Diabetes & obesity

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OVERVIEW OF DIABETES MELLITUS

- Heterogenous group of multifactorial polygenic syndrome-
- elevated fasting blood glucose caused by a relative or absolute deficiency in insulin
- Type 1
- Type 2

	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35 years; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	<10% of diagnosed diabetics	>90% of diagnosed diabetics
GENETIC PREDISPOSITION	Moderate	Very strong
DEFECT OR DEFICIENCY	β Cells are destroyed, eliminating production of insulin	Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin
FREQUENCY OF KETOSIS	Common	Rare
PLASMA INSULIN	Low to absent	High early in disease; low to absent in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar hyperglycemic state
RESPONSE TO ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, insulin (may or may not be necessary); reduction of risk factors (weight reduction, smoking cessation, blood pressure control, treatment of dyslipidemia) is essential to therapy

Figure 25.1
Comparison of type 1 and type 2 diabetes mellitus. [Note: The name of the disease reflects the clinical presentation of copious amounts of glucose-containing urine and is derived from the Greek word for siphon (diabetes) and the Latin word for honey-sweet (mellitus).]

Type 1 diabetes

- Absolute deficiency of insulin caused by autoimmune attack on the β cells of pancreas
- β cells destruction required both environmental stimulus and a genetic determinant that allows the cells to be recognized as nonself.
- Polyuria(frequent urination)
- Polydipsia(excessive thirst)
- Polyphagia(excessive hunger)
- Diagnosis by glycosylated hemoglobin:

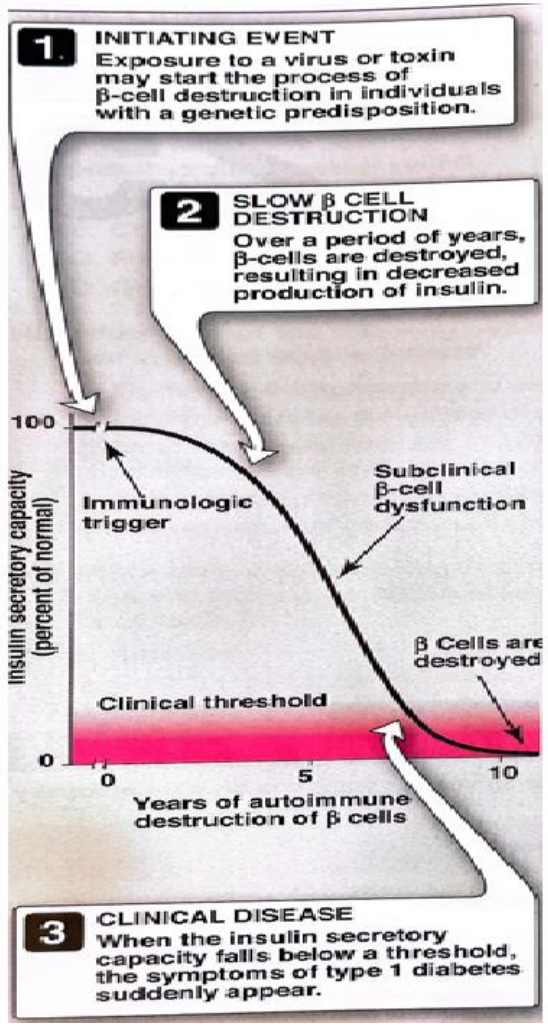
➢ ≥6.5 mg/dl, normal ≤5.7 or

➢ FBS ≥126 mg/dl, normal=70-99

➢ Impaired FBS of 100-125 mg/dl-prediabetic

➢ could be diagnosed if RBS>200 MG/DL

Figure 25.2
Insulin secretory capacity during onset of type 1 diabetes. [Note: Rate of autoimmune destruction of β cells may be faster or slower than shown.]



Metabolic changes in type 1 diabetes

Deficiency of insulin that will affect liver, muscle and adipose.

1. Hyperglycemia and ketoacidosis

- Hyperglycemia due to gluconeogenesis and no uptake of glucose by muscle an adipose Glut4
- Ketosis due to increased lipolysis from adipose and beta-oxidation of FA and increase synthesis of acetoacetate and beta-hydroxyl butyrate

2. hypertriglyceridemia:

- Not all FA are oxidized, but some of them is used for synthesis of TAG in the liver packaged as VLDL
- Chylomicrons are synthesized by intestinal cells
- LPL is not working bcz insulin absence

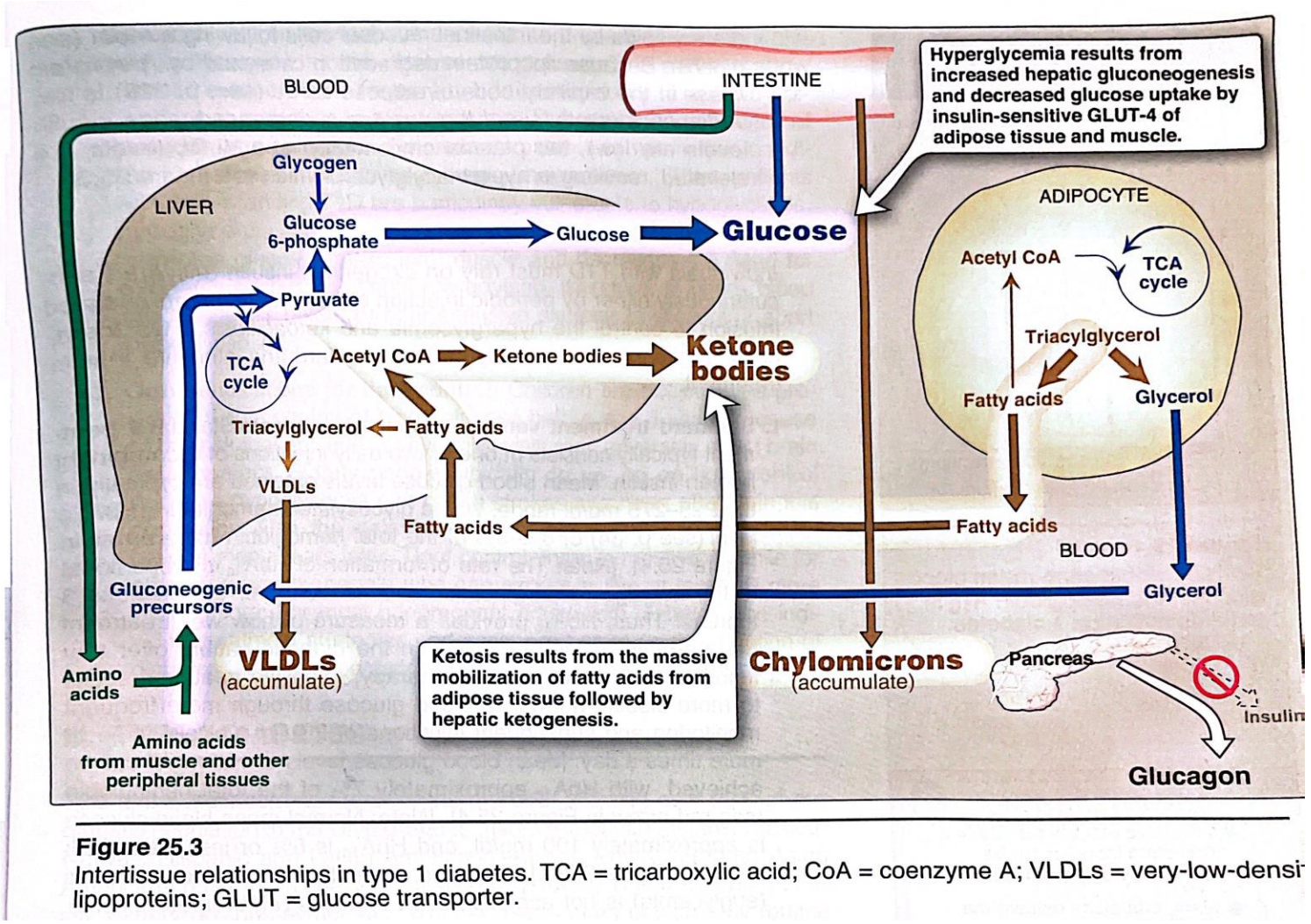


Figure 25.3
Intertissue relationships in type 1 diabetes. TCA = tricarboxylic acid; CoA = coenzyme A; VLDLs = very-low-densi lipoproteins; GLUT = glucose transporter.

Treatment of type 1 diabetes

Exogenous insulin is needed.

1. **Standard** treatment versus intensive treatment: **one or two daily injections**

- **Intensive** treatment: **3 or more** insulin injections daily.
- Normalization is not achieved even intensive treatment
- 50% or more reduction of complications in intensively treated patients

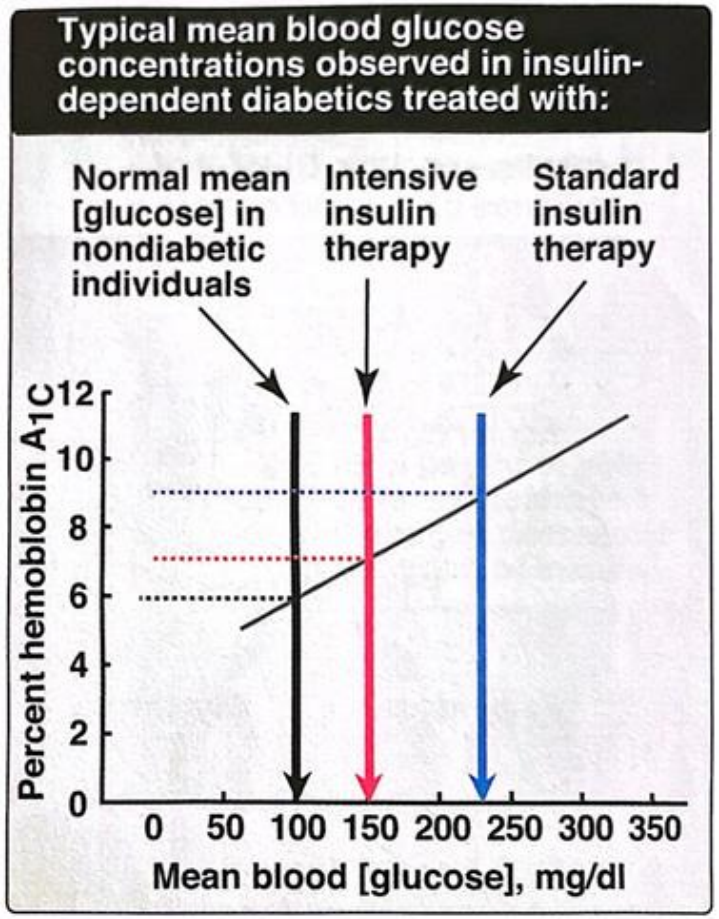
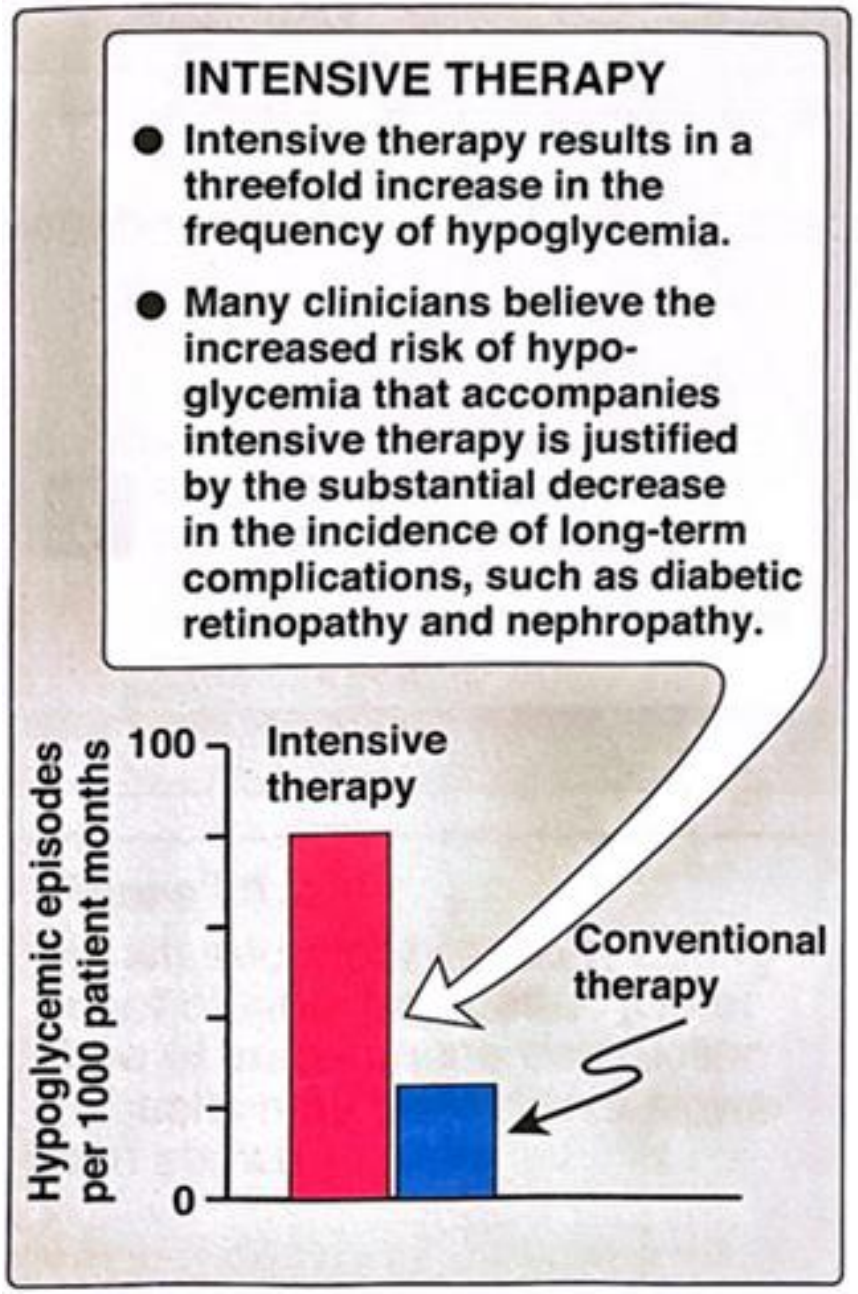


Figure 25.4
Correlation between mean blood glucose and hemoglobin A_{1C} in patients with type 1 diabetes.

Effect of tight glucose control on hypoglycemic episodes in a population of patients on intensive therapy or conventional therapy.

2. Hypoglycemia in type 1 diabetes; caused by excess insulin is the most common complication of insulin therapy

- Type 1 diabetic patients develop **deficiency of glucagon**, but rely on **epinephrine** to prevent severe hypoglycemia,
- Type 1 diabetics show **impaired ability to secrete epinephrine in response to hypoglycemia.**
- Hypoglycemia can also be caused by strenuous exercise, exercise promotes glucose uptake into muscle



TYPE 2 DIABETES

- Polyuria, polydipsia, polyphagia may be present but is less common.
- Combination of insulin resistance and dysfunctional beta cells.
- Metabolic alterations are milder than type 1
- Diagnosis is based on hyperglycemia
- No virus or autoimmune antibodies
- Hyperosmolar hyperglycemic→ hyperglycemia and dehydration

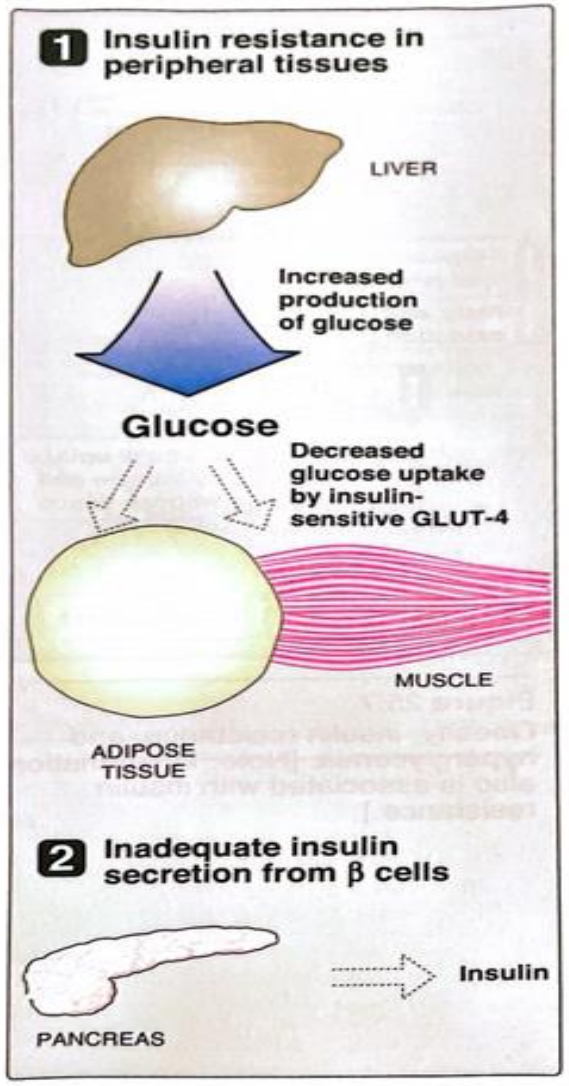


Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes. GLUT = glucose transporter.

A. Insulin resistance

- Is the decreased ability of target tissues, such as liver, adipose, and muscle to respond properly to normal or elevated circulating concentrations of insulin.
- Increase in adipose lipolysis with production of free FAs
- Increase in hepatic gluconeogenesis
- Decreased uptake of glucose by muscle and adipose tissue

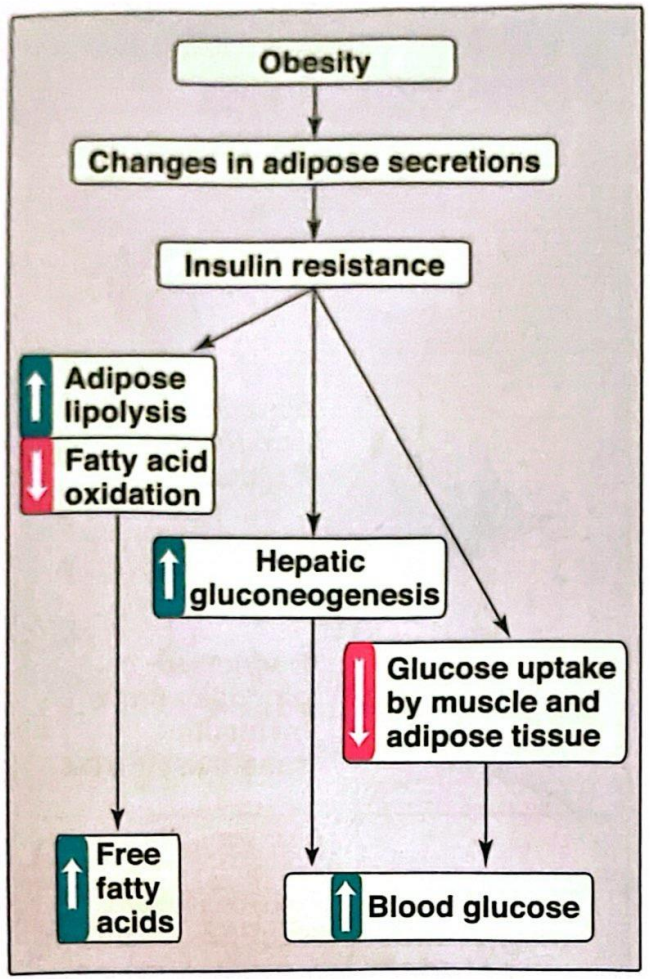


Figure 25.7
Obesity, insulin resistance, and hyperglycemia. [Note: Inflammation also is associated with insulin resistance.]

1. Insulin resistance and obesity

- Obesity causes insulin resistance.
- Most people with obesity and insulin resistance do not develop T2 diabetes
- In the absence of a defected beta cells function, nondiabetic, obese individuals can compensate for insulin resistance with elevated levels of insulin

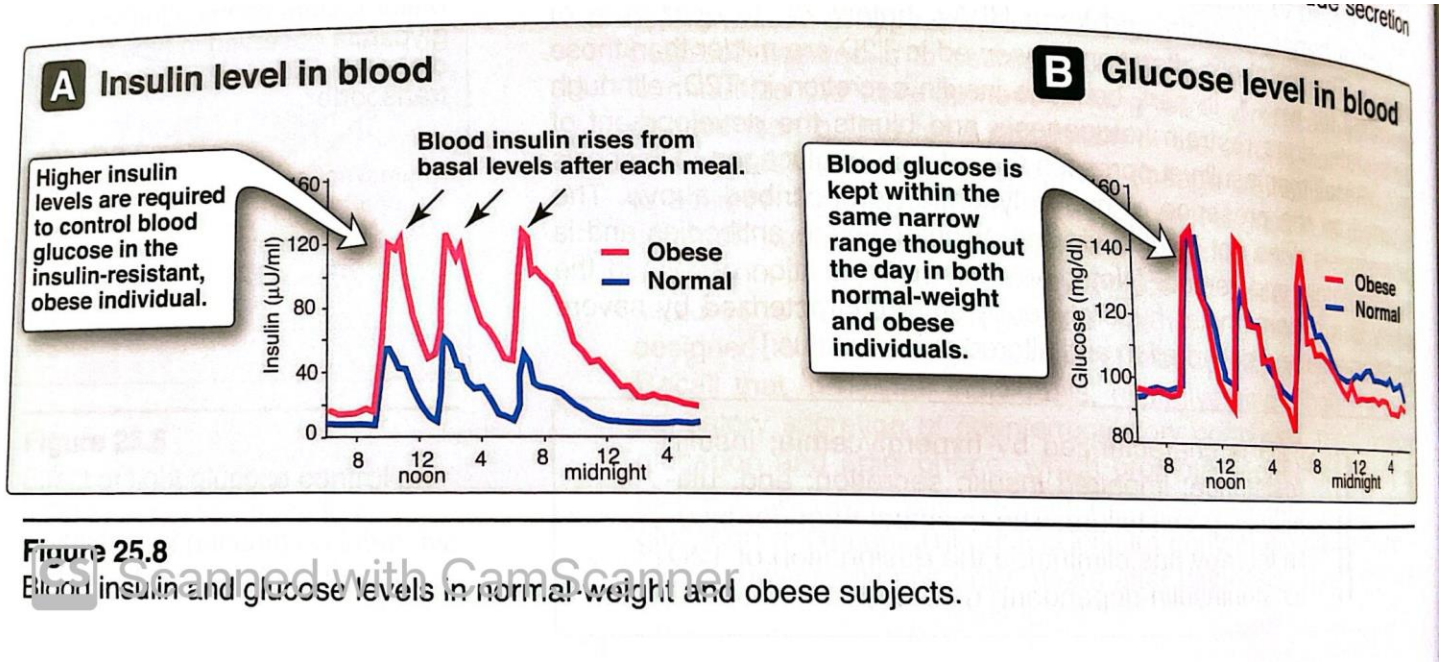


Figure 25.8
Blood insulin and glucose levels in normal-weight and obese subjects.

Insulin resistance and T2 diabetes.

- Polyuria, polydepsis, and some polyphagia
- Combination of insulin resistance and dysfunction of beta cells.
- Metabolic alteration is milder than T1D with a restrain ketogenesis and DKA.
- Diagnosis is based on hyperglycemia
- Acute complication is hyperosmolar hyperglycemic state characterized by hyperglycemia and dehydration

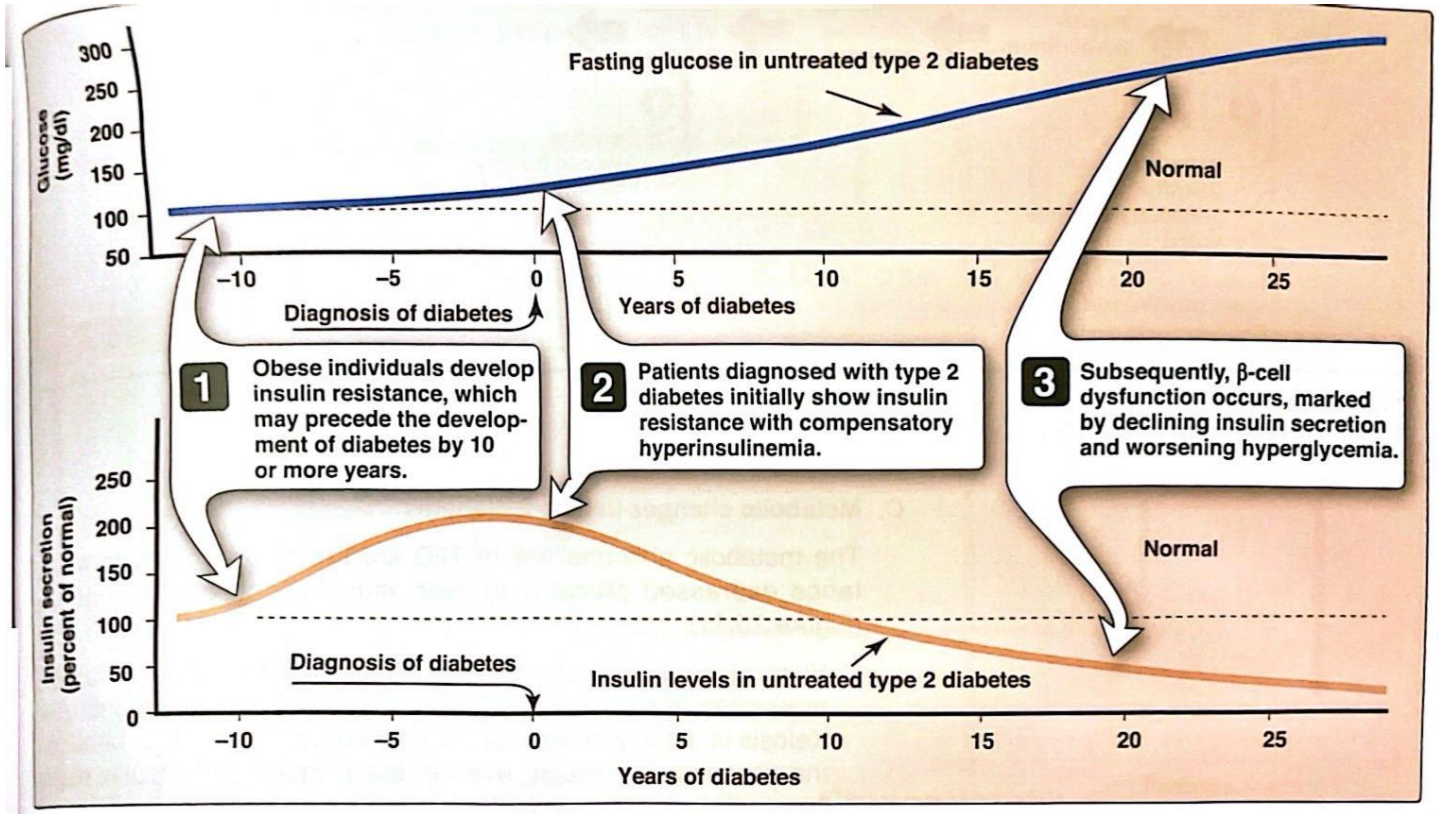


Figure 25.9
Progression of blood glucose and insulin levels in patients with type 2 diabetes.

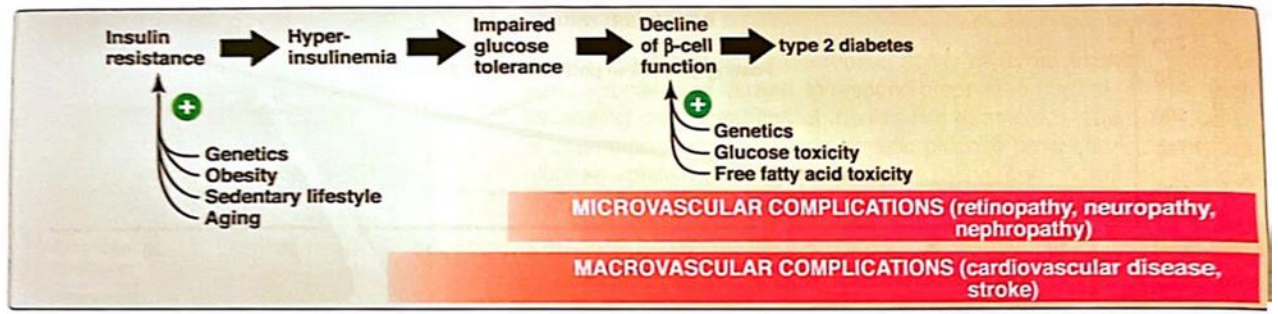


Figure 25.10
Typical progression of type 2 diabetes.

Causes and effects of insulin resistance

- **With obesity , adipose tissue secretes**:

➢ ↑proinfalmmatory cytokines such as IL-6

➢ ↑leptin-proinflammatory

➢ ↓adiponectin-antiinfalmmatory

➢ Adiponectin increases FA oxidation

- Effects of insulin resistance is

➢ increased lipolysis and production of FFAs.

➢ FFAs decrease glucose consumption leading to **hyperglycemia** and **increase of TAG in liver(hepatic steatosis**).

➢ FFAs are proinflammatory, and in long-term they suppress glucose-induced insulin release

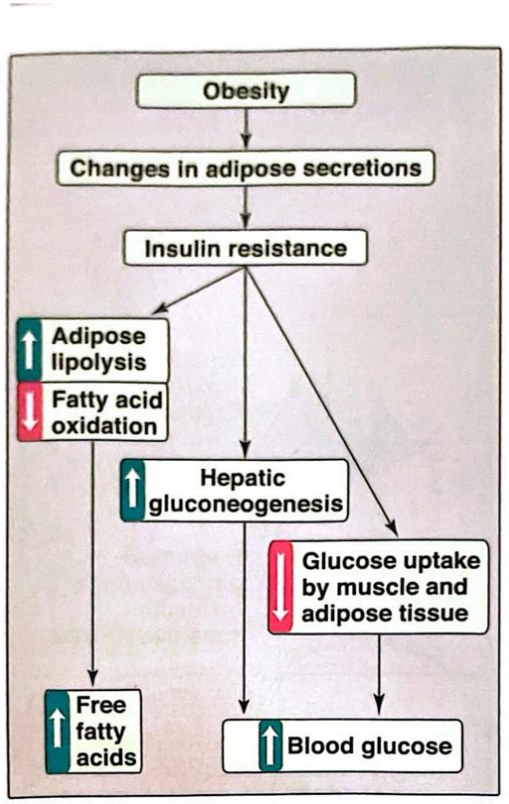


Figure 25.7
Obesity, insulin resistance, and hyperglycemia. [Note: Inflammation also is associated with insulin resistance.]

Metabolic changes in T2-D.

- Metabolic abnormalities are the result of insulin resistance in liver, muscle, and adipose tssue.

1. hyperglycemia:

- Caused by increased hepatic production of glucose combined with diminished peripheral use
- No ketosis, because of insulin presence.

2. dyslipidemia: ↑ VLDL, ↑chylomicrons, ↓HDL

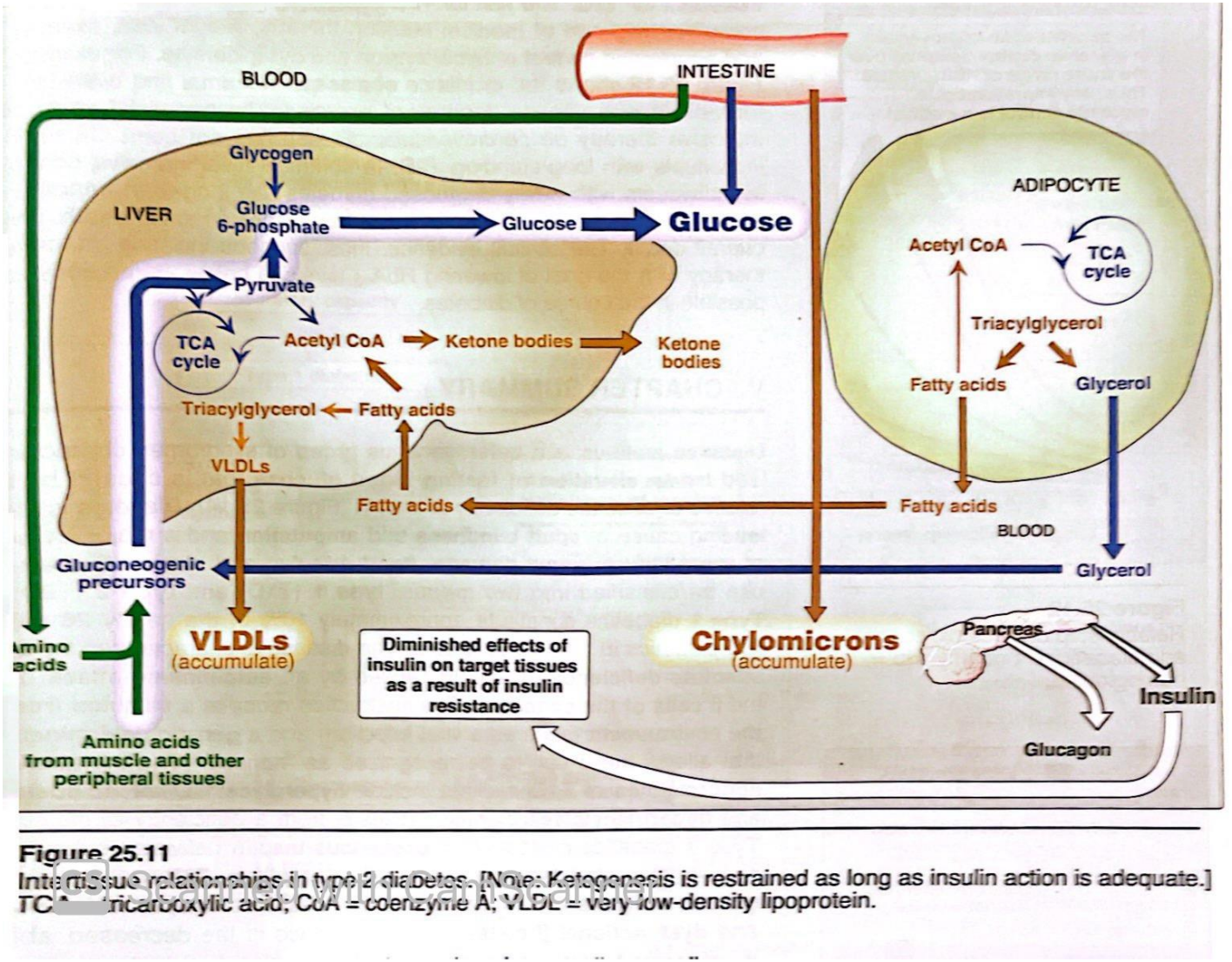


Figure 25.11
Intertissue relationships in type 2 diabetes. [Note: Ketogenesis is restrained as long as insulin action is adequate.]
TCA = tricarboxylic acid; CoA = coenzyme A; VLDL = very-low-density lipoprotein.

Treatment of T2-D

- The goal is to maintain blood glucose concentration within normal limits and to prevent long term complications,

1. Weight reduction
2. Exercise
3. diet
4. Hypoglycemic agents: metformin(inhibits gluconeogenesis), sulfonylureas(increase insulin secretion), thiazolidinediones(increase insulin sensitivity, α-glucosidase inhibitors(decrease absorption), or insulin therapy.

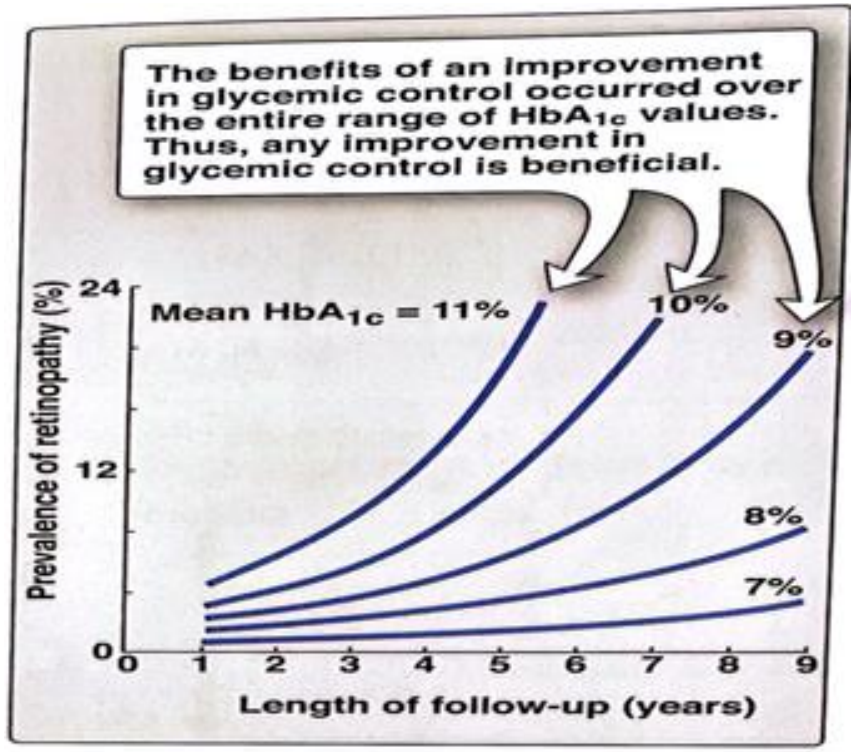


Figure 25.12
Relationship of glycemic control and diabetic retinopathy. Hb = hemoglobin.

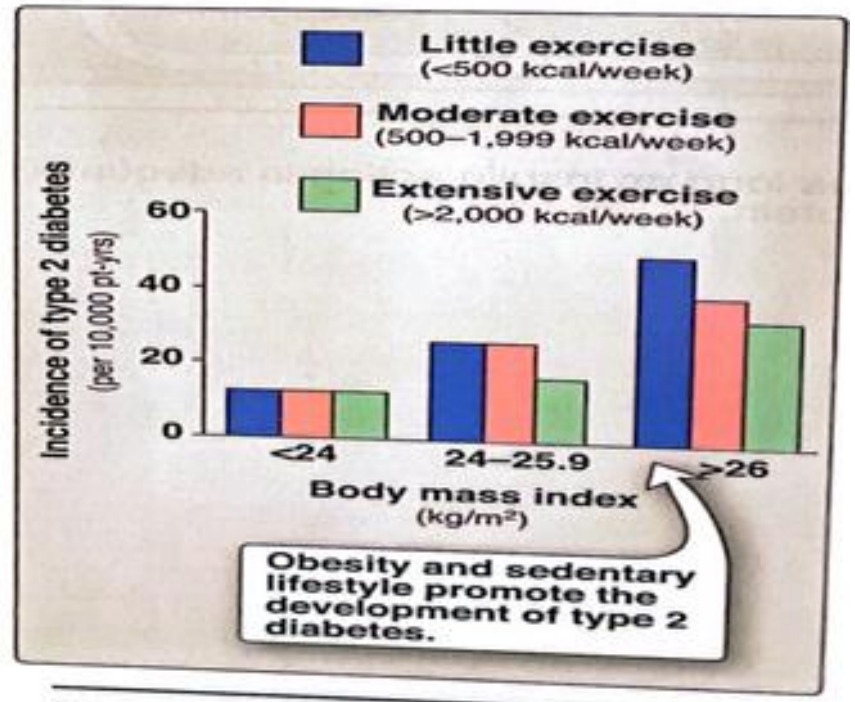


Figure 25.13
Effect of body weight and exercise on the development of type 2 diabetes.

Obesity

- Accumulation of excess body fat
- Obesity measure: waist size, measures the amount of fat in the central abdominal area of the body
- Waist size; Men ≥ 101.6 cm,

  Woman: ≥88.9 cm
- Body mass index BMI:

weight in kg/(height in meters)^2

- Healthy range; 18.5-24.9

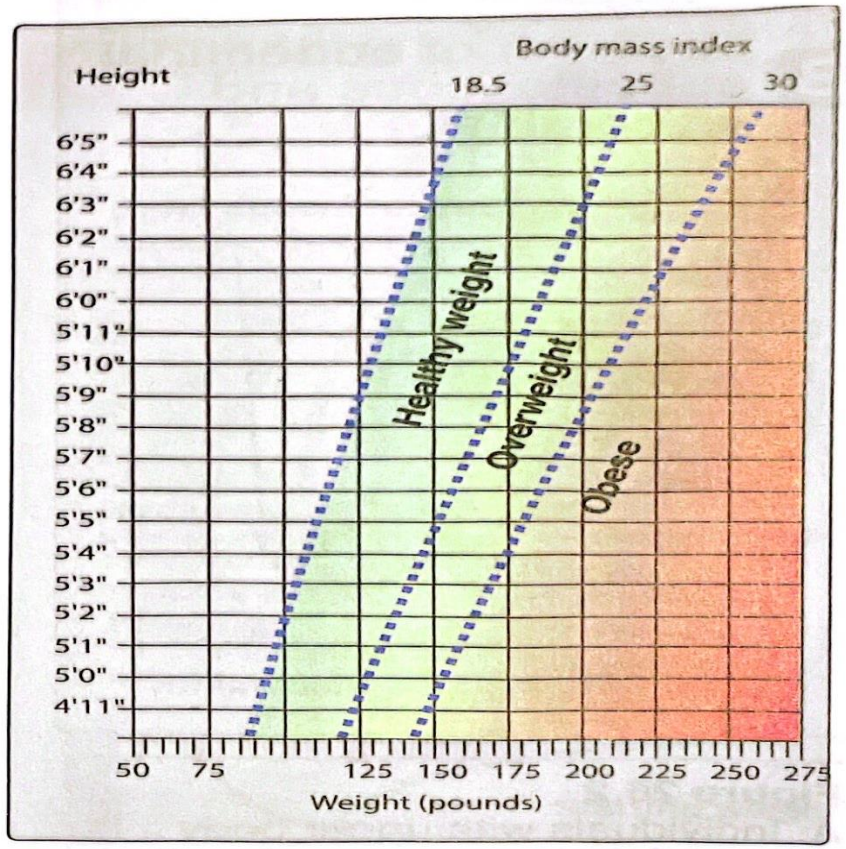


Figure 26.1
Body mass index (BMI) Chart. To use the BMI Chart, find height in the left-hand column. Move across the row to weight. Height and weight intersect at the individual's BMI. [Note: To calculate BMI using inches and pounds, use BMI = [weight in pounds/(height in inches)^2] × 703.

Anatomic differences in fat deposition

- **Upper body obesity:**

-apple shape

-waist/hip>0.8 for women, >1.0 for men

- **Lower body obesity**

-pear shape

-waist/hip<0.8 for women, ,<1.0 for men

-lower risk of metabolic disease, protective

- 80%-90% of stored fat is subcutaneous
- 10%-20%-visceral
- Subcutaneous abdominal and visceral fat increase health risks associates with obesity

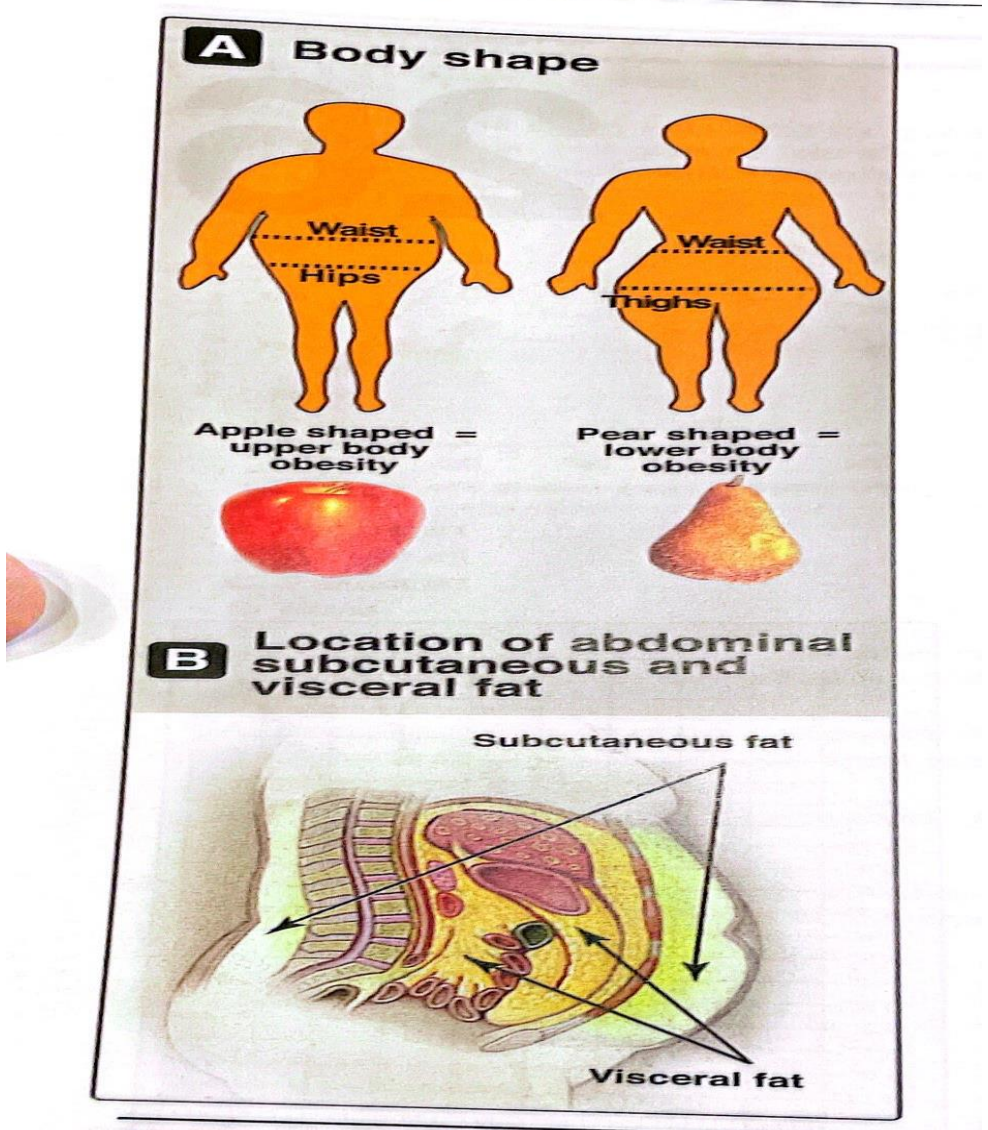


Figure 26.2
A. Individuals with upper body obesity (left) have greater health risks than individuals with lower body obesity (right). B. Visceral fat is located inside the abdominal cavity, packed in between the internal organs. Subcutaneous fat is found underneath the skin.

Biochemical differences in regional fat deposits

- Subcutaneous adipocytes from the lower body are larger, efficient in TG storage, and more slowly fatty acid mobilization than abdominal subcutaneous adipocytes
- Visceral adipocytes are the most metabolically active
- Subcutaneous and visceral fat from obese individuals have high rate of lipolysis and high FFA
- Upper body obese have higher risk because of these metabolic differences
- Adipocytes produce protein regulators such as leptin and adiponectin hormones

➢ leptin : regulates appetite and metabolism. Increases as body weight increases

➢ Adiponectin: reduces FFAs, improved lipid profile, increasing insulin sensitivity, and reduces inflammation in diabetes. It decreases as body weight increases.

- FFAs and cytokines released from upper subcutaneous & visceral enter portal vein direct to liver , and lead to insulin resistance, increased hepatic TG, VLDL, hyper TG
- By contrast FFAs from lower body enter general circulation and oxidized in muscle and reach the liver in lower concentration.

Obesity is due to combination of increased fat cell size (hypertrophy) and number(hyperplasia)

Ectopic fat: when excess fat cannot fit in adipose tissue , will spill over into other tissues (muscle and liver)-insulin resistance

With weight loss in obese individual, the size of the fat cell will decrease but the number is not affected.

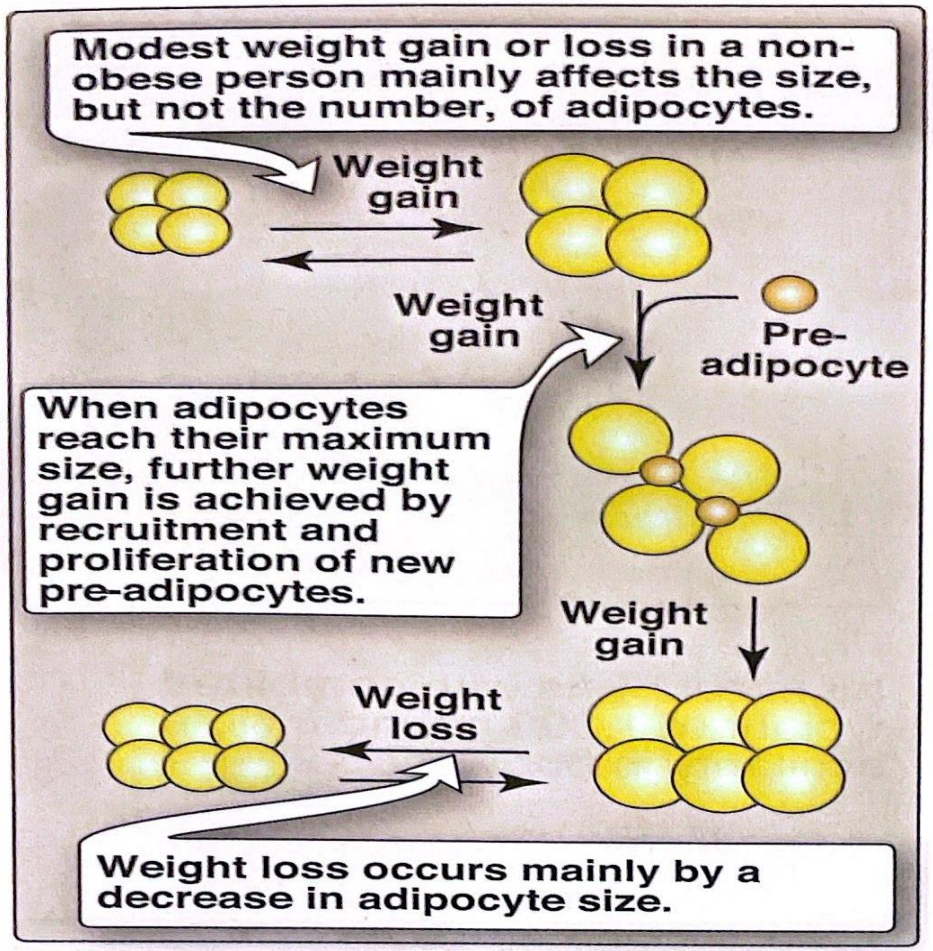


Figure 26.3
Hypertrophic (increased size) and hyperplastic (increased number) changes to adipocytes are thought to occur in severe obesity.

Genetic contribution to obesity

- Identical twins have very similar BMI
- Adoptive children show body weight that correlates with their biologic rather than adoptive parents
- Mutation to leptin gene or its receptor produce hyperphagia
- Most obese humans have elevated leptin levels but appear to be resistant to the appetite-regulating effects of this hormone.

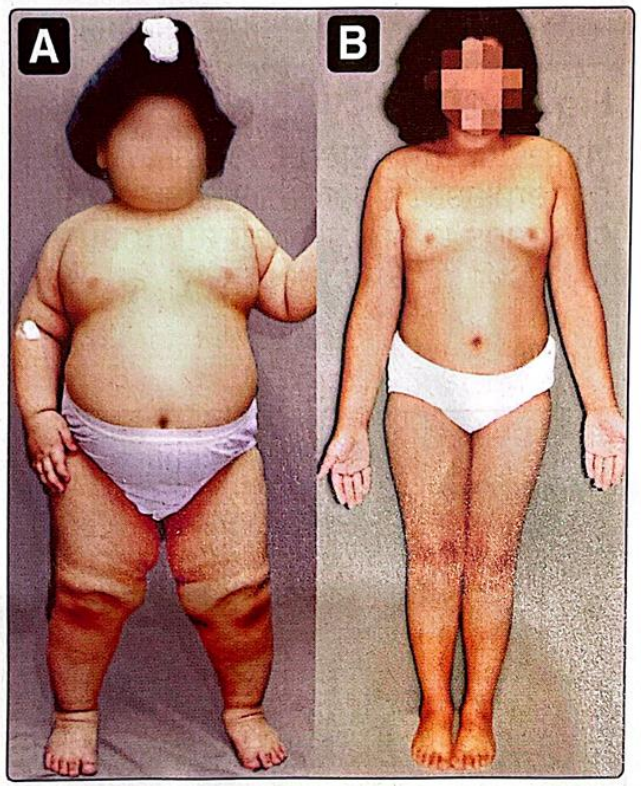


Figure 26.6
A. Patient with leptin deficiency before initiation of therapy at age 5 years. B. Patient at age 9 years after 48 months of therapy with subcutaneous injection of recombinant leptin.

igure 26.5
dentical twins with combined veight of 1,300 pounds. Note imilarity in body shape.

Molecular basis of obesity

A. Long term signals: status of TAG

1. leptin: adipocyte peptide hormone secreted in proportion to size of the fat stores.
2. Describe panel A
3. Describe panel B
4. Insulin: obese individuals are hyperinsulinemic

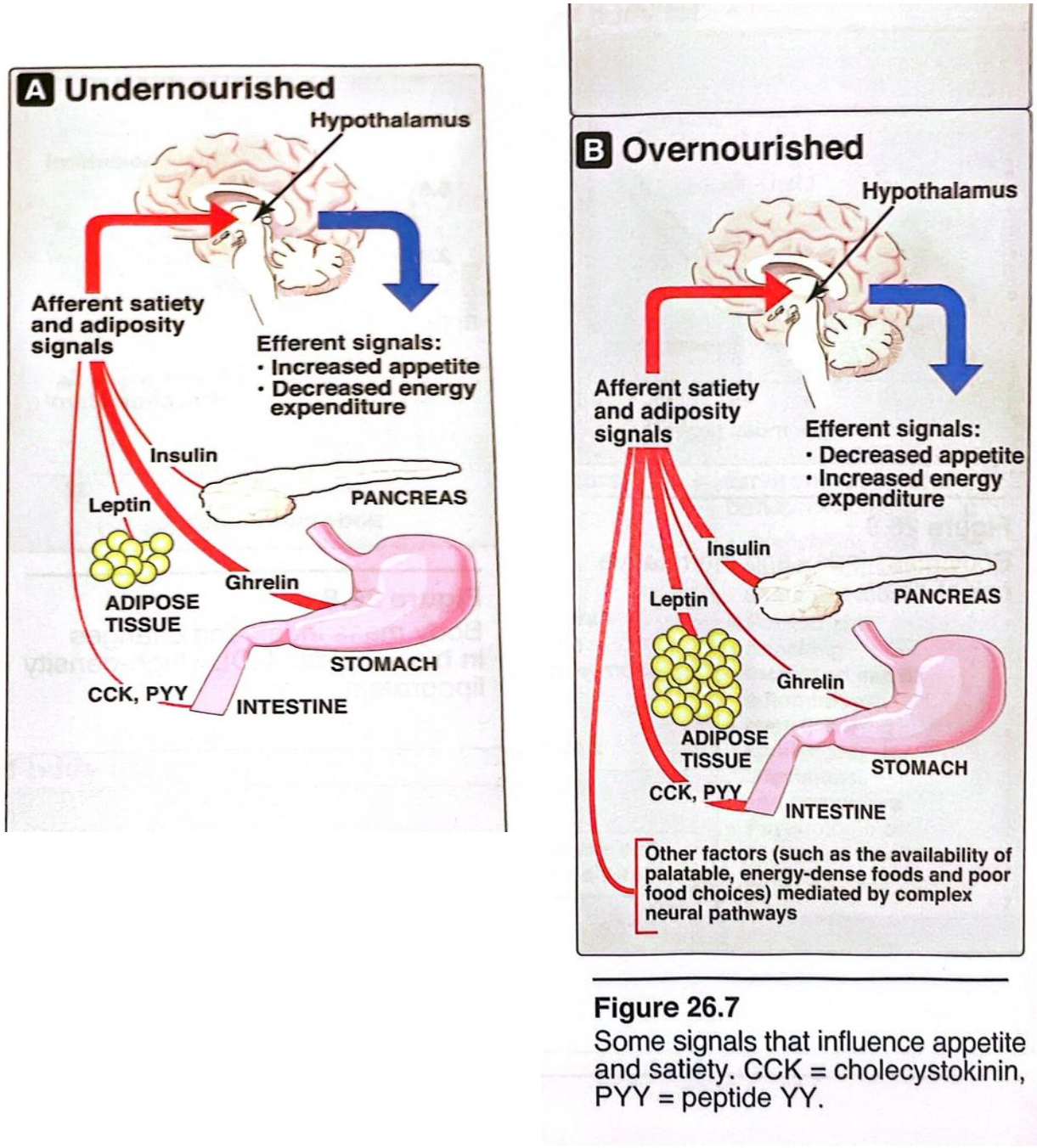
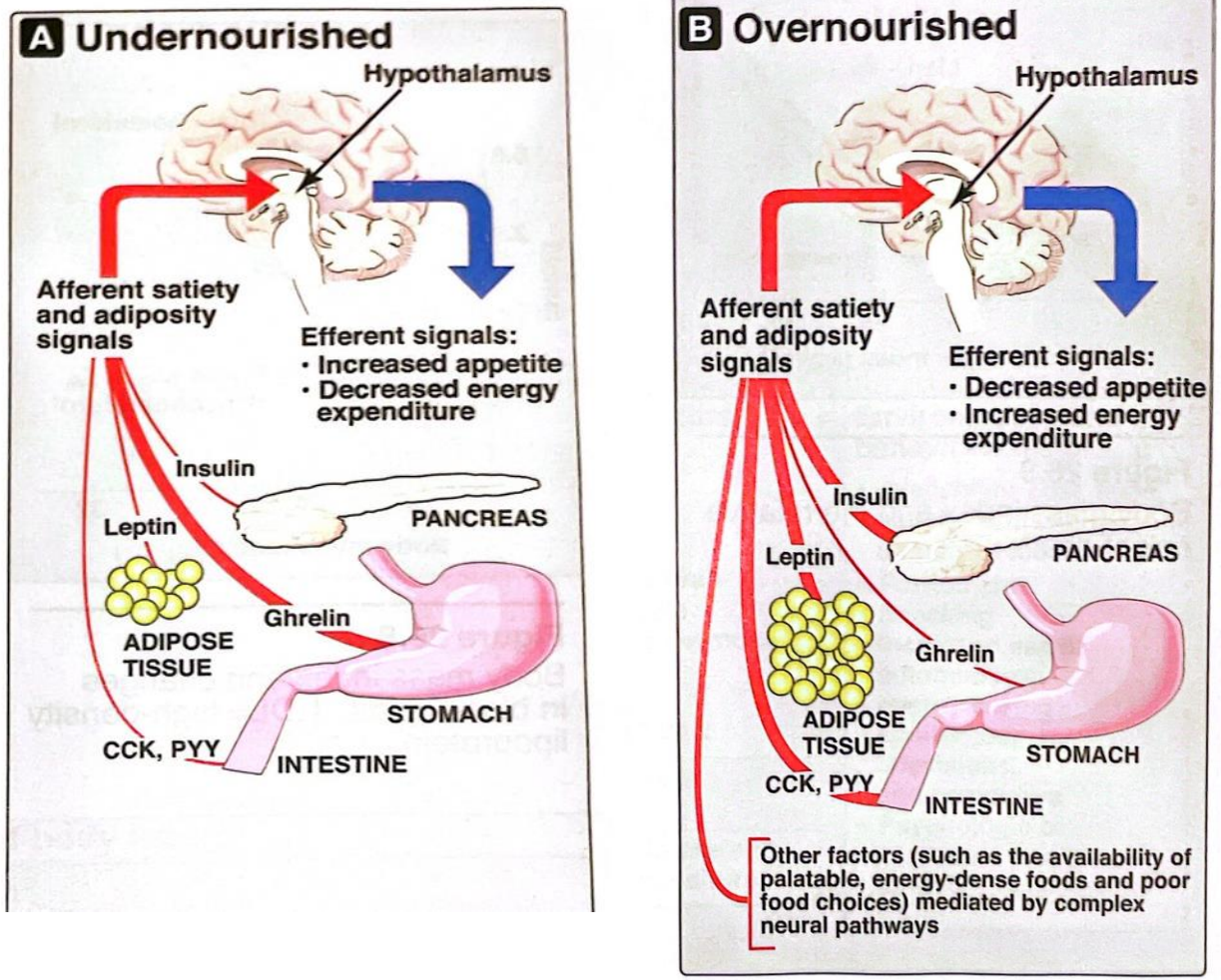


Figure 26.7
Some signals that influence appetite and satiety. CCK = cholecystokinin, PYY = peptide YY.

B. Short-term signals: from GI control hunger and satiety

In the absence of food intake ghrelin(apetite stimulant) drives hunger.



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Some signals that influence appetite and satiety. CCK = cholecystokinin, PYY = peptide YY.

Metabolic changes in obesity

- Metabolic syndrome
  - ➢ Glucose intolerance-hyperglycemia
  - ➢ Insulin resistance
  - ➢ Hyperinsulinemia
  - ➢ Dyslipidemia (low HDL, high TG)
  - ➢ Hypertension
- Chronic systemic inflammation-atherosclerosis
- Release of proinflammatory mediators IL-6
- Low level of adiponectin which normally dampens inflammation and sensitizing tissue (liver) to insulin→ T2D

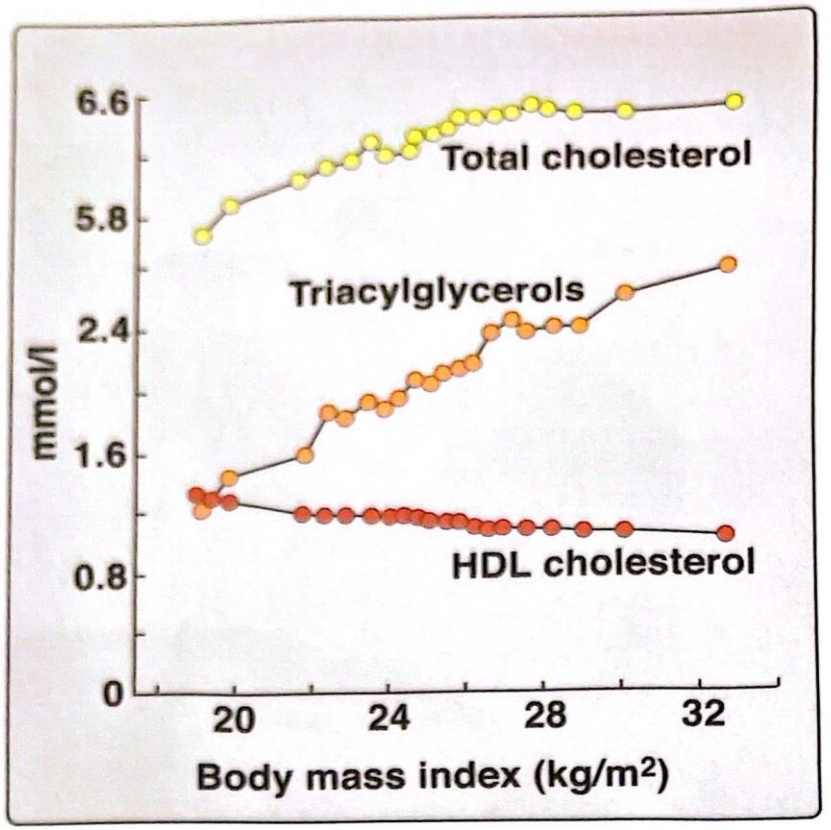

Figure 26.8
Body mass index and changes in blood lipids. HDL= high-density lipoprotein.