Metabolism

فريق طوفان الأقصى

Modified N: 25 (Last one)

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اللهم اني أسألك فهم النبيين وحفظ المرسلين, والملائكة المقربين, اللهم اجعل ألسنتنا عامرة بذكرك, وقلوبنا بخشيتك, و اسرارنا بطاعتك, انك على كل شيء قدير

Diabetes & obesity

Dr. Nabil Bashir

OVERVIEW OF DIABETES MELLITUS

- Heterogenous group of multifactorial polygenic syndrome-

NOTE: There are many causes and many clinical pictures associated with diabetes

- elevated fasting blood glucose caused by a relative or absolute deficiency in insulin
- Type 1
- Type 2

NOTE: Study the table well

	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

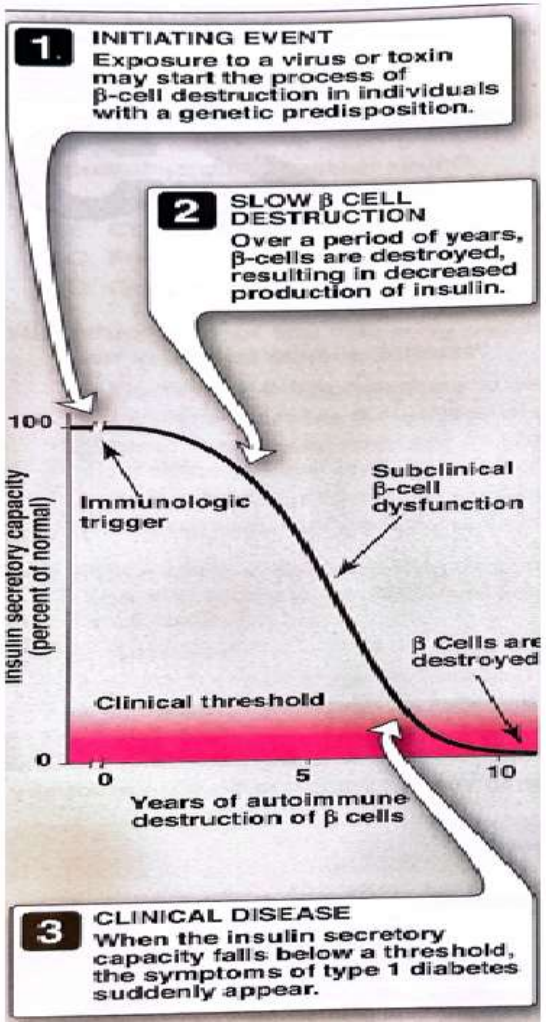
NOTE: RBS is Random Blood Sugar, which is measured 1 or 2 hours after having a meal (post-absorptive state).

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.]

NOTE: This figure shows you the gradual destruction of β cells.

NOTE: Glycosylated hemoglobin is hemoglobin attached to sugar, it stays in RBCs, so when it is measured it indicates the levels of glucose in the previous 3 months, as this is the age for a normal RBC.

NOTE: FBS is Fasting Blood Suger



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 and adipose Glut4

NOTE: GLUT 4 is insulin-dependent. No insulin, no GLUT 4, no intake of glucose by muscles and adipose tissue. Note that entry of glucose into liver is not insulin-dependent, but it will not be phosphorylated, so it will exit the liver into the blood, thus **hyperglycemia**.

- Ketosis due to increased lipolysis from adipose and beta-oxidation of FA and increase synthesis of acetoacetate and beta-hydroxyl butyrate.

NOTE: Some of the acetyl-CoA released from beta-oxidation of fatty acids will be used in TCA cycle, but the rest will be used to synthesize ketone bodies.

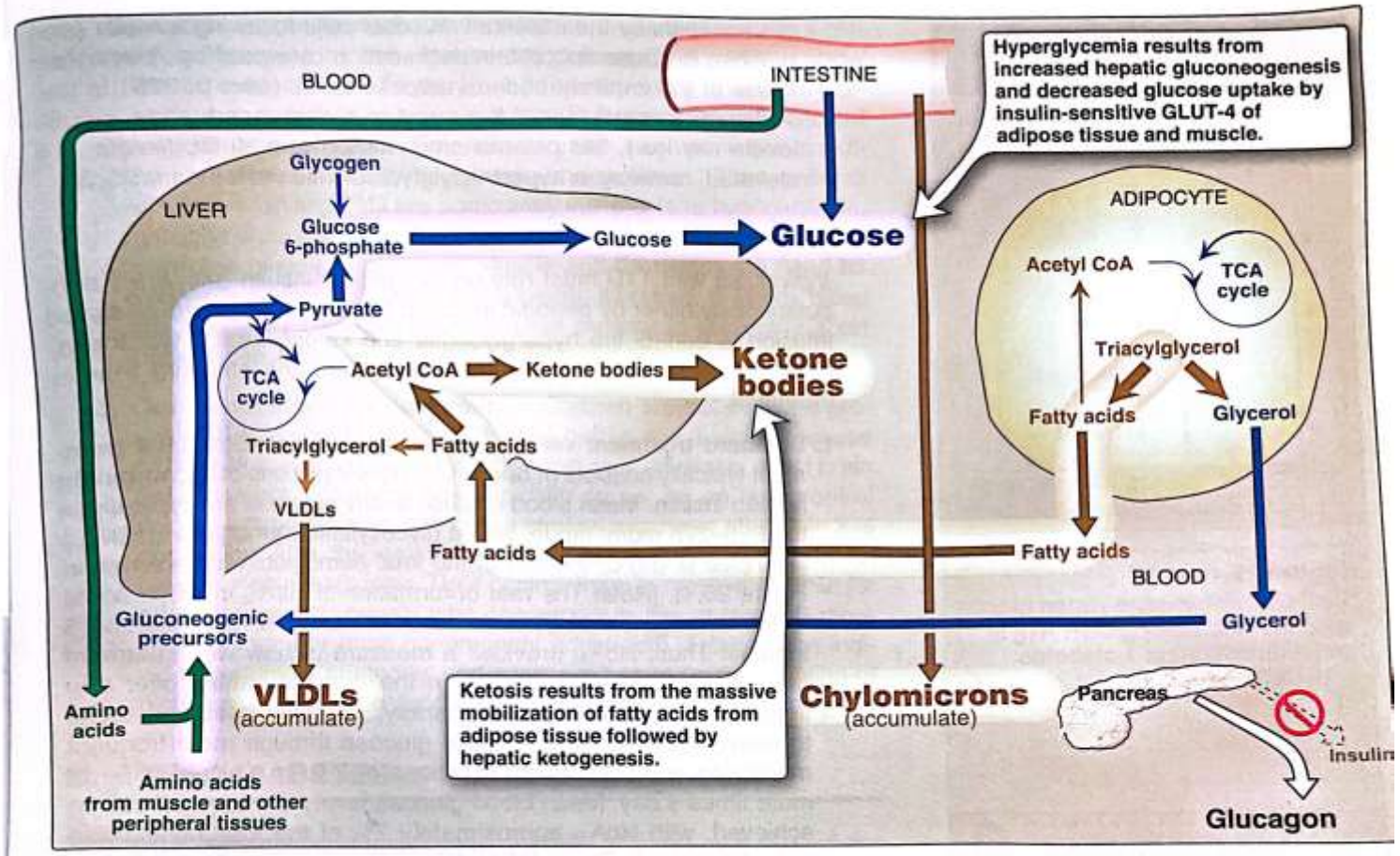


Figure 25.3
Intertissue relationships in type 1 diabetes. TCA = tricarboxylic acid; CoA = coenzyme A; VLDLs = very-low-densi lipoproteins; GLUT = glucose transporter.

2. hypertriglyceridemia:

NOTE: Hypertriglyceridemia occurs because not all fatty acids are oxidized, some of them are used to synthesize TAGs which are packaged in VLDLs, and these VLDLs accumulate in the blood. TAG-rich chylomicrons also accumulate. Why do they accumulate? Because **lipoprotein lipases are not working due to absent insulin.**

- 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

NOTE: Exogenous insulin in type 1 diabetes is needed because there are insufficient amounts of insulin in the body. There are 2 types of treatment, the **standard treatment** and the **intensive treatment**. In **standard treatment, one or two daily injections are given, the level of glucose is above normal, it is about 250 mg/dl and the level of HbA1c is about 9, still higher than normal** (glucose=100 mg/dl, HbA1c=6, follow the curve as you read).

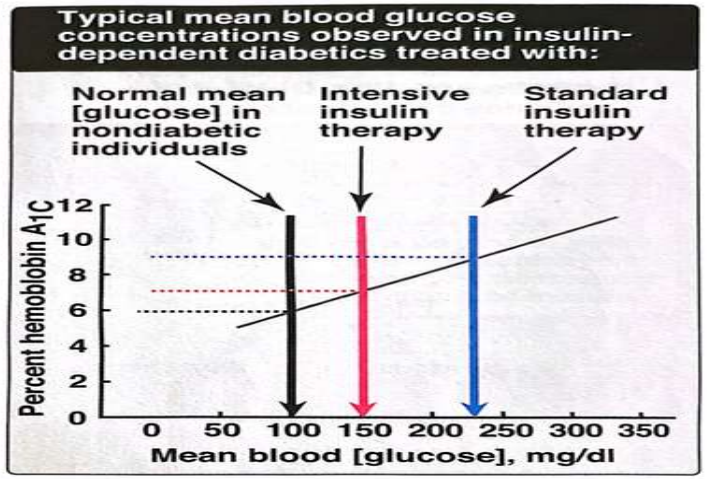


Figure 25.4
Correlation between mean blood glucose and hemoglobin A_{1C} in patients with type 1 diabetes.

Treatment of type 1 diabetes

NOTE: In **intensive treatment (3 or more injections)**, the glucose levels and HbA1c are less than in the standard, but still not reaching normal levels. It was found that **intensive treatment** resulted in 50% reduction in complications such as: **neuropathy ,retinopathy, and nephropathy**.

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

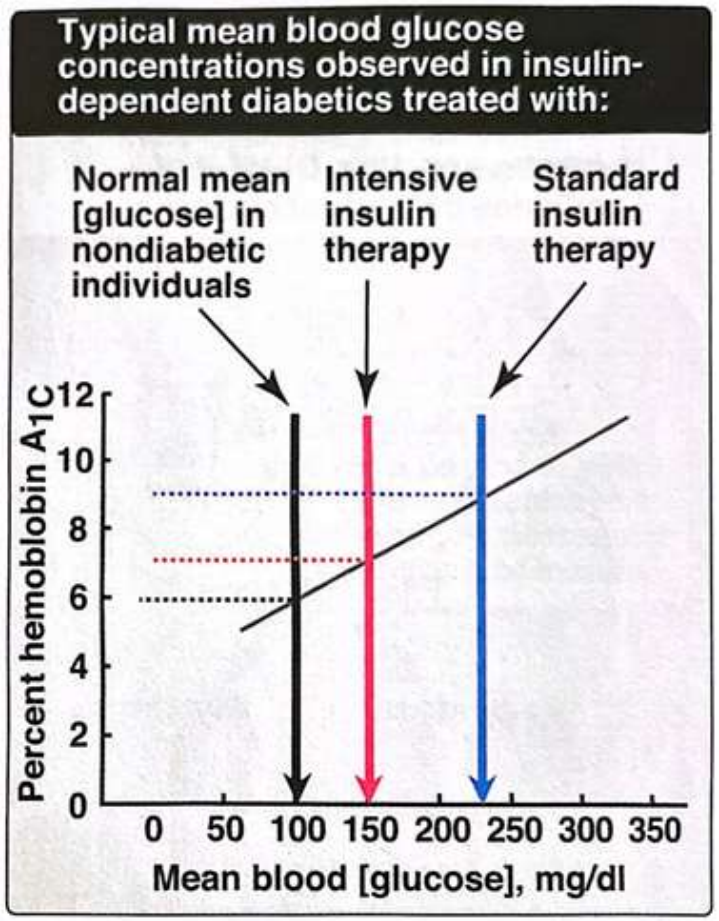
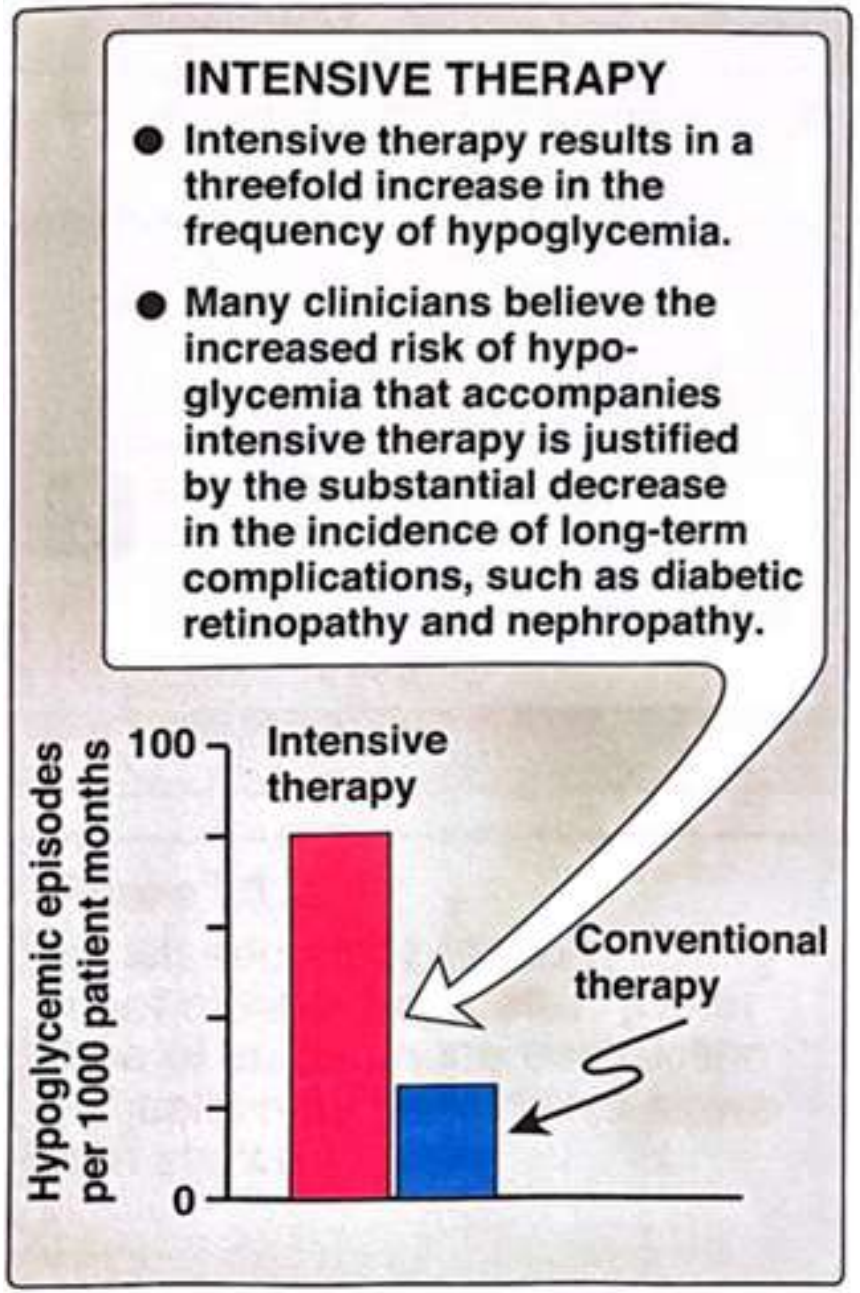


Figure 25.4
Correlation between mean blood glucose and hemoglobin A_{1C} in patients with type 1 diabetes.

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



- **Additional from Lippincott:** One of the therapeutic goals in cases of diabetes is to decrease blood glucose levels in an effort to minimize the development of long-term complications of the disease. However, appropriate dosage of insulin is difficult to achieve. Hypoglycemia caused by excess insulin is the most common complication of insulin therapy, occurring in >90% of patients. The frequency of hypoglycemic episodes, seizures, and coma is particularly high with intensive treatment regimens designed to achieve tight control of blood glucose. In normal individuals, hypoglycemia triggers a compensatory secretion of counterregulatory hormones, most notably glucagon and epinephrine, which promote hepatic production of glucose. However, patients with T1D also develop a deficiency of glucagon secretion. Therefore, these patients rely on epinephrine secretion to prevent severe hypoglycemia. However, as the disease progresses, T1D patients show diabetic autonomic neuropathy and impaired ability to secrete epinephrine in response to hypoglycemia. The combined deficiency of glucagon and epinephrine secretion creates a symptom-free condition sometimes called “hypoglycemia unawareness.” Thus, patients with long-standing T1D are particularly vulnerable to hypoglycemia.

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, using FBS, Hb1Ac, and RBS.
- No virus or autoimmune antibodies
- Hyperosmolar hyperglycemic→ hyperglycemia and dehydration

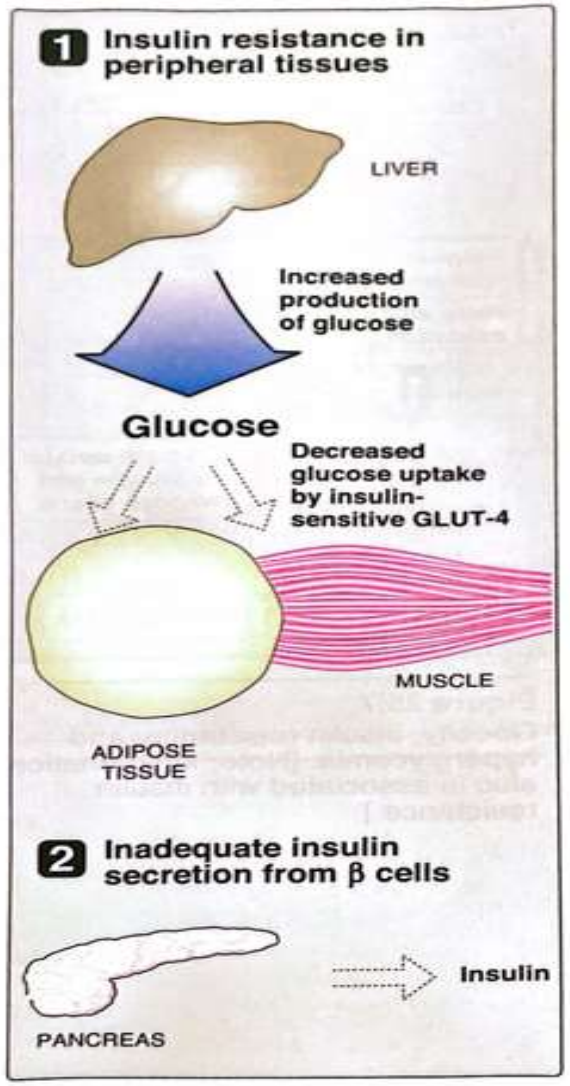


Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes. GLUT = glucose transporter.

- **NOTE:** In type 2 diabetes, there is an increased production of glucose in the liver by gluconeogenesis and glycogenolysis, and this glucose accumulates in the blood due to decreased GLUT 4 activity in muscles and adipose tissue because of insulin resistance, and inadequate insulin secretion from the pancreas.
- **Additional:** When you have high blood sugar, your **kidneys** try to get rid of the excess sugar through the urine. Through this process, you also lose fluids (water) that your body needs. It also causes your blood to become more concentrated than normal. This is called hyperosmolarity.

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

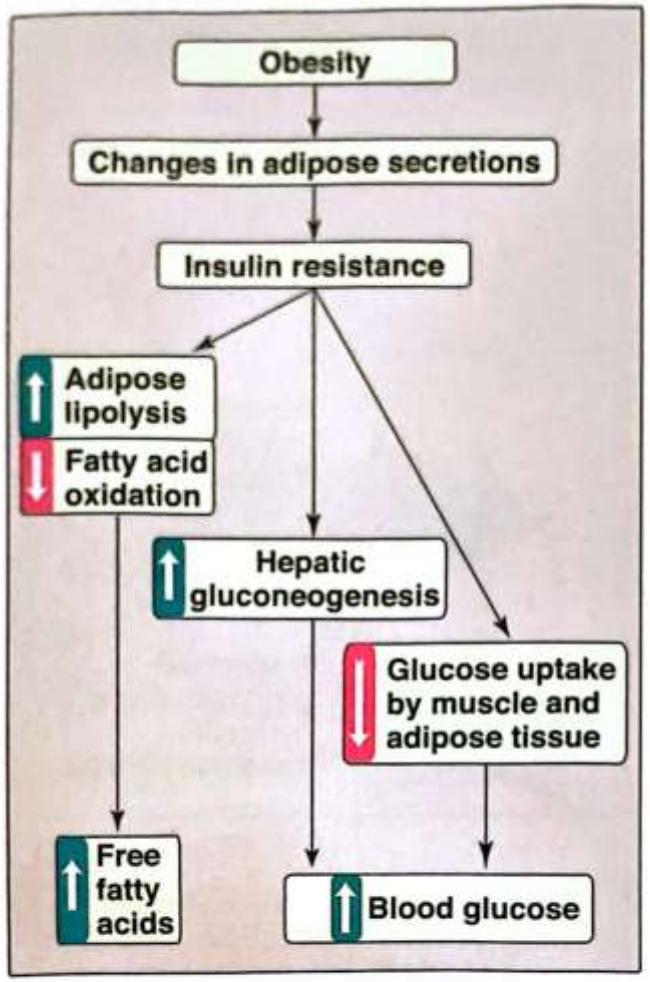


Figure 25.7
Obesity, insulin resistance, and hyperglycemia. [Note: Inflammation also is associated with insulin resistance.]

Note: (this was explained by the doctor, but I took the explanation from Lippincott)

Insulin resistance increases with weight gain and decreases with weight loss, and excess adipose tissue (particularly in the abdomen) is key in the development of insulin resistance. Adipose is not simply an energy storage tissue, but also a secretory tissue. With obesity, there are changes in adipose secretions that result in insulin resistance.

- **The complement in this slide:**
  These include secretion of proinflammatory cytokines such as interleukin 6 and tumor necrosis factor-α by activated macrophages (inflammation is associated with insulin resistance); increased synthesis of leptin, a protein with proinflammatory effects; and decreased secretion of adiponectin, a protein with anti-inflammatory effects. The net result is chronic, low-grade inflammation. One effect of insulin resistance is increased lipolysis and production of FFA .FFA availability decreases use of glucose, contributing to hyperglycemia, and increases ectopic deposition of TAG in liver (hepatic steatosis). FFA also have a proinflammatory effect. In the long term, FFA impair insulin signaling. [Note: Adiponectin increases FA β-oxidation. Consequently, a decrease in this adipocyte protein contributes to FFA availability.] So, in an obese person, high amounts of free fatty acids are because of increased adipose lipolysis and decreased beta-oxidation, and blood glucose is high because of decreased uptake by muscles and adipose tissue.

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

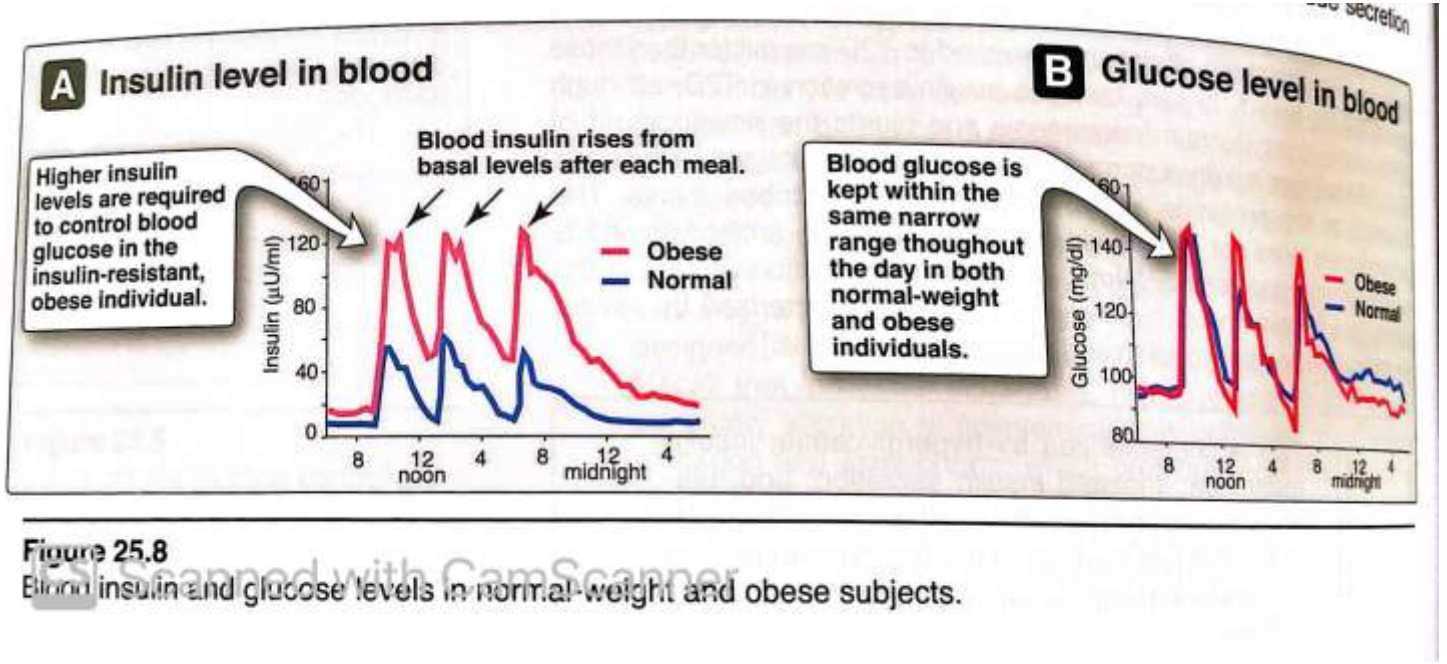


Figure 25.8
Blood insulin and glucose levels in normal-weight and obese subjects.

Further explanation: Although obesity is the most common cause of insulin resistance and increases the risk of T2D, most people with obesity and insulin resistance do not develop diabetes. In the absence of a defect in β-cell function, obese individuals can compensate for insulin resistance with elevated levels of insulin. For example, Figure 25.8A shows that insulin secretion is two to three times higher in obese subjects than it is in lean individuals. This higher insulin concentration compensates for the diminished effect of the hormone (as a result of insulin resistance) and produces blood glucose levels similar to those observed in lean individuals (Fig. 25.8B).

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

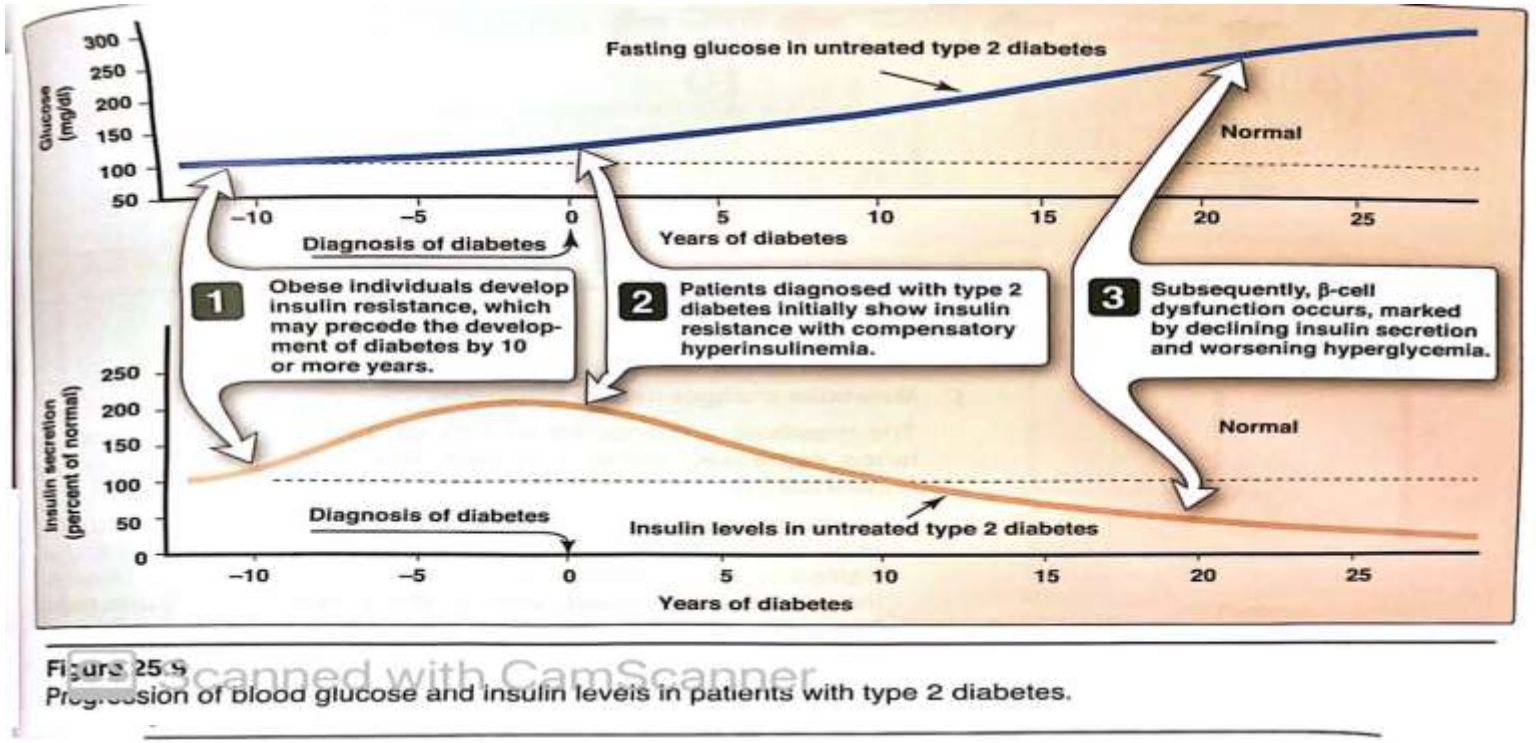


Figure 25.9
Progression of blood glucose and insulin levels in patients with type 2 diabetes.

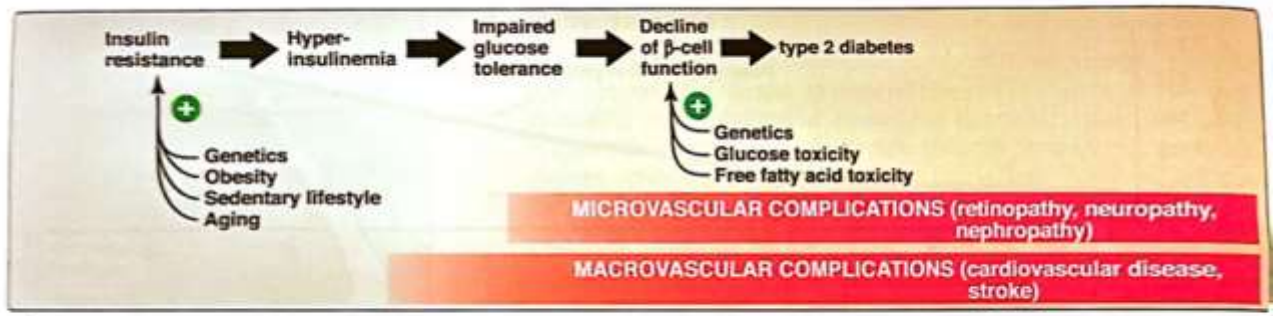


Figure 25.10
Typical progression of type 2 diabetes.

NOTE: In figure 25.9 , note that in stage 2, the glucose level is still not extremely high. At stage 3, β-cell dysfunction occurs, so there will be a marked decrease in insulin and a marked increase in glucose.

NOTE: note the risk factors and the complications

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

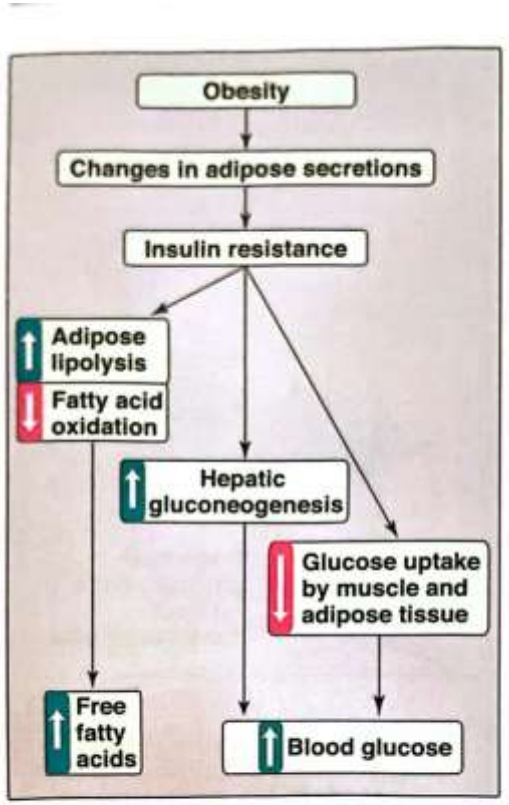


Figure 25.7
Obesity, insulin resistance, and hyperglycemia. [Note: Inflammation also is associated with insulin resistance.]

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

NOTE: Increased gluconeogenesis from dietary amino acids to form pyruvate. Little of pyruvate will be used to produce acetyl-CoA, rather it is used in gluconeogenesis.

➢ No ketosis, because of insulin presence.

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

NOTE: Fatty acids from lipolysis from adipose tissue, some will be oxidized to acetyl-CoA which will be used for ketogenesis, others will be used to synthesize TAGs which will packaged inside VLDLs.

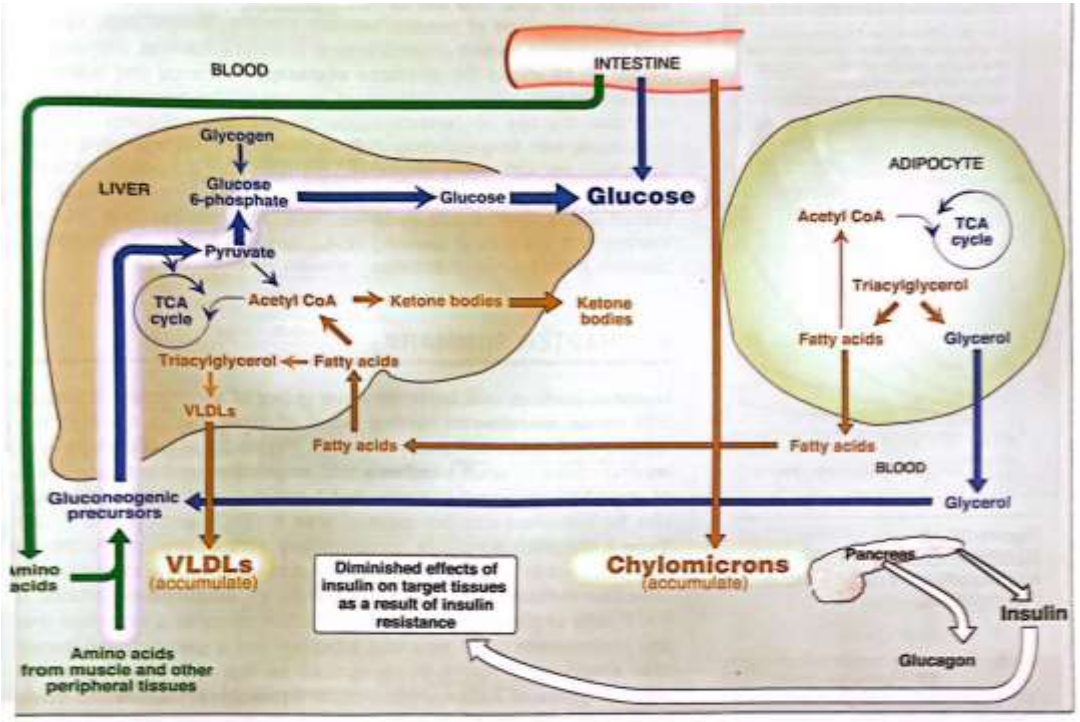


Figure 25.11
Interrelationships in type 2 diabetes. [Note: Ketogenesis is restrained as long as insulin action is adequate.]
TCA = tricarboxylic acid; CoA = coenzyme A; VLDL = very low-density lipoprotein.

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.

NOTE: Ponder these figures well

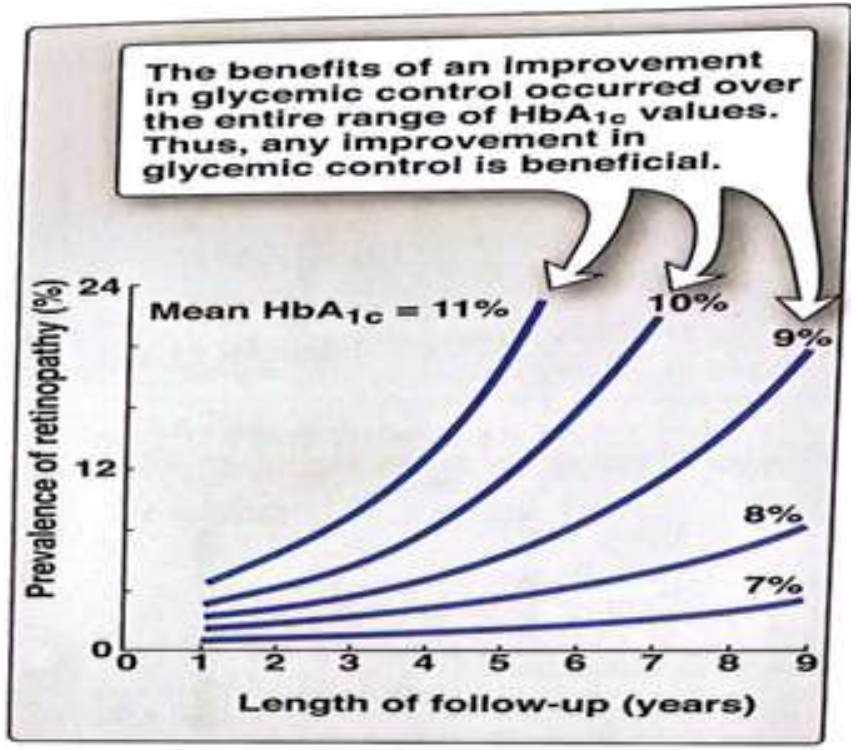


Figure 25.12
Relationship of glycemic control and diabetic retinopathy. Hb = hemoglobin.

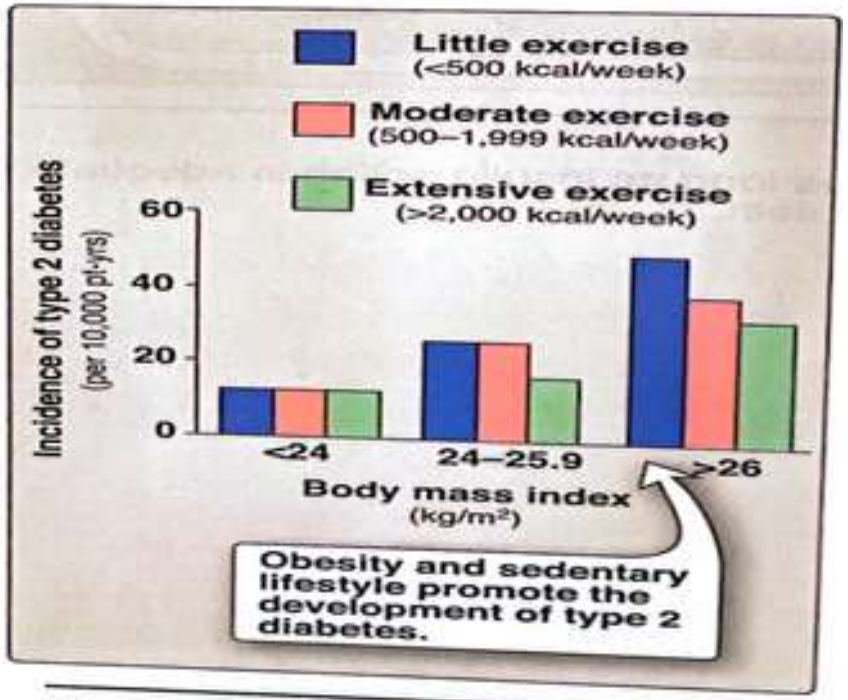


Figure 25.13
Effect of body weight and exercise on the development of type 2 diabetes.

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

NOTE: The above are normal levels. (in the original slides, signs were >, but the doctor corrected them in the lecture.

- Body mass index BMI:
- weight in kg/(height in meters)$_2$
- Healthy range; 18.5-24.9

NOTE: For a person who weighs 70 Kg and his height is 170 cm, his BMI would be:
70/(1.7 m)^2=24.2

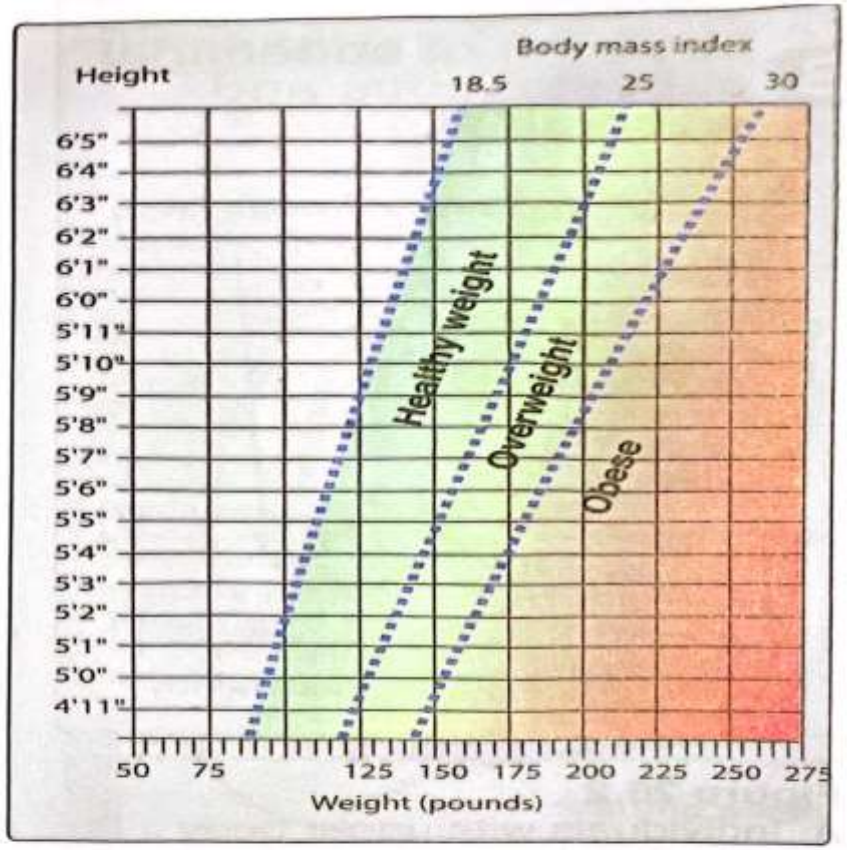
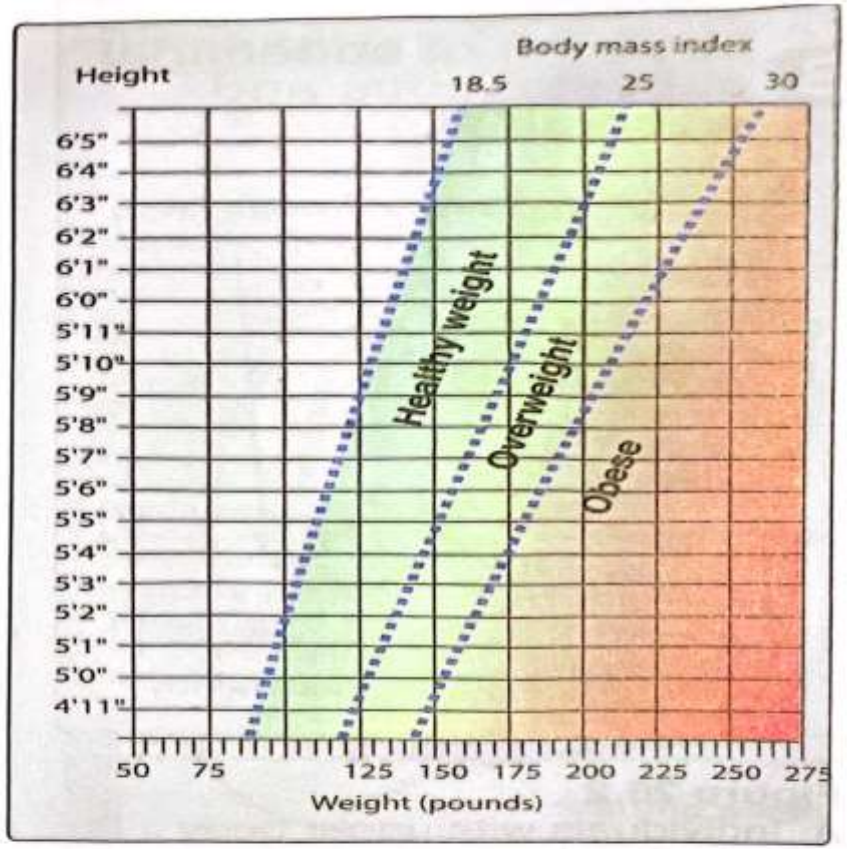


Figure 26.1
Body mass index (BMI) Chart. To use the BMI Chart, find height in the left-hand column. Move across the row to weight. Height and weight intersect at the individual's BMI. [Note: To calculate BMI using inches and pounds, use BMI = [weight in pounds/(height in inches)^2] × 703.

- **The complement in this slide:** This chart correlates weight with height.
  - BMI=18.5-25 : healthy weight
  - BMI=25-30 : overweight
  - BMI>30 : obese



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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.

NOTE: Obesity depends on the accumulation of lipids, which could be in the upper region or lower region. Accumulation in upper region poses a higher risk of obesity-related diseases than in the lower region. Lipids could be subcutaneous, and visceral, with abdominal lipids being the most dangerous, because when lipolysis occurs, they will go directly to the liver.

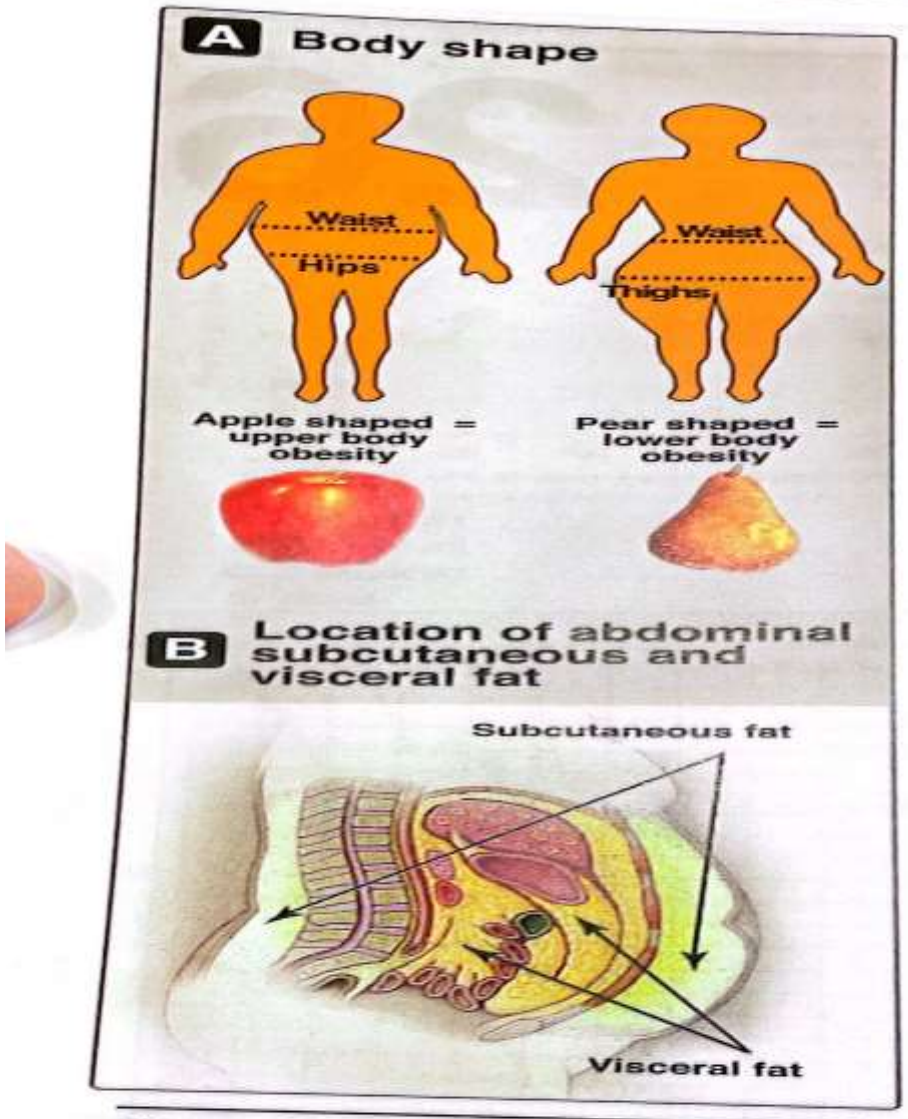


Figure 26.2
A. Individuals with upper body obesity (left) have greater health risks than individuals with lower body obesity (right). B. Visceral fat is located inside the abdominal cavity, packed in between the internal organs. Subcutaneous fat is found underneath the skin.

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 (important)

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

- 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.

NOTE: Note the difference between weight gain and loss.

Weight gain: increase in number and size of adipocytes

Weight loss: decrease only in size

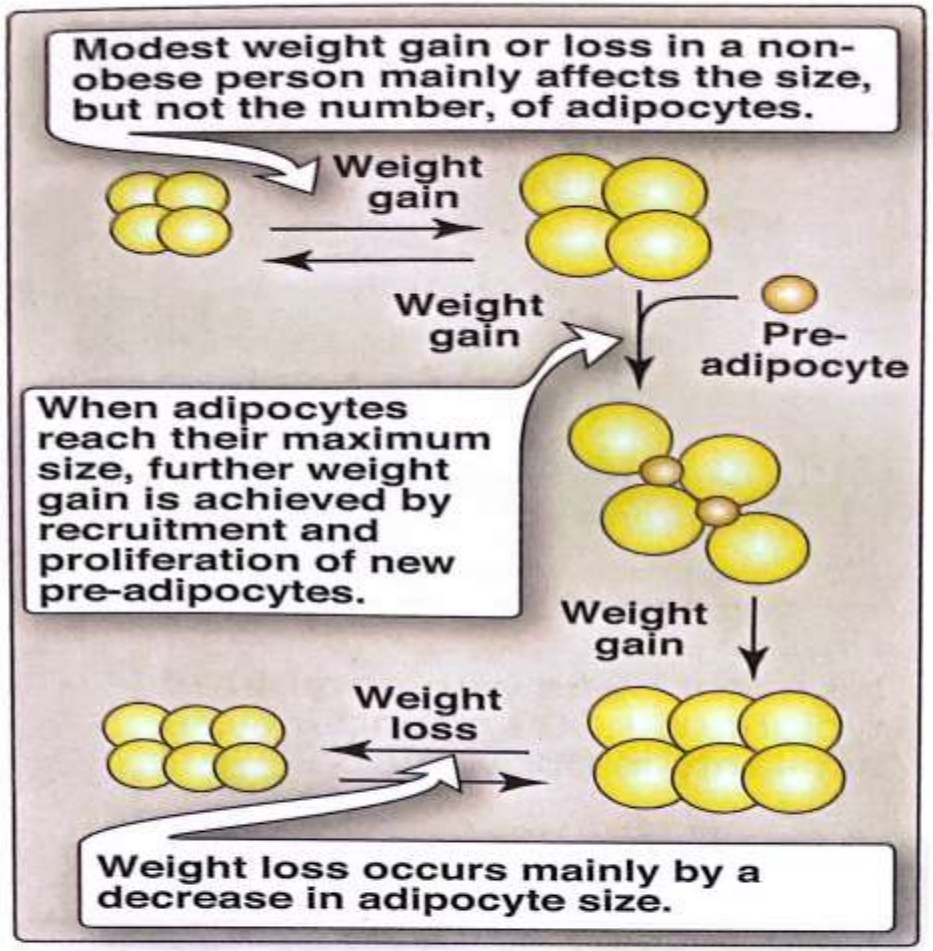


Figure 26.3
Hypertrophic (increased size) and hyperplastic (increased number) changes to adipocytes are thought to occur in severe obesity.

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.

NOTE: **Genetics could contribute to obesity, but also the lifestyle. For example, adoptive children could have similar BMI due to the similarities in lifestyle.**

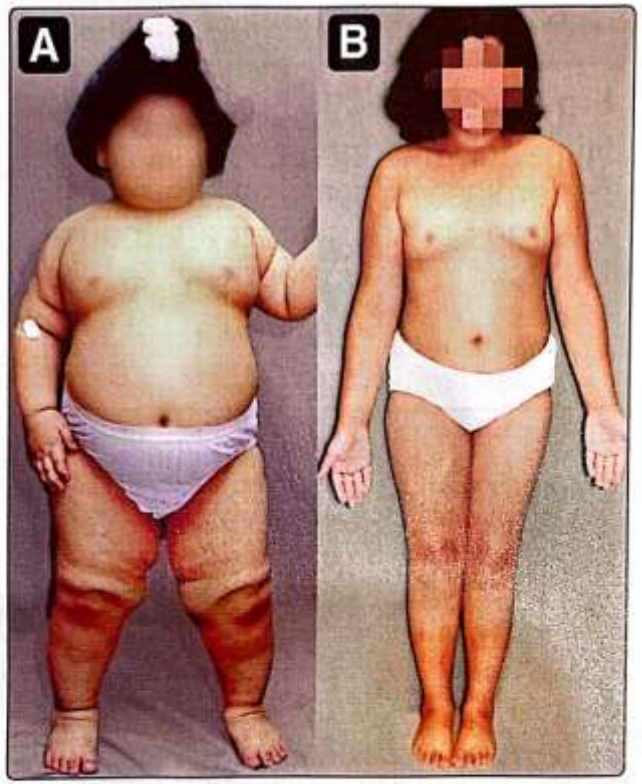
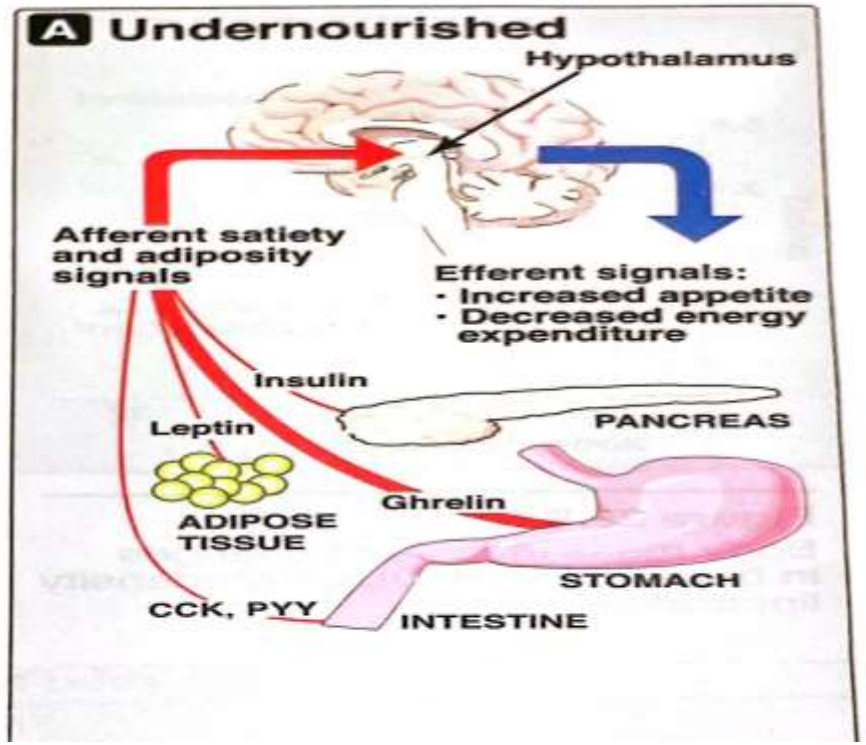


Figure 26.6
A. Patient with leptin deficiency before initiation of therapy at age 5 years. B. Patient at age 9 years after 48 months of therapy with subcutaneous injection of recombinant leptin.

Figure 26.5
Identical twins with combined weight of 1,300 pounds. Note similarity in body shape.

- **NOTE:** In undernourished individuals, secretion of leptin leads to control centers in the brain, and the brain will send signals to **increase the appetite and to decrease energy expenditure.**

- **NOTE:** In overnourished individuals, the number of adipocytes is large, so there will be higher amounts of leptin sending signals to the brain, and the brain will send signals to **decrease appetite and increase energy expenditure.** In obese people, leptin might not work efficiently.



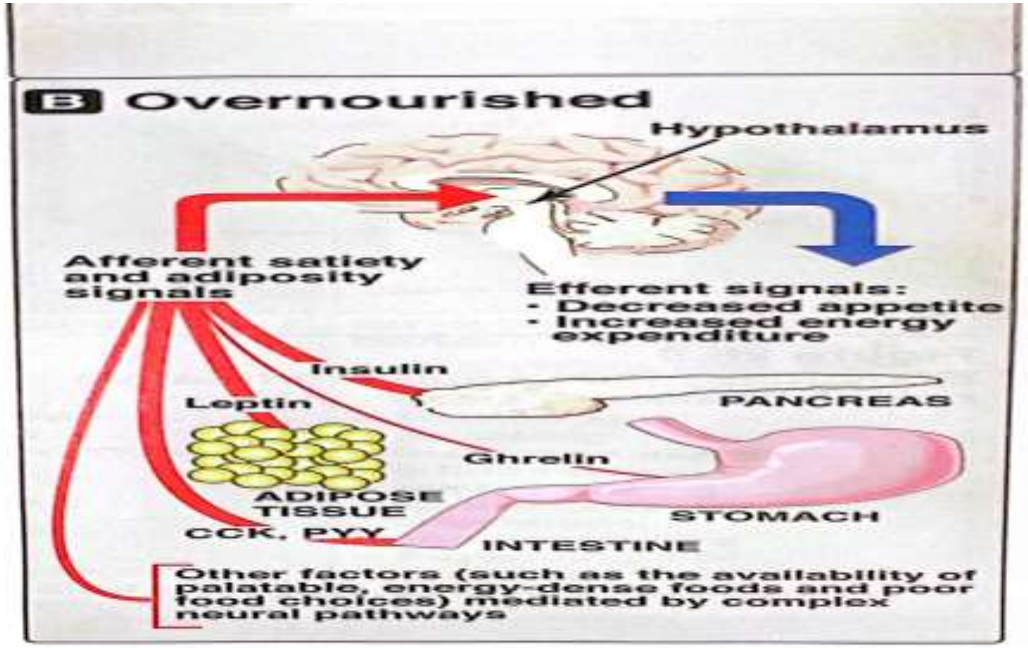
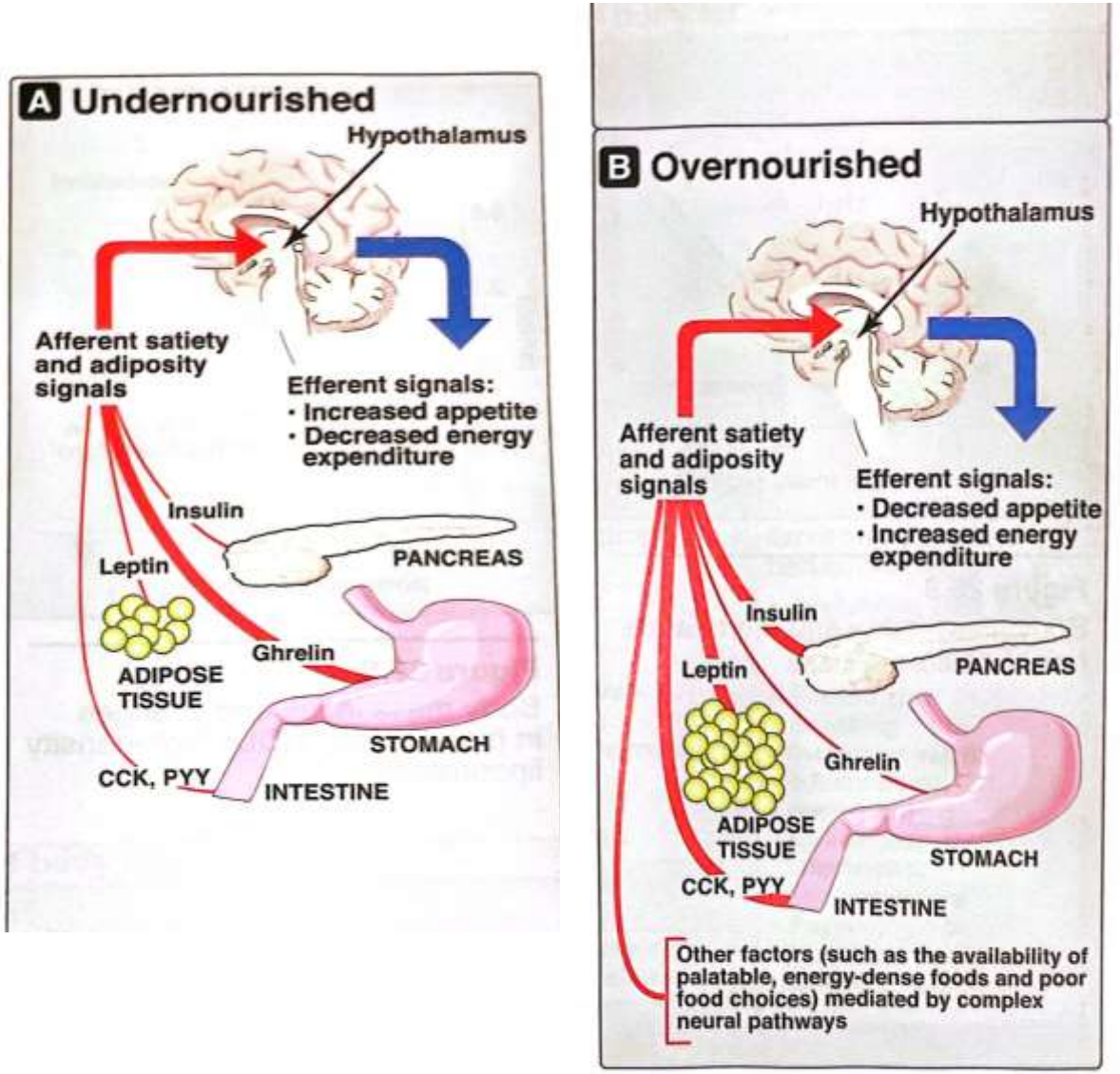


Figure 26.7
Some signals that influence appetite and satiety. CCK = cholecystokinin, PYY = peptide YY.

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



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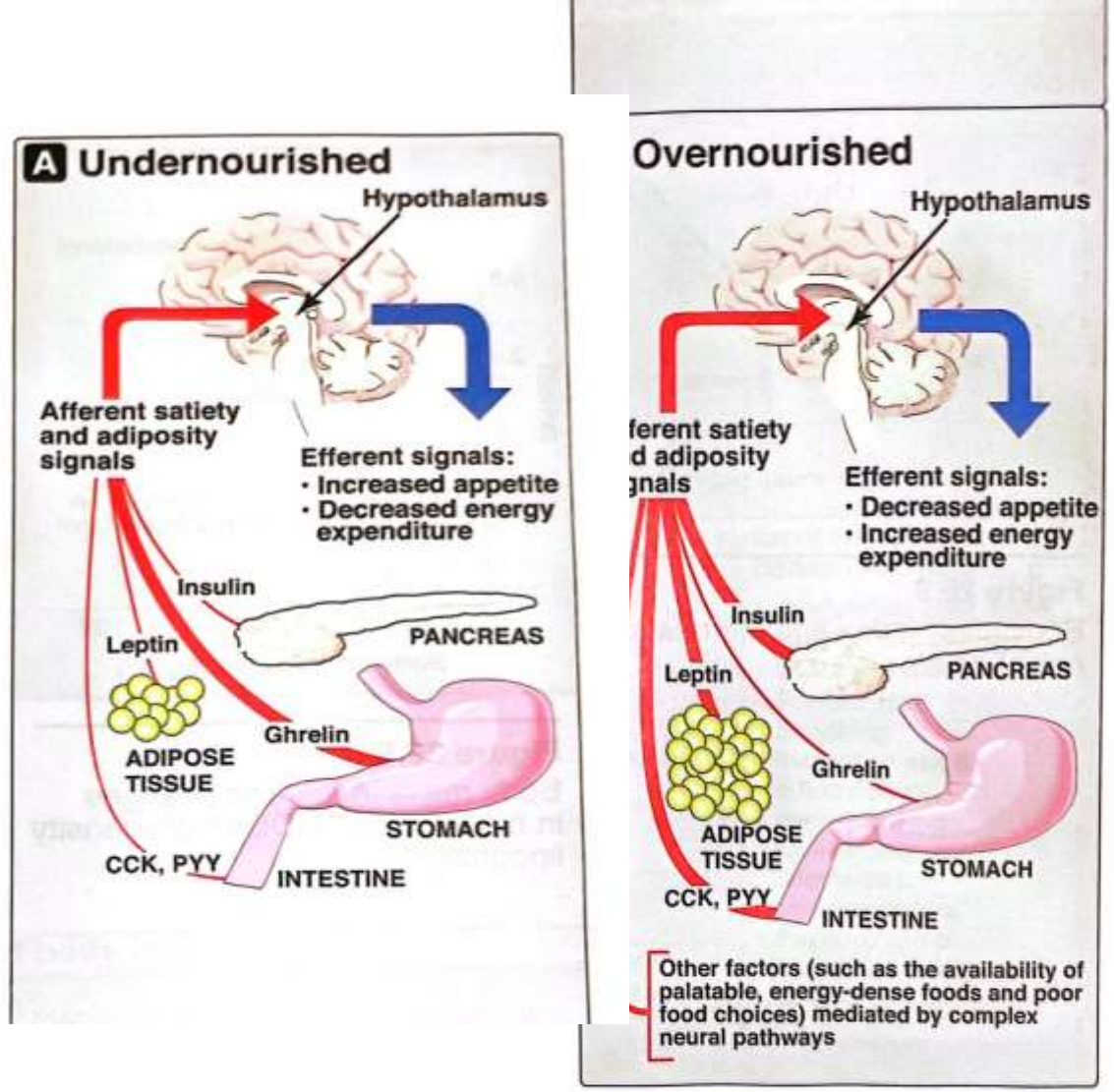
Some signals that influence appetite and satiety. CCK = cholecystokinin, PYY = peptide YY.

- B. Short-term signals: from GI control hunger and satiety
- In the absence of food intake ghrelin(apetite stimulant) drives hunger.

NOTE: There is another hormone, called **ghrelin**, and it is a signal for hunger in undernourished individuals, as its concentration will be increased, and it will also send signals to the brain to increase appetite and decrease energy expenditure. The opposite happens in overnourished people.



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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**

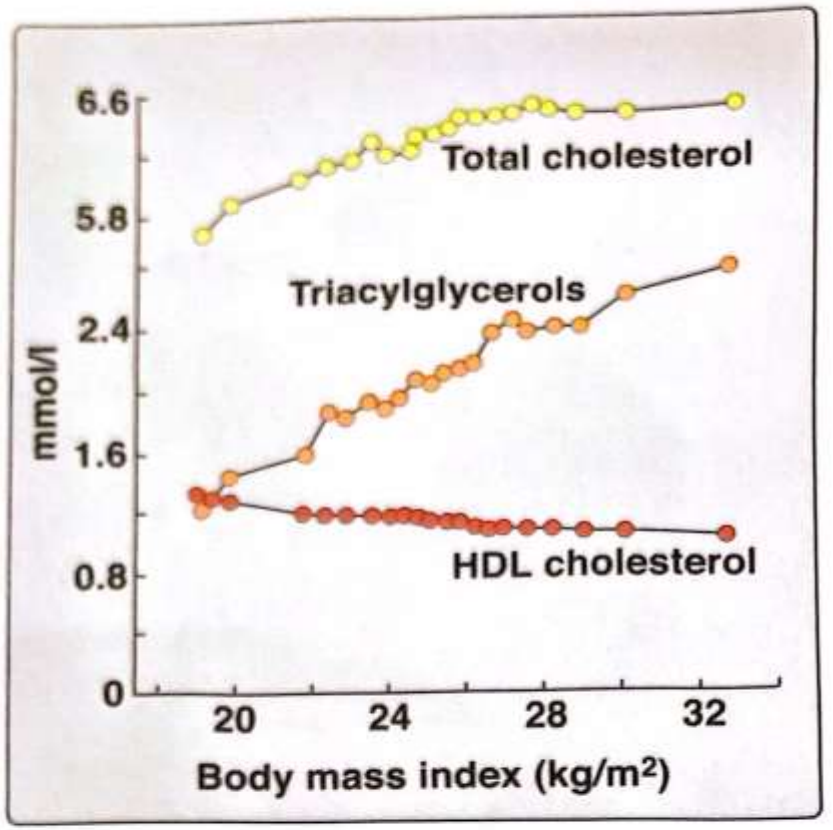

Figure 26.8
Body mass index and changes in blood lipids. HDL= high-density lipoprotein.

اللهم اني استودعتك ما قرأت وما حفظت وما تعلمت فرده عند حاجتي اليه انك على كل شيء قدير

"اللهمَّ ارفع البلاء والأذى عن أمّة محمّدٍ -صلّى الله عليه وسلّم-، اللهمَّ ارحم واستر وتولَّ أمّة نبيّك محمّدٍ واحفظها، واكفها ما أهمّها وما أغمّها، اللهمَّ الطف بها واغفر لها وأكرمها ولا تهنها وأعنها ولا تُعن عليها يا أرحم الراحمين".