Integration of Metabolism

Dr. Diala Abu-Hassan

Hormones and Metabolism

Metabolic effects of insulin

Carbohydrate metabolism

- ✓ Glucose storage mostly in three tissues: liver, muscle, and adipose.
- ✓ In the liver and muscle, insulin increases glycogen synthesis.
- ✓ In the muscle and adipose, insulin increases glucose uptake by increasing the number of glucose transporters in the cell membrane.
- ✓ In the liver, insulin decreases the production of glucose through the inhibition of glycogenolysis and gluconeogenesis.

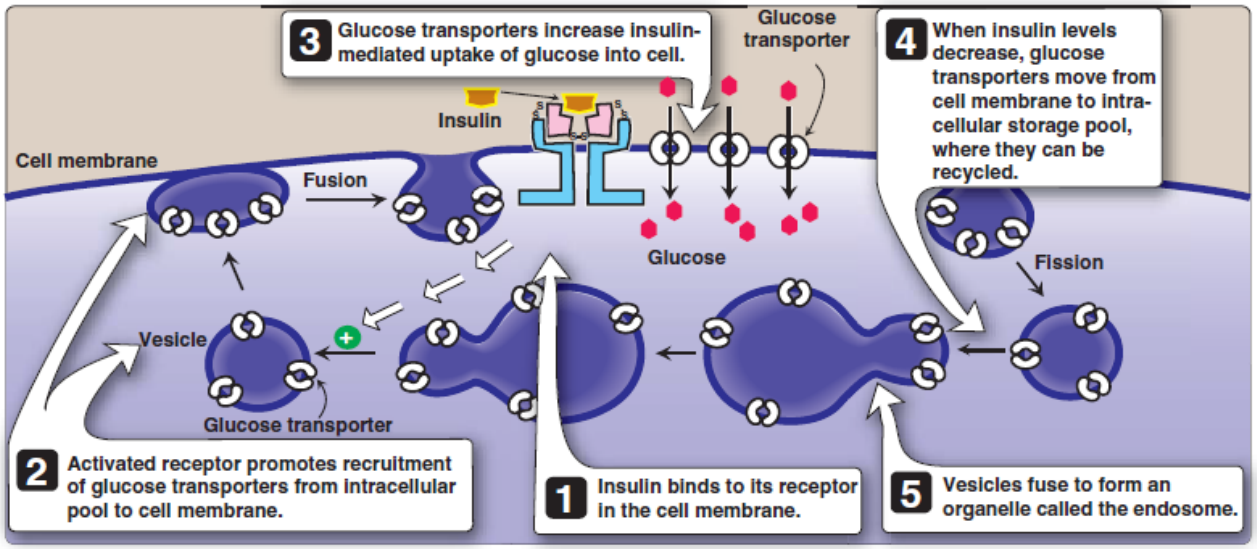


Figure 23.8
Insulin causes the recruitment of glucose transporters (GLUTs) from intracellular stores in skeletal and cardiac muscle and adipose tissue.

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.

Metabolic effects of insulin

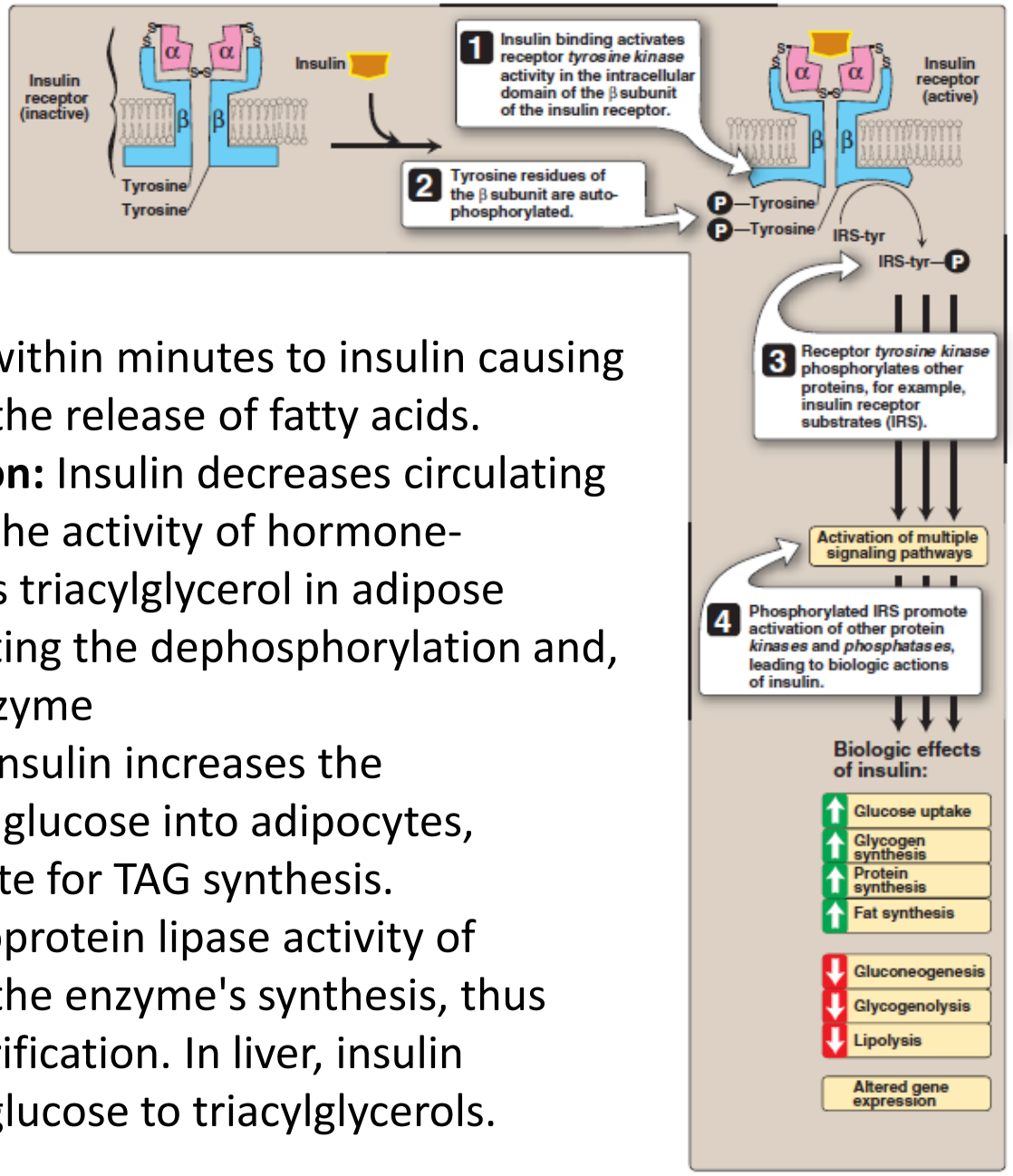


Figure 23.7
Insulin receptor. IRS = Insulin receptor substrate.

Effects on lipid metabolism

✓ Adipose tissue responds within minutes to insulin causing a significant reduction in the release of fatty acids.

a. Decreased TAG degradation: Insulin decreases circulating free fatty acids by inhibiting the activity of hormone-sensitive lipase that degrades triacylglycerol in adipose tissue. Insulin acts by promoting the dephosphorylation and, hence, inactivation of the enzyme

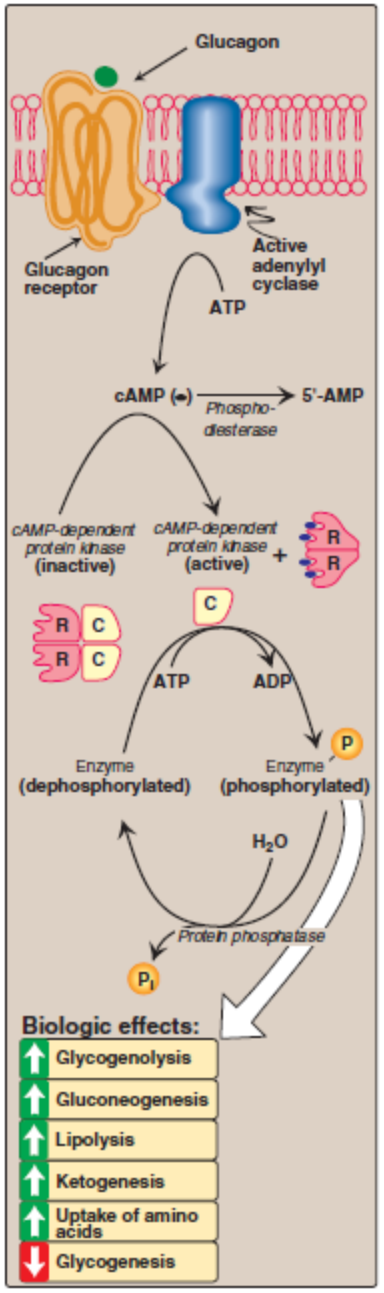
b. Increased TAG synthesis: Insulin increases the transport and metabolism of glucose into adipocytes, providing glycerol 3-phosphate for TAG synthesis. Insulin also increases the lipoprotein lipase activity of adipose tissue by increasing the enzyme's synthesis, thus providing fatty acids for esterification. In liver, insulin promotes the conversion of glucose to triacylglycerols.

Metabolic effects of glucagon

- ✓ Glucagon is a polypeptide (29 aa) hormone secreted by the α cells of the pancreatic islets of Langerhans.
- ✓ Glucagon, along with epinephrine, cortisol, and growth hormone (the "counter-regulatory hormones"), opposes many of the actions of insulin
- ✓ Glucagon receptors are found in hepatocytes but not on skeletal muscle.
- ✓ Glucagon acts to maintain blood glucose levels by activation of hepatic **glycogenolysis** and **gluconeogenesis**.
- ✓ Glucagon secretion is increased by:

1. Low blood glucose.
2. Amino acids derived from a meal containing protein.
3. Epinephrine or norepinephrine.

- ✓ Glucagon secretion is inhibited by elevated blood glucose and by insulin.



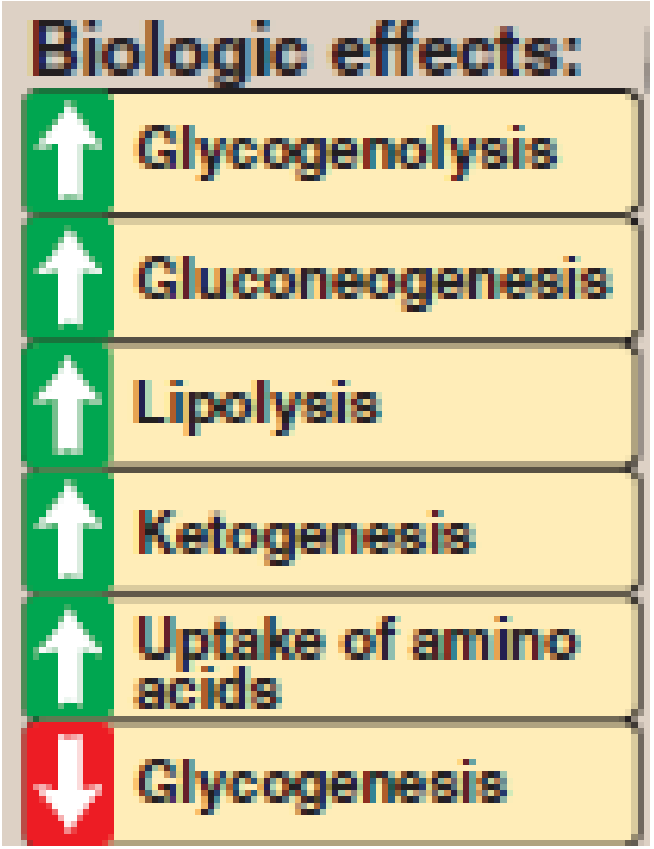
Metabolic effects of glucagon

1. Effects on carbohydrate metabolism: increase in the breakdown of liver (not muscle) glycogen and an increase in gluconeogenesis.

2. Effects on lipid metabolism: Glucagon activates lipolysis in adipose.

The free fatty acids released are taken up by liver and oxidized to acetyl coenzyme A, which is used in ketone body synthesis.

3. Effects on protein metabolism: 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.



Insulin vs Glucagon

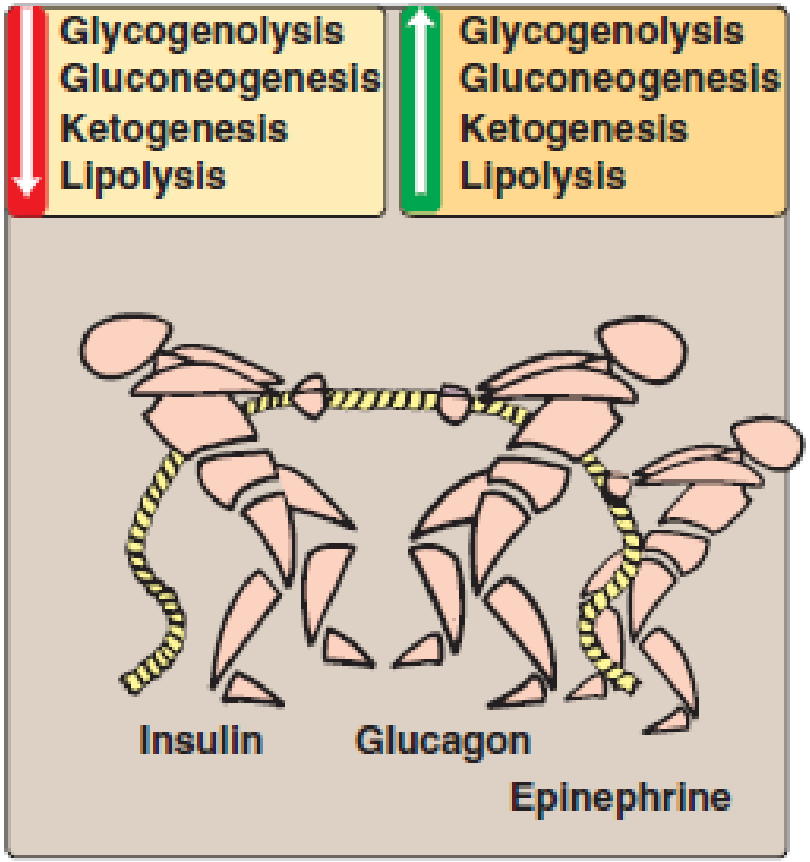
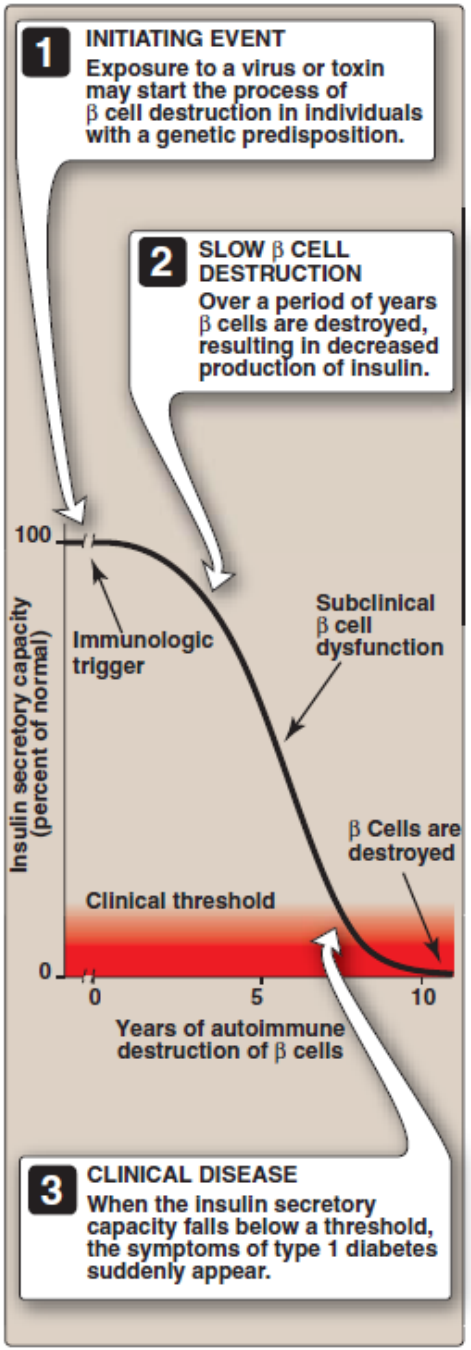


Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

Diabetes and Metabolism

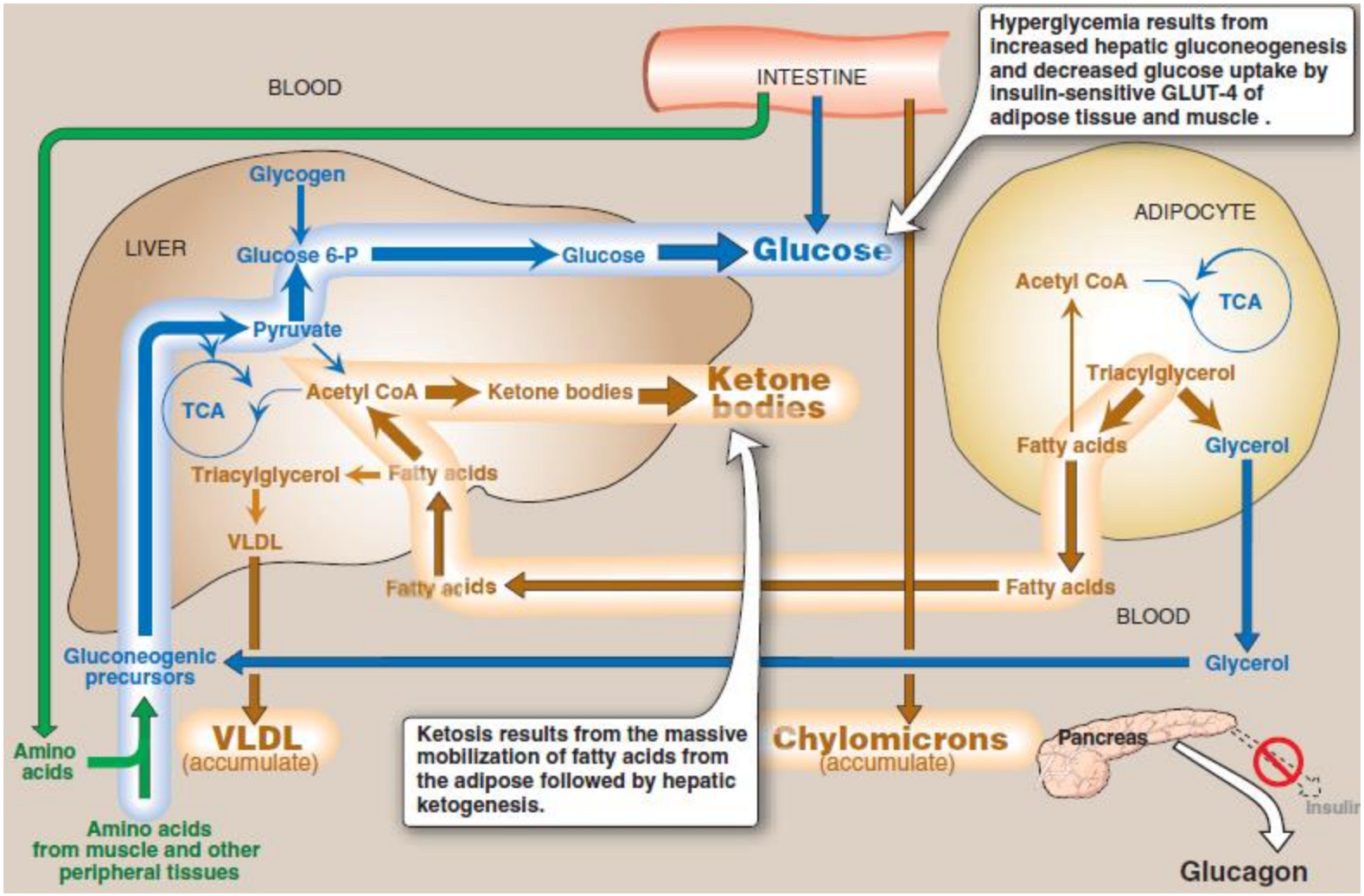
Type I Diabetes Mellitus (DM)

- Insulin deficiency



Metabolic changes in type 1 DM

- The metabolic abnormalities result from a insulin deficiency
- Affects metabolism in three tissues: liver, muscle, and adipose tissue



Hyperglycemia and ketoacidosis

- Elevated levels of blood glucose and ketones are the hallmarks of untreated type 1
- Hyperglycemia is caused by increased hepatic production of glucose, combined with diminished peripheral utilization (muscle and adipose have the insulin-sensitive GLUT-4)
- Ketosis results from increased mobilization of fatty acids from adipose tissue, combined with accelerated hepatic fatty acid β-oxidation and synthesis of 3-hydroxybutyrate and acetoacetate

Hypertriacylglycerolemia

- 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 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 hypertriacylglycerolemia.

Type II Diabetes Mellitus (DM)

- Most common (90%)
- Develops gradually without obvious symptoms
- Polyuria and polydipsia and polyphagia
- A combination of insulin resistance and dysfunctional β cells
- The metabolic alterations are milder than those for type 1, because insulin secretion in type 2, although not adequate, does restrain ketogenesis and blunts the development of diabetic ketoacidosis (DKA)
- Pathogenesis does not involve viruses or autoimmune antibodies.

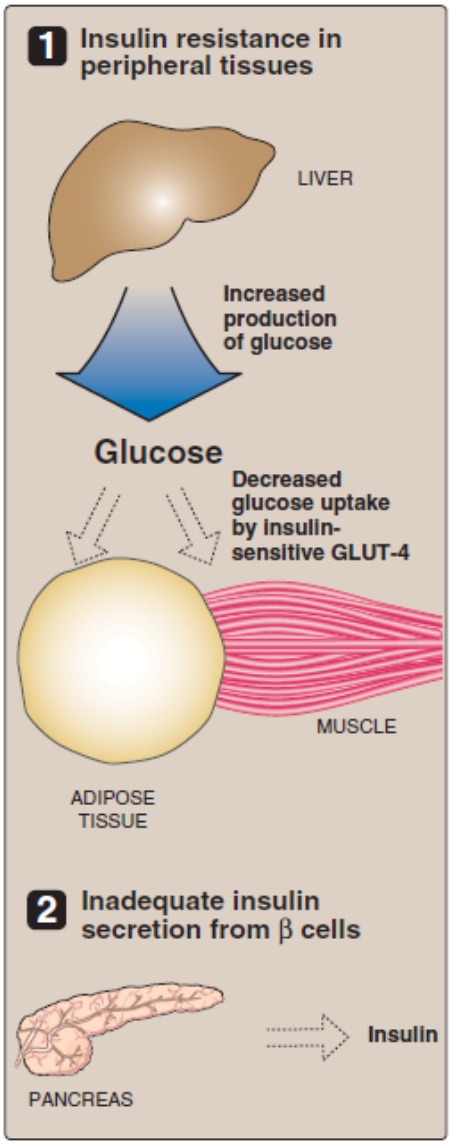


Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes.

Insulin Resistance (IR)

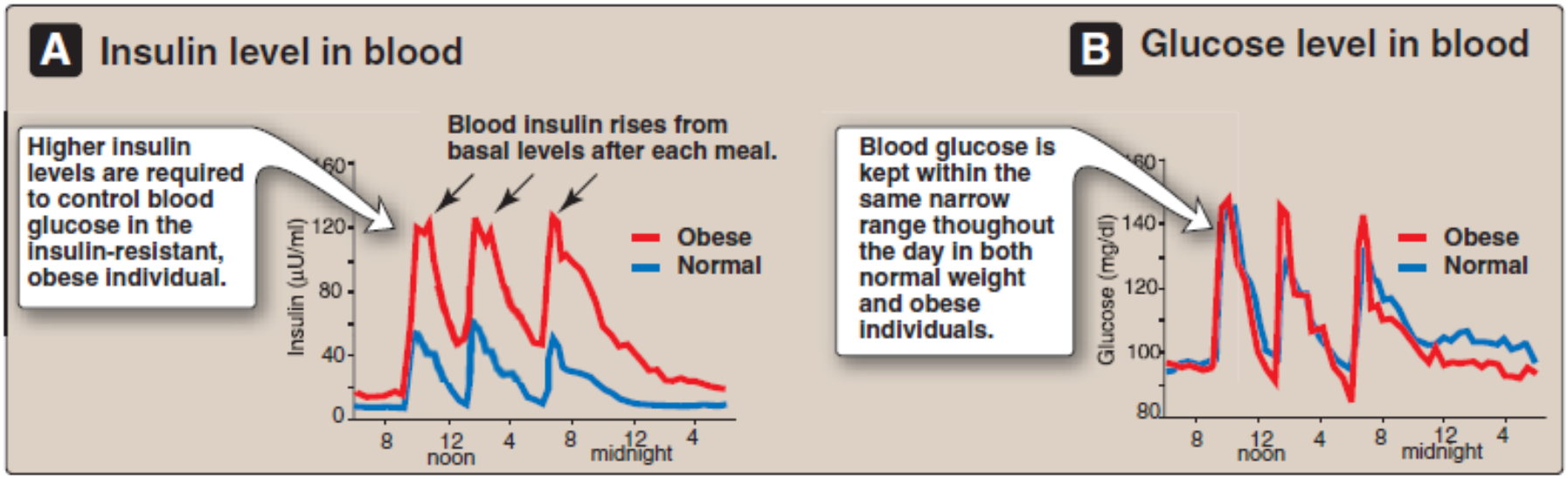


Figure 25.7
Blood insulin and glucose levels in normal weight and obese subjects.

- ✓ 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.
- ✓ IR is characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue.
- ✓ Obesity is the most common cause of IR.
- ✓ IR alone will not lead to type 2 diabetes.
- ✓ Type 2 diabetes develops in insulin-resistant individuals who also show impaired β-cell function.

Metabolic changes in type 2 DM

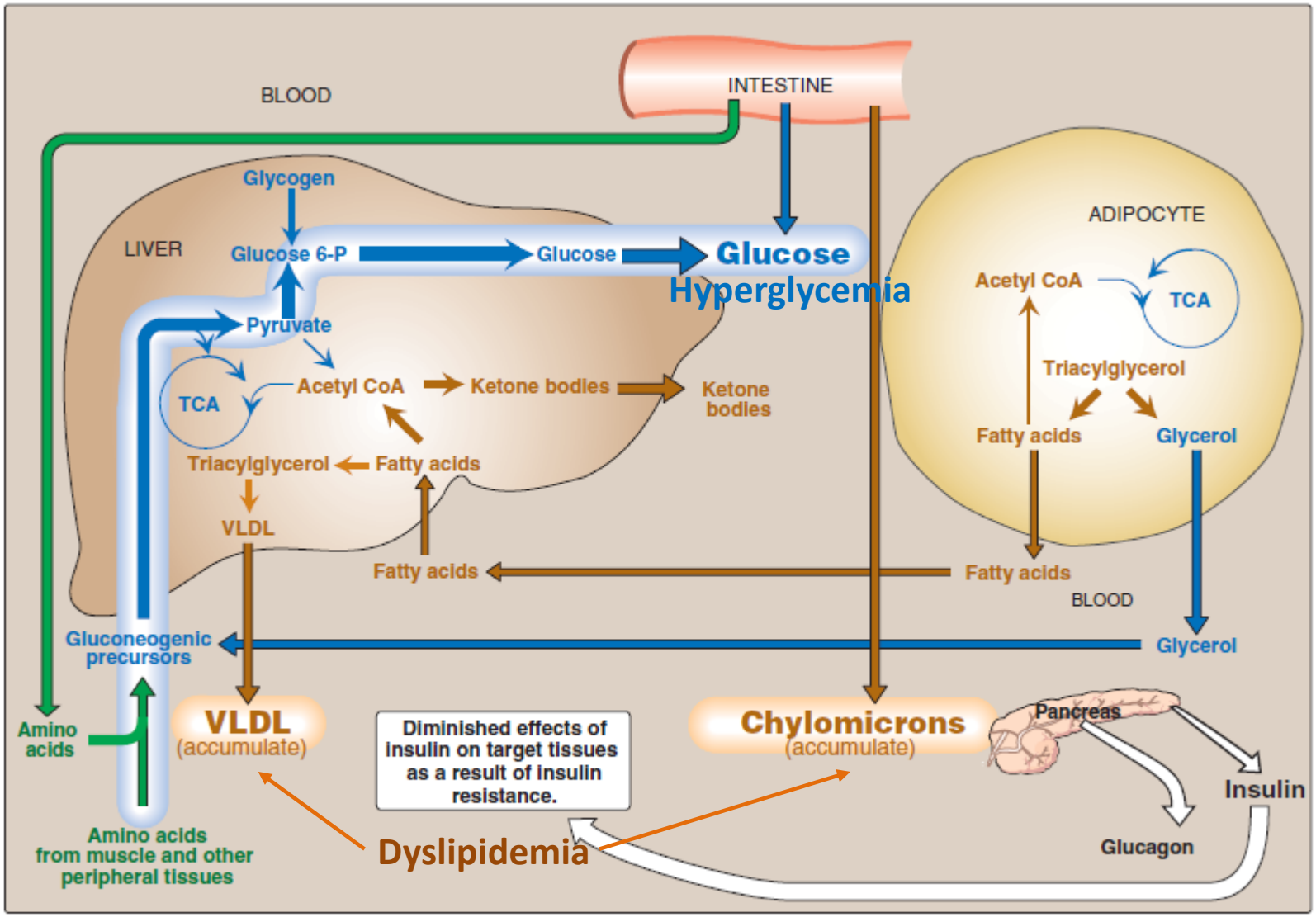


Figure 25.10
Intertissue relationships in type 2 diabetes.

Metabolic changes in type 2 DM

1. Hyperglycemia

- Caused by increased hepatic production of glucose, combined with diminished peripheral use.
- Ketosis is usually minimal or absent in type 2 DM because the presence of insulin—even in the presence of IR— diminishes hepatic ketogenesis.

2. 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
- Because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is low in diabetics, the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia Low HDL levels are also associated with type 2 diabetes.

Fasting and Metabolism

OVERVIEW OF FASTING

- Fasting begins if no food is ingested after the absorptive period.
- Result 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 period characterized by degradation of TAG, glycogen, and protein.
- Priorities:

1) to maintain adequate plasma levels of glucose to sustain energy metabolism of the brain, red blood cells, and other glucose-requiring tissues
2) 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.

OVERVIEW OF FASTING

Fuel stores

- Although protein is an energy source, each 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.

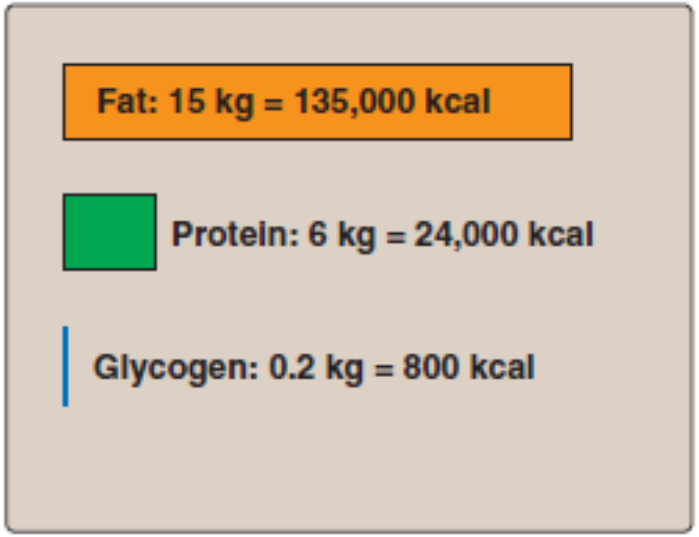


Figure 24.9
Metabolic fuels present in a 70-kg man at the beginning of a fast. Fat stores are sufficient to meet energy needs for about 3 months.

Enzymic changes in fasting

- The flow of intermediates through the pathways of energy metabolism is controlled by four mechanisms:

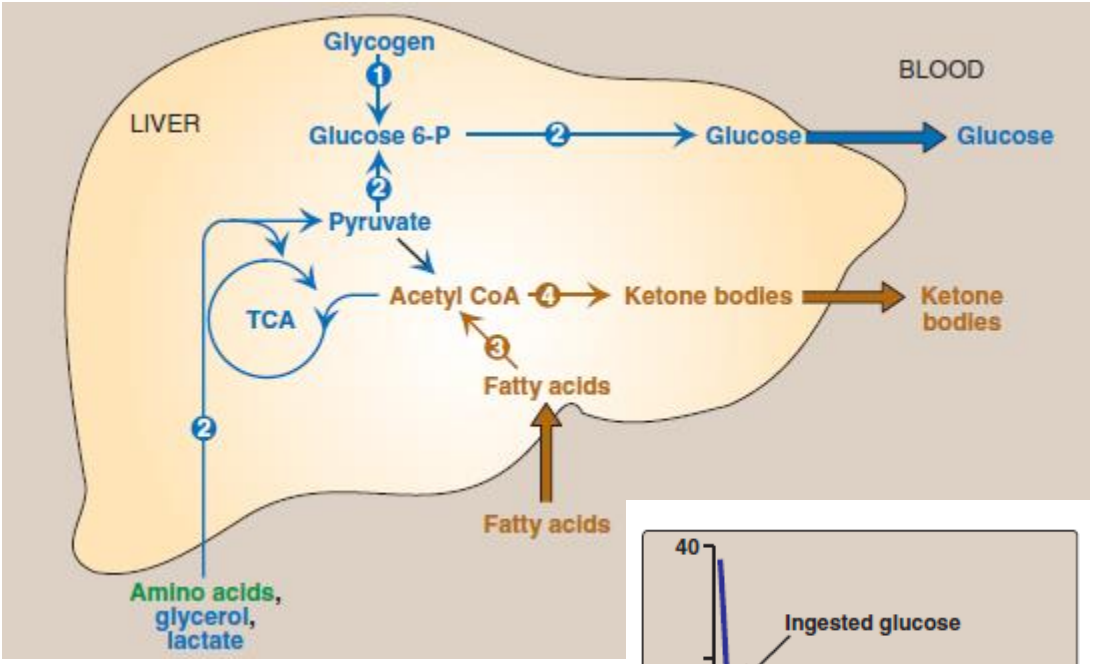
1) the availability of substrates
2) allosteric regulation of enzymes
3) covalent modification of enzymes
4) induction-repression of enzyme synthesis.

- The metabolic changes observed in fasting are generally opposite to those in the absorptive state
- 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 active.
- 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.

Fasting and Metabolism

LIVER IN FASTING

- 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 (postabsorptive) state.
- Increased fatty acid oxidation as a major source of energy for liver
- Increased synthesis of ketone bodies especially 3-hydroxybutyrate



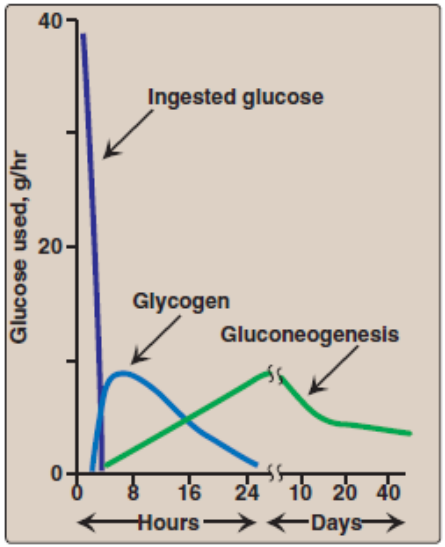
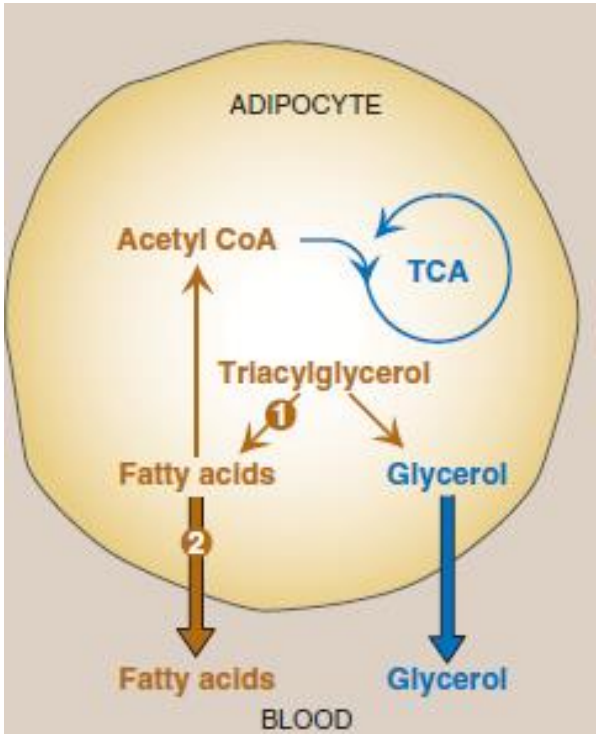


Figure 24.10
Sources of blood glucose after ingestion of 100 g of glucose.

Fasting and Metabolism

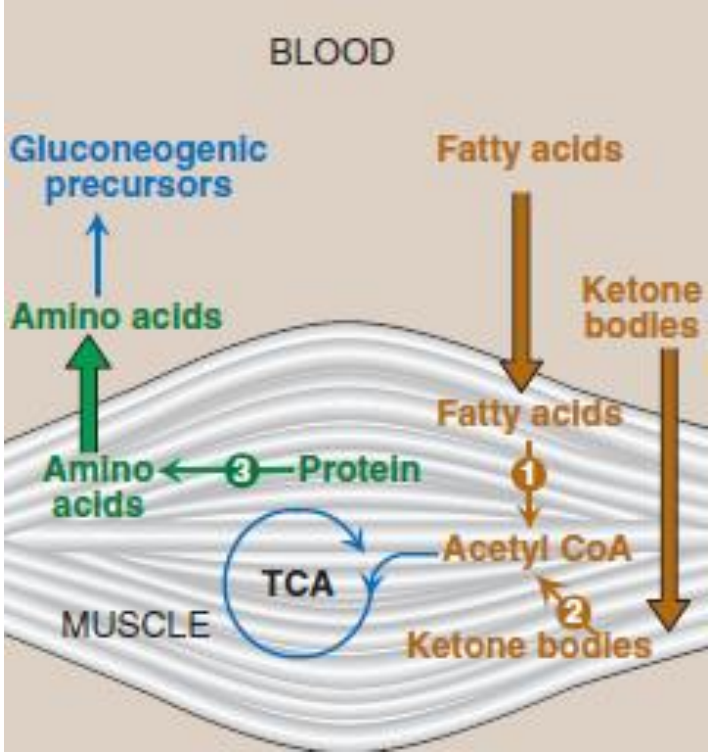
ADIPOSE TISSUE IN FASTING

- 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.



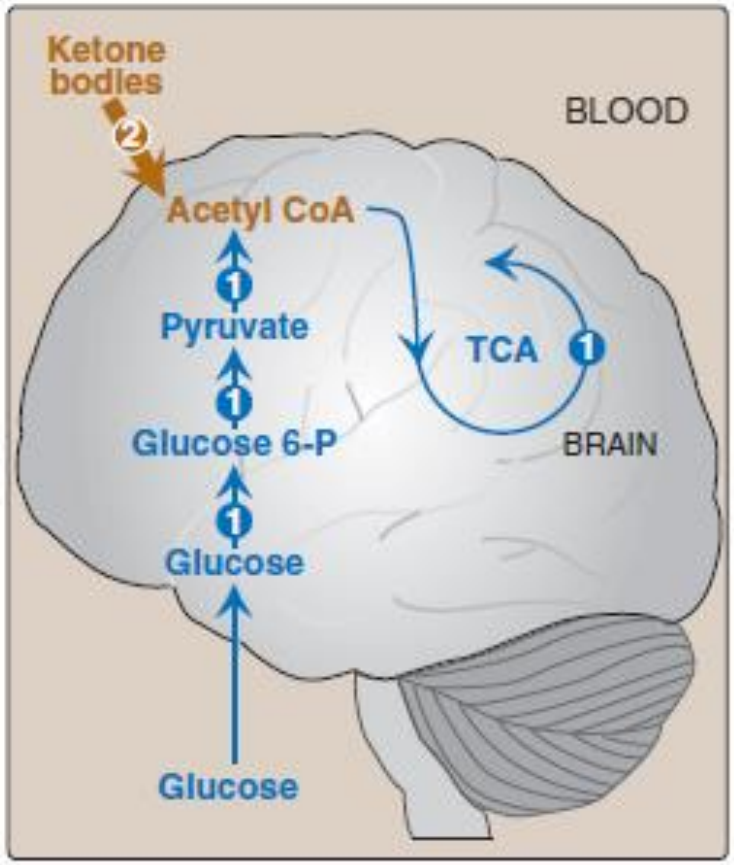
- Decreased uptake of fatty acids since lipoprotein lipase activity of adipose tissue is low during fasting. Consequently, circulating TAG of lipoproteins is not available to adipose tissue.

Fasting and Metabolism



RESTING SKELETAL MUSCLE IN FASTING

- Resting muscle uses fatty acids as its major fuel source.
- Exercising muscle initially uses its glycogen stores as a source of energy.
- 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 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 and oxidizes fatty acids almost exclusively.
- Rapid breakdown of muscle protein during the first few days of fasting to provide AAs (Ala, Gln) for gluconeogenesis in the liver.



Fasting and Metabolism

BRAIN IN FASTING

- 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.

Fasting and Metabolism

KIDNEY IN LONG-TERM FASTING

- 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
- NH3 produced from deamination picks up H+ from ketone body dissociation, and is excreted in the urine as NH4+, decreasing the acid load in the body.
- In long-term fasting, nitrogen disposal occurs in the form of ammonia rather than urea.

Obesity

Obesity

- The amount of body fat is difficult to measure directly
- Usually indirectly determined from the body mass index (BMI)
- BMI correlates the amount of body fat in most individuals.
- BMI= (weight in kg)/(height in meters)^2

BMI

- 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.

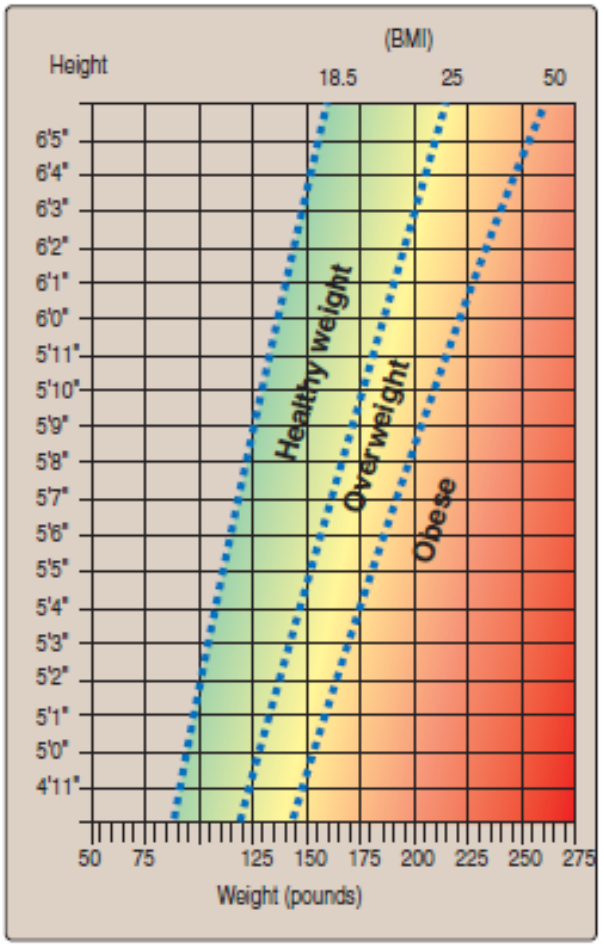
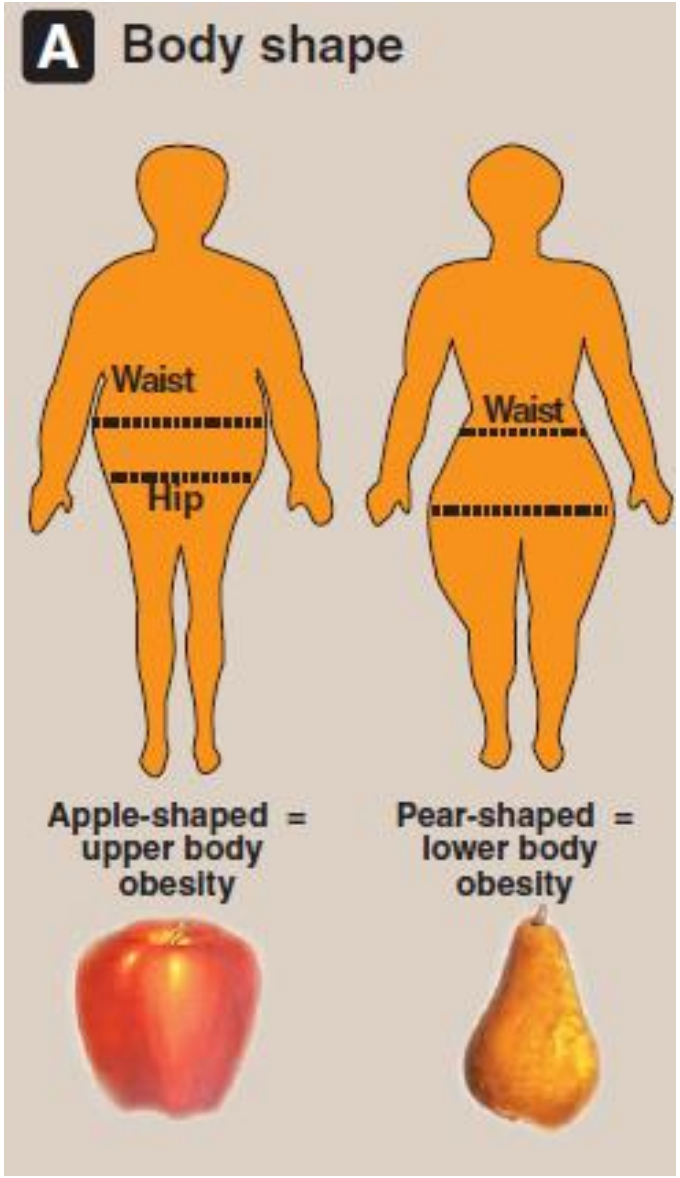


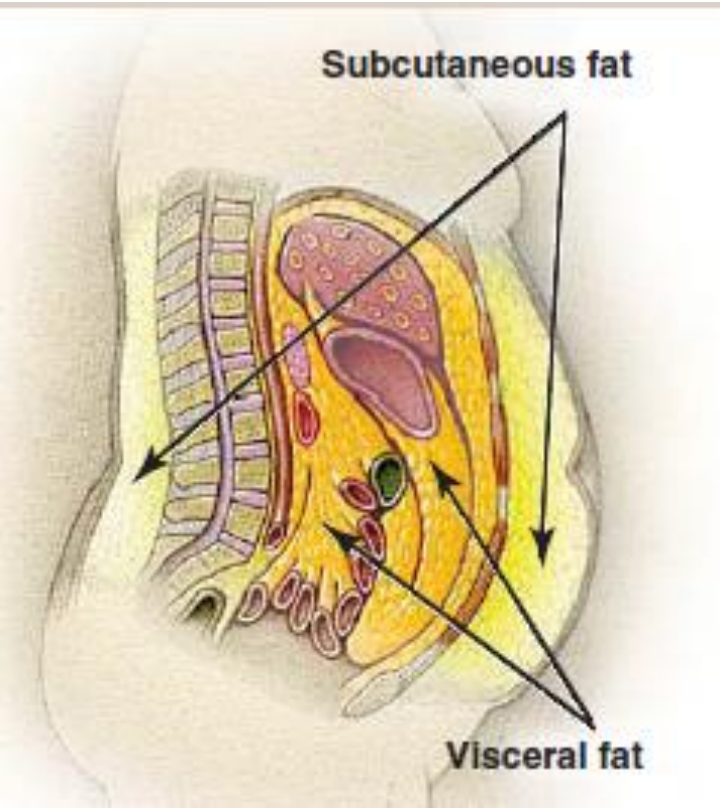
Figure 26.1
To use the BMI Chart, find height in the left-hand column. Move across the row to weight. Height and weight intersect at the individual's BMI.

Anatomic differences in fat deposition



- 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,” or upper body obesity, and is associated with more fat deposition in the trunk.
- A lower waist 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.

Subcutaneous and visceral depots



- ✓ ~ 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.
- ✓ 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 tract
- ✓ Excess fat in visceral stores and in abdominal subcutaneous fat increases health risks associated with obesity.

Adipose tissue has an endocrine function

- Adipose tissue plays an active role in body weight regulation by secretion of hormones, such as

1. **leptin**, which regulates appetite as well as metabolism
2. **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.

Biochemical differences in regional fat depots

- **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 most metabolically active, therefore they have a large influence on metabolic dysfunction in obesity.
- 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
- **Subcutaneous** body adipose depots enter the general circulation where they can be oxidized in muscle, therefore, reach the liver in lower concentration.

Size and number of fat cells

- As TAGs are stored, adipocytes can expand to 2-3 times their normal volume.
- The ability of a fat cell to expand is limited.
- With prolonged over-nutrition, preadipocytes in adipose tissue proliferate 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).
- The average age of an adipocyte is 10 years.
- Obese individuals can have up to five times the normal number of fat cells.
- If excess calories cannot be accommodated within adipose tissue, the excess fatty acids 'spillover' into other tissues, such as muscle and liver (ectopic fat).
- The amount of ectopic fat is associated with insulin resistance.
- 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 reaccumulating fat, and this may drive appetite and weight regain.

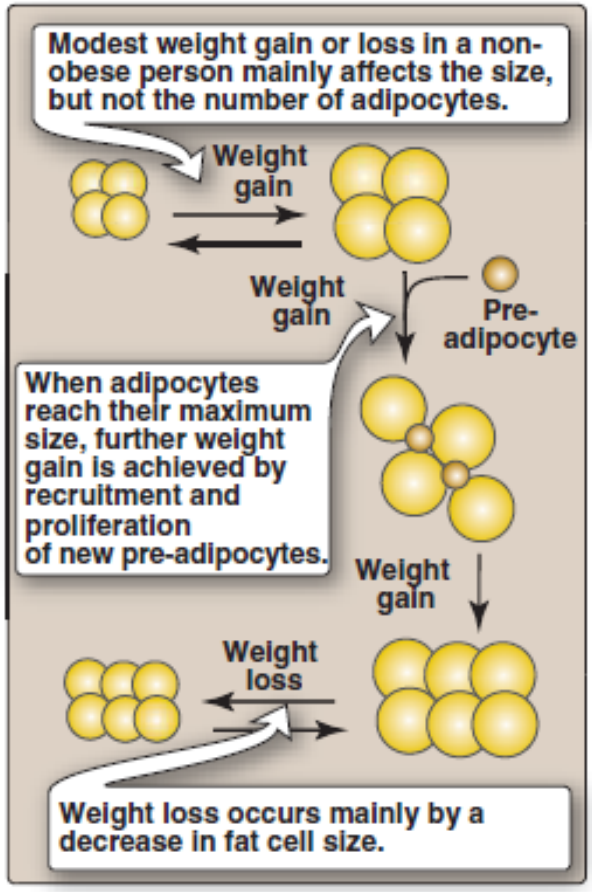


Figure 26.3
Hypertrophic and hyperplastic changes are thought to occur in severe obesity.

BODY WEIGHT REGULATION

- 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.
- For example, with weight loss, appetite increases and energy expenditure falls, whereas with overfeeding, appetite falls and energy expenditure may slightly increase.
- Body weight seems to drift around a "settling point," reflecting a balance between environmental factors that influence food intake and energy expenditure, and biologic factors that control body weight.
- **Genetic contributions to obesity**
- **Environmental (**environment availability of food and exercise) **and behavioral contributions**

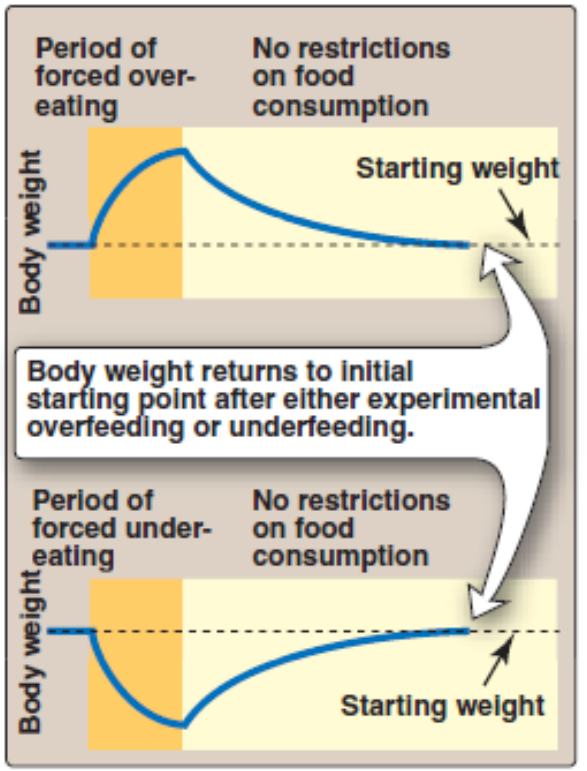


Figure 26.4
Weight changes following episodes of overfeeding or underfeeding followed by feeding with no restrictions.

MOLECULES THAT INFLUENCE OBESITY

- ✓ Obesity results when energy intake exceeds energy expenditure.
- ✓ This balance involves a complex interaction of biochemical, neurologic, environmental, and psychologic factors.
- ✓ 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.

MOLECULES THAT INFLUENCE OBESITY

Long-term signals

1. Leptin:

- An adipocyte hormone
- 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
- Unfortunately, in many individuals, the leptin system may be better at preventing weight loss than preventing weight gain.
- A meal or overeating increases leptin that dampen appetite and prevent overconsumption of calories, but other cues that stimulate appetite can overcome the leptin system in many individuals.

2. Insulin

- Obese individuals are also hyperinsulinemic.
- Like leptin, insulin acts on hypothalamic neurons to dampen appetite.

MOLECULES THAT INFLUENCE OBESITY

- **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.

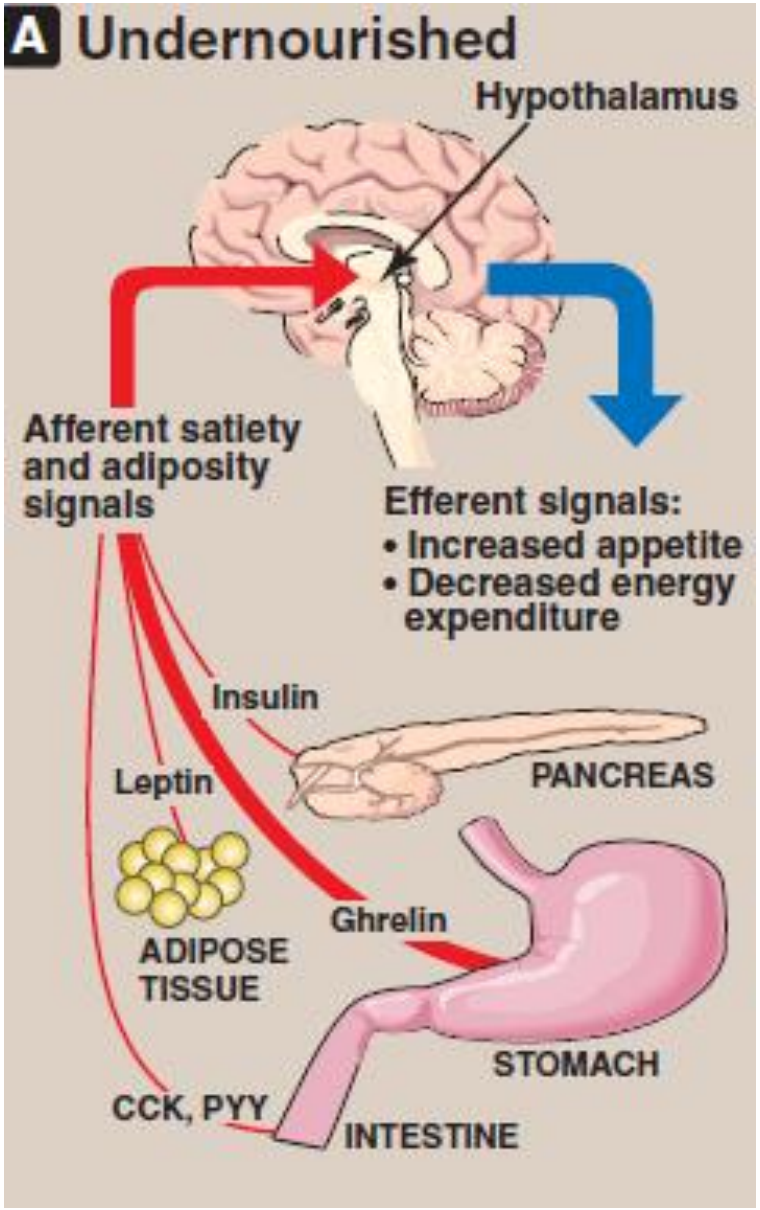
- In the absence of food intake (between meals), the stomach produces ghrelin, an orexigenic (appetite-stimulating) hormone that drives hunger.

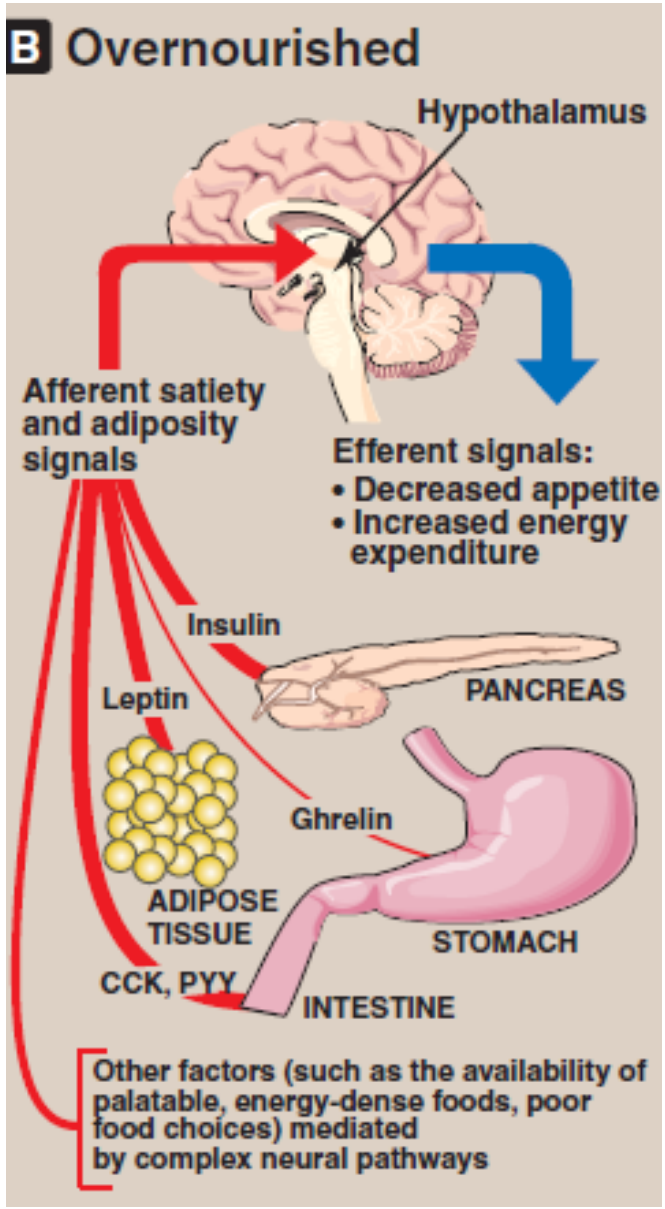
- During a meal, gut hormones, including cholecystokinin (CCK) and peptide YY (PYY), cause satiety and meals are terminated by actions on the gastric empyting and neural signals to the hypothalamus

- 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.
- There are many and complex regulatory loops that control the size and number of meals in relationship to the status of body fat stores.

Undernourished vs Overnourished





METABOLIC CHANGES IN OBESITY

- ✓ The primary metabolic effects of obesity include **dyslipidemias**, **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.

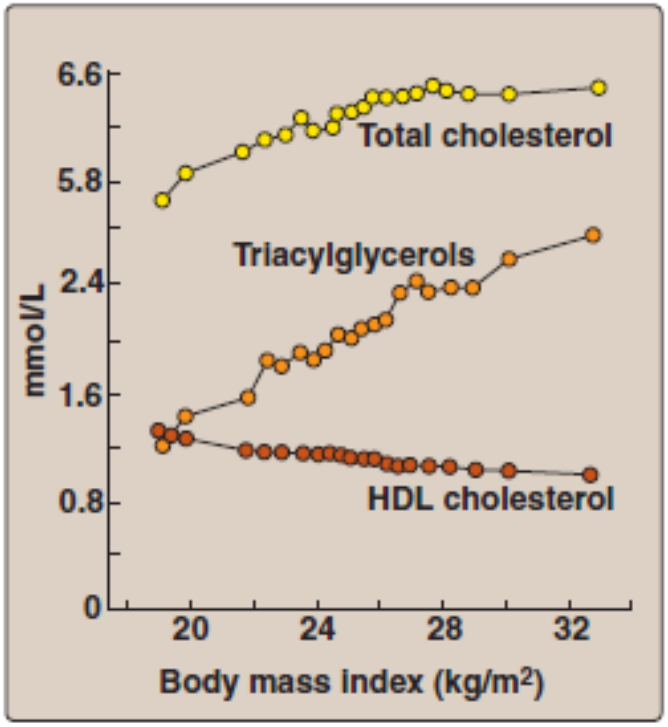


Figure 26.8
Body mass index and changes in blood lipids.

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.