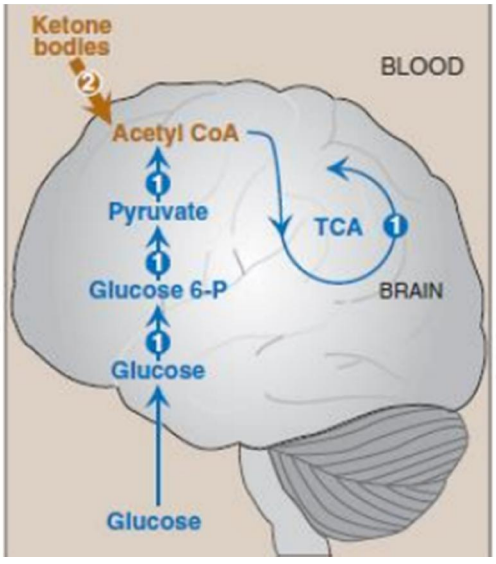
• As glycogen reserves are **depleted**, free fatty acids from TAG of adipose tissue become the **dominant energy source**.

• Glucose transport (GLUT-4) and metabolism are **decreased**↓ due to **low**↓ insulin.

• During the first 2 weeks of fasting, muscle uses **fatty acids** from adipose tissue and **ketone bodies** from the liver as fuels.

• After about 3 weeks of fasting, muscle **decreases**↓ its use of ketone bodies (to spare it for the **brain, you'll see below**) and oxidizes fatty acids almost exclusively.

• Rapid breakdown of muscle protein during the first few days of fasting to provide amino acids (Ala, Gln) for gluconeogenesis in the liver.



In the brain

• During the first days of fasting, the **brain** continues to use glucose exclusively as a fuel. • Blood glucose is maintained by hepatic **gluconeogenesis** from glucogenic precursors, such as amino acids from proteolysis and glycerol from lipolysis.

• In **prolonged** fasting (greater than 2–3 weeks), plasma ketone bodies reach significantly **elevated**↑ levels, and replace **glucose** as the primary fuel for the **brain** reducing the need for protein catabolism for gluconeogenesis and sparing glucose and, thus, muscle protein.

In the kidney

• Kidney expresses the enzymes of gluconeogenesis, **including G-6-phosphatase**, and in late fasting about 50% of **gluconeogenesis** occurs here!!

• The Gln released from the muscle's metabolism of branched-chain amino acids is taken up by the kidney and acted upon by renal **glutaminase** and **glutamate dehydrogenase**, producing **α-ketoglutarate** that can be used as a substrate for gluconeogenesis.

• Kidney also provides compensation for the acidosis that accompanies the increased production of ketone bodies.

• Ammonia NH_3 produced from deamination picks up H+ from ketone body dissociation, and is excreted in the urine as NH_4^+, decreasing the acid load in the body.

**Urea cycle -in the liver- consumes energy to get rid of NH_3, here↑ the kidney decreases the amount of energy required to get rid of ammonia*.*

• In long-term fasting, nitrogen disposal occurs in the form of ammonia rather than urea.

Obesity

The amount of body fat is **difficult** to measure directly and is usually indirectly determined from the body mass index (BMI) which correlates the amount of body fat in most individuals.

• BMI= (weight in kg)/(height in meters)^2

• BMI ranges 18.5-24.9 healthy 25-29.9 overweight > 30 obese > 40 extremely obese .

• These cutoffs are based on studies that examined the relationship of BMI to **premature death**, and are similar in men and women.

The anatomic distribution of body fat has a major influence on associated health risks.

A waist to hip ratio of more than 0.8 for women and more than 1.0 for men is defined as android, "apple-shaped", "Android", or upper body obesity, and is associated with more fat deposition in the trunk.

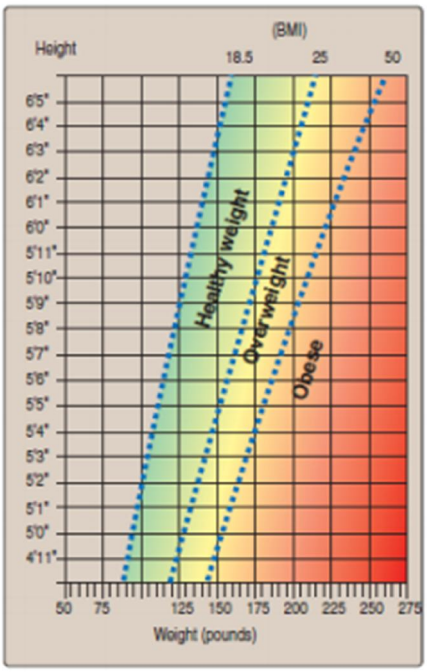
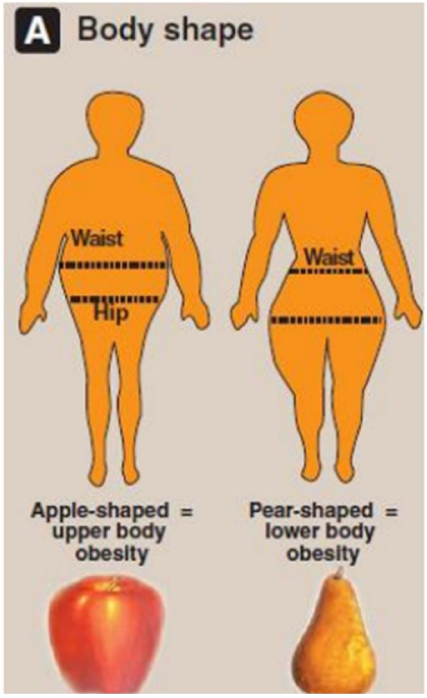


Figure 26.1
To use the BMI Chart, find height in the left-hand column. Move across the row to weight. Height and weight intersect at the individual's BMI.

Lower waists to hip ratio reflects more fat distributed in the hips and thighs and is called "gynoid", "pear-shaped," or lower body obesity.

It is defined as a waist to hip ratio of less than 0.8 for women and less than 1.0 for men.

The pear shape, **more commonly found in women**, presents a much **lower**↓ risk of metabolic disease, and some studies indicate it may actually be protective.



About ~ 80–90% of the fat stored in the human body is in **subcutaneous** depots (just under the skin), in the abdominal (upper body) and the gluteal-femoral (lower body) regions.

However, 10–20% of body fat is stored in **visceral** depots (omental and mesenteric), which are located within the abdominal cavity in **close association with the digestive trac**t.

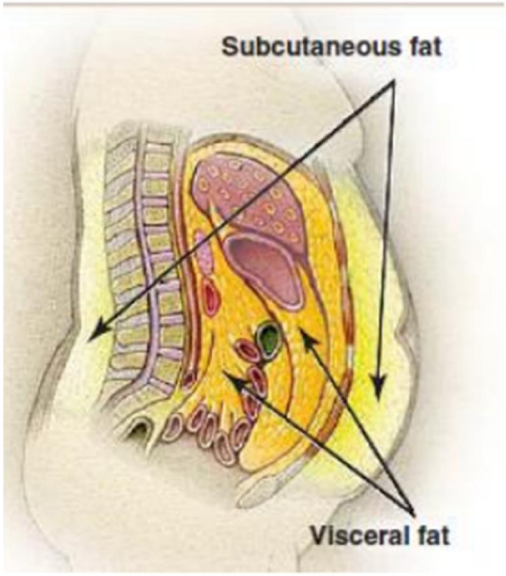
Excess fat in visceral stores and in abdominal subcutaneous fat **increases**↑ health risks associated with obesity.

Adipose tissue plays an active role in body weight regulation by secretion of hormones, such as **leptin, which regulates (reduces↓) appetite as well as metabolism**, and **adiponectin**, an adipocyte-derived **cytokine**, **reduces**↓ levels of blood free fatty acids and **improves** lipid profiles and glycemic control, and **reduces** ↓ inflammation in diabetic patients.

Subcutaneous adipocytes from the lower body (gluteal-femoral), particularly in women, are **larger**, **very** efficient at fat deposition, and tend to mobilize fatty acids more slowly than those from the abdominal subcutaneous depots.

Visceral adipocytes are the **more metabolically active**, therefore they have a large influence on metabolic dysfunction in obesity.

However, both abdominal subcutaneous and visceral depots of obese subjects have **high rates of lipolysis**↑, and contribute to **increased**↑ availability of free fatty acids (higher risk to diseases).



Visceral adipose tissue cytokines and free fatty acids released from abdominal fat, enter the **portal vein and enter the liver** therefore, have direct access to the liver leading to insulin resistance and **increased**↑ synthesis of TAGs, which are released as VLDL and contribute to hypertriglyceridemia↑.

On the other hand, subcutaneous body adipose depots enter the **general circulation** where they can be oxidized in **muscle** (not only the liver), therefore, reach the liver in **lower** concentration.

As TAGs are stored, adipocytes can expand to 2-3 times their normal volume. However, their ability to **expand** (hypertrophy) is limited.

With **prolonged** over-nutrition, **pre-adipocytes in adipose tissue** proliferate (**increase**↑ in number) and differentiate into mature fat cells, increasing the number of adipocytes.

Most obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia).

We were born with a limited number of adipocytes and the average age of an adipocyte is 10 years. Obese individuals can have up to five times the normal number of fat cells.

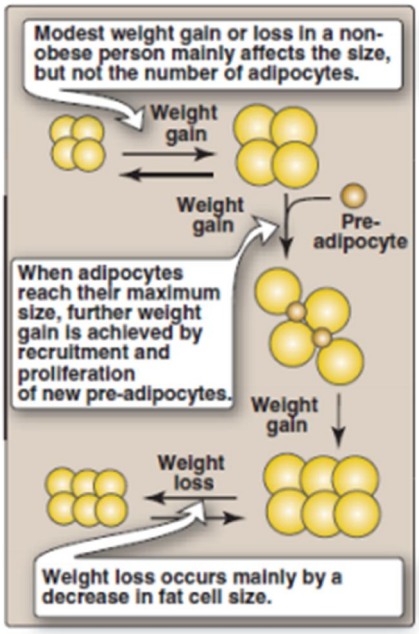


Figure 26.3
Hypertrophic and hyperplastic changes are thought to occur in severe obesity.

If excess calories cannot be accommodated within adipose tissue, the excess fatty acids 'spillover' into other tissues, such as muscle and liver (ectopic fat) and the amount of ectopic fat is associated with insulin resistance. (This is not mentioned by the doctor)

With weight loss, the size of the fat cells is reduced, but the number of fat cells is **not** usually affected.

Small fat cells are very efficient at re-accumulating fat, and this may **drive**↑ appetite and weight **regain**. ☹

The body weight of most individuals tends to be relatively stable over time. This observation prompted the **hypothesis** that each individual has a biologically predetermined "set point" for body weight.

The body attempts to add to adipose stores when the body weight falls below the set point and to **lose**↓ adipose stores when the body weight is **higher** than the set point.

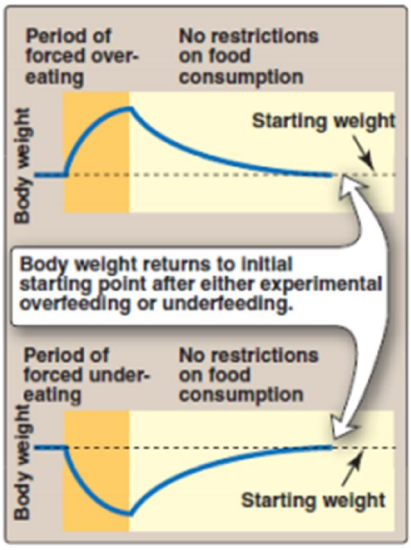


Figure 26.4
Weight changes following episodes of overfeeding or underfeeding followed by feeding with no restrictions.

For example, with weight loss, appetite **increases**↑ and energy expenditure **falls**↓, whereas with overfeeding, appetite **falls**↓ and energy expenditure may slightly **increase**↑.

To recap; body weight seems to drift around a "settling point," reflecting a balance between behavioral / environmental factors (food intake and exercise), and biologic factors (genetic contribution) that control body weight.

This balance involves a complex interaction of biochemical, neurologic, environmental, and psychologic factors.

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*The basic **neural and humoral** pathways that regulate **appetite**, **energy** expenditure, and body weight involve:

1. Systems that regulate short-term food intake (meal to meal).

2. Signals for the long-term (day to day, week to week, year to year) regulation of body weight.

Long-term signals (days)

1. Leptin: an adipocyte **hormone** that is secreted in proportion to the **size** of fat stores (**decreases**↓ when we consume **fewer** calories than we need). The body adapts by minimizing energy utilization (**decreasing**↓ activity) and **increasing** appetite. (When leptin↑ appetite↓)

-Unfortunately, in many individuals, the leptin system may be better at preventing weight **loss** than preventing weight **gain**. ☹

-A meal or overeating **increases**↑ leptin which acts on hypothalamus to dampen↓ appetite and prevent overconsumption of calories, but other cues that stimulate appetite can overcome the leptin system in many individuals.

2. Insulin: like **leptin**, insulin acts on hypothalamic neurons to dampen appetite. *Obese individuals are also **hyperinsulinemic**↑ **see the picture in page 5***

Short-term signals

Short-term signals from the GIT control hunger and satiety, which affect the size and number of meals over a time course of minutes to hours.

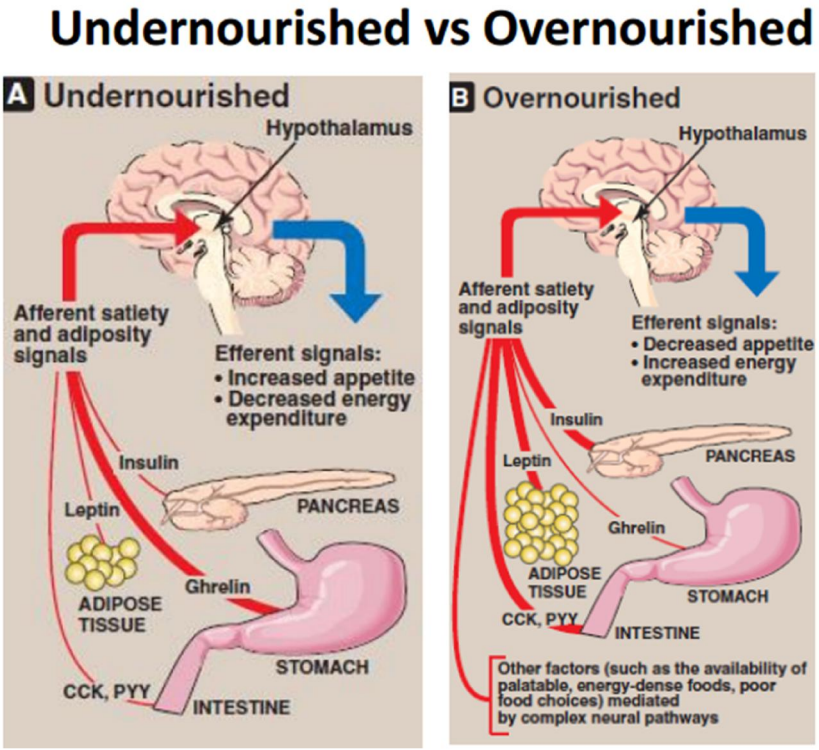
In the absence↓ of food intake (between meals), the **stomach** produces **ghrelin**, an orexigenic (**appetite-stimulating**) hormone that drives **hunger**↑.

During a meal, **gut hormones,** including **cholecystokinin (CCK)** and **peptide YY (PYY)**, cause **satiety** and meals are terminated by actions on the gastric emptying and neural signals to the hypothalamus.

Within the **hypothalamus**, neuropeptides such as **NPY** and **α-melanocyte stimulating hormone** (α-MSH), and neurotransmitters such as **serotonin** and **dopamine** are important in regulating hunger and satiety.

-Long-term and short-term signals interaction→

- **Leptin** can affect the **sensitivity** of hypothalamic neurons to short term signals such as CCK (**decreases↓** appetite).



The primary metabolic **effects** of obesity include dyslipidemias (discussed before), glucose intolerance (hyperglycemia below that classified as diabetes, and insulin resistance) expressed primarily in the **liver, muscle, and adipose** tissue.

The increased mass of adipocytes **releases** signals that cause metabolic abnormalities.

(Metabolic syndrome is not mentioned by the doctor)

Metabolic syndrome: A cluster of metabolic abnormalities associated with abdominal obesity. Includes glucose intolerance, insulin resistance, hyperinsulinemia, dyslipidemia (low high-density lipoprotein (LDL) and elevated triacylglycerols), and hypertension.

The metabolic syndrome is also associated with chronic systemic inflammation that contributes to the pathogenesis of insulin resistance and atherosclerosis.

In obesity, **low↓** levels of the adipocyte hormone adiponectin that normally **dampens↓ inflammation** and **sensitizes↑** tissues, especially the **liver**, to **insulin**, may contribute to the metabolic syndrome and therefore the risk of type 2 diabetes and heart disease

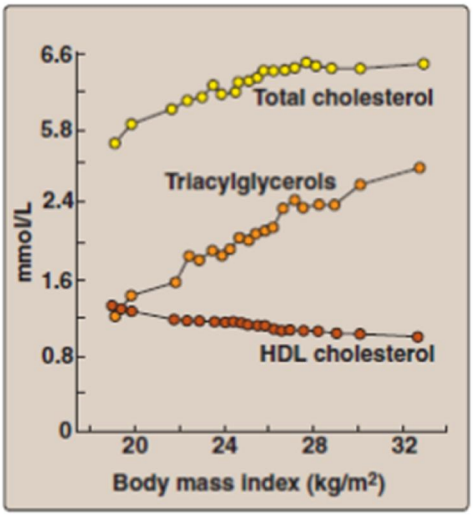


Figure 26.8
Body mass index and changes in blood lipids.