PANCREATIC HORMONES AND DIABETES MELLITUS

Introduction

The pancreas comprises two functionally distinct organs: the **exocrine pancreas,** the major digestive gland of the body; and the **endocrine pancreas,** the source of insulin, glucagon, somatostatin, and pancreatic polypeptide (PP). Whereas the major role of the products of the exocrine pancreas (the digestive enzymes) is the processing of ingested foodstuffs so that they become available for absorption, the hormones of the endocrine pancreas modulate every other aspect of cellular nutrition from rate of adsorption of foodstuffs to cellular storage or metabolism of nutrients. Dysfunction of the endocrine pancreas or abnormal responses to its hormones by target tissues result in serious disturbances in nutrient homeostasis, including the important clinical syndromes grouped under the name of **diabetes mellitus.**

Anatomy & Histology

The endocrine pancreas consists of approximately 1 million small endocrine glands—the islets of Langerhans—scattered throughout the glandular substance of the exocrine pancreas. The islet volume comprises 1–1.5% of the total mass of the pancreas and weighs about 1–2 g in adult humans. At least four cell types—A, B, D, and PP (also called α, β, δ, and F)—have been identified in the islets (Table 18–1). These cell types are not distributed uniformly throughout the pancreas. The PP cell, which secretes PP, has been found primarily in islets in the posterior portion.

Table 18–1. Cell Types in Pancreatic Islets of Langerhans.

	Approximate Percentage of Islet Volume		
Cell Types	**Dorsally Derived (Anterior Head, Body, Tail)**	**Ventrally Derived (Posterior Portion of Head)**	**Secretory Products**
A cell (α)	10%	< 0.5%	Glucagon, proglucagon, glucagon-like peptides (GLP-1 and GLP-2)
B cell (β)	70–80%	15–20%	Insulin, C peptide, proinsulin, amylin, γ-aminobutyric acid (GABA)
D cell (δ)	3–5%	< 1%	Somatostatin
PP cell (F cell)	< 2%	80–85%	Pancreatic polypeptide

Islets in the posterior lobe area consist of 80–85% PP cells, 15–20% β cells, and less than 0.5% glucagon-producing α cells. The PP cell volume varies with age and sex—the volume tends to be larger in men and in older persons. In contrast to the posterior lobe, the PP-poor islets located in the tail, body, and anterior portion of the head of the pancreas, arising from the embryonic dorsal

bud, contain predominantly insulin-secreting β cells (70–80% of the islet cells), with approximately 20% of the cells being glucagon-secreting α cells and about 3–5% δ cells that produce somatostatin.

Islet Vascularization

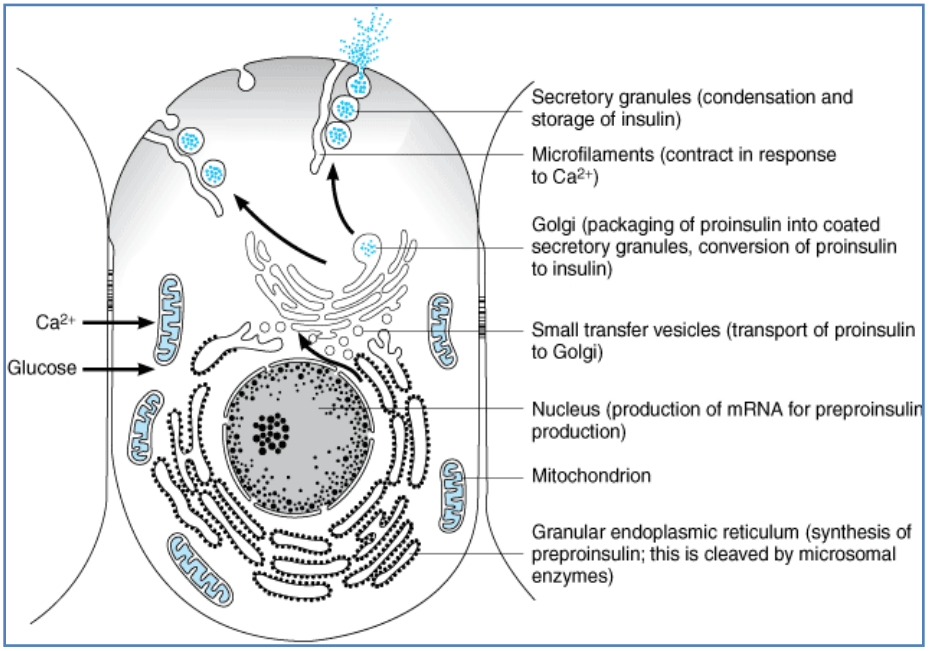
The islets are richly vascularized, receiving five to ten times the blood flow of a comparable portion of exocrine pancreatic tissues. The direction of the blood flow within the islet has been postulated to play a role in carrying insulin secreted from the central region of an islet to its peripheral zone—where the insulin modulates and decreases glucagon release from α cells, which are mainly located in the periphery of islets.

Hormones of the Endocrine Pancreas

Insulin

Biosynthesis

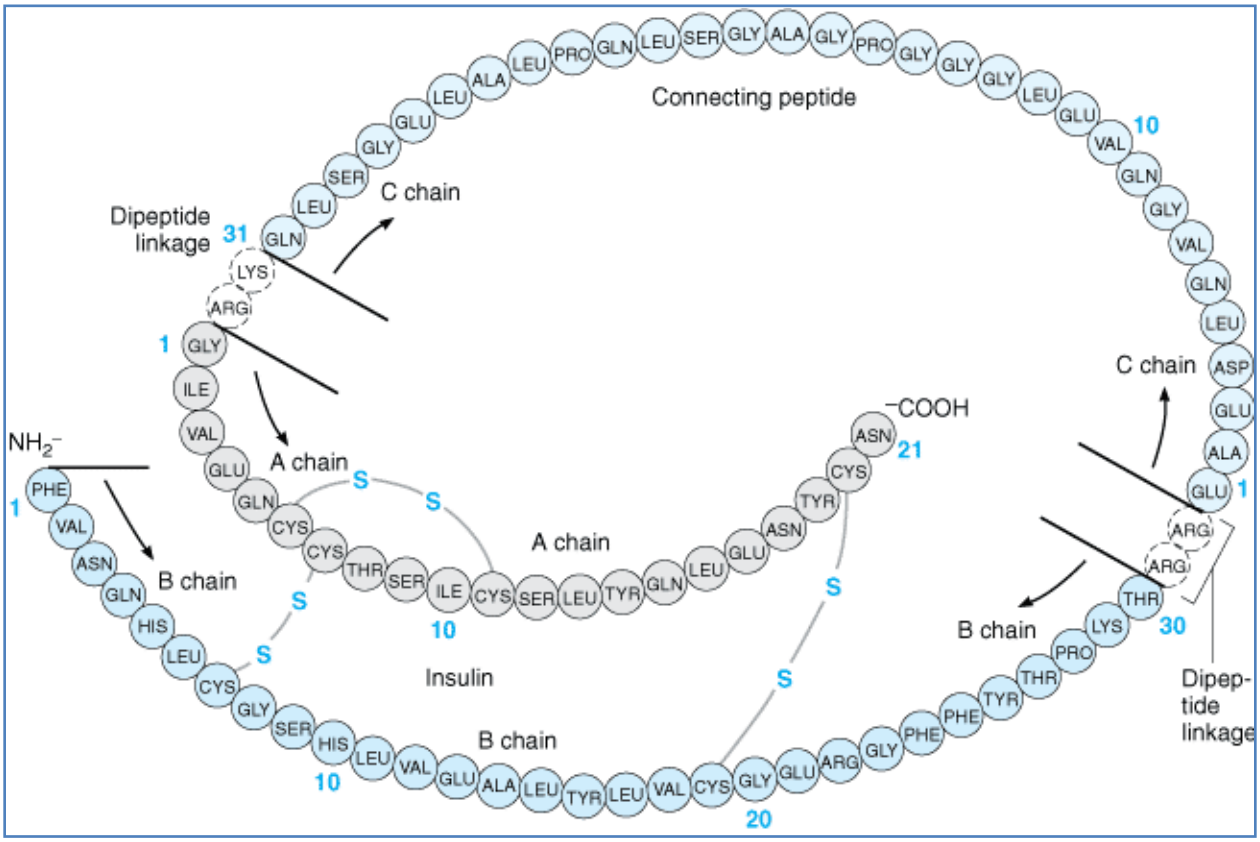
Figure 18-2. Photomicrograph of a section of the pancreas. In the islet of Langerhans, A cells appear mainly in the periphery as large cells with dark cytoplasm. Some D cells are also present in the periphery, whereas the central core is composed chiefly of B cells.



The human insulin gene is located on the short arm of chromosome 11. A precursor molecule, **preproinsulin,** a peptide of MW 11,500, is translated from the preproinsulin messenger RNA in the rough endoplasmic reticulum of pancreatic β cells (Figure 18–2). Microsomal enzymes cleave preproinsulin to **proinsulin** (MW ~ 9000) immediately after synthesis. Proinsulin (Figure 18–2) is transported to the Golgi apparatus, where packaging into clathrin-coated secretory granules takes place. Maturation of the secretory granule is associated with loss of the clathrin coating and conversion of proinsulin into **insulin** and a smaller connecting peptide, or **C peptide,** by proteolytic cleavage at two sites along the peptide chain. Normal mature (uncoated) secretory granules contain insulin and C peptide in equimolar amounts and only small quantities of proinsulin, a small portion of which consists of partially cleaved intermediates.

Proinsulin (Figure 18–3) consists of a single chain of 86 amino acids, which includes the A and B chains of the insulin molecule plus a connecting segment of 35 amino acids. Two prohormone-converting enzymes are packaged with proinsulin in the immature secretory granules. These enzymes recognize and cut at pairs of basic amino acids, thereby removing the intervening sequence. After the two pairs of basic amino acids are removed by carboxypeptidase E, the result is a 51-amino-acid insulin molecule and a 31-amino-acid residue, the C peptide, as shown in Figure 18–3.

Figure 18-3. Structure of human proinsulin C peptides and insulin molecules connected at two sites by dipeptide links.



A small amount of proinsulin produced by the pancreas escapes cleavage and is secreted intact into the bloodstream, along with insulin and C peptide. Most anti-insulin sera used in the standard immunoassay for insulin cross-react with proinsulin; about 3–5% of immunoreactive insulin extracted from human pancreas is actually proinsulin. Because proinsulin is not removed by the liver, it has a half-life three to four times that of insulin. Its long half-life allows proinsulin to accumulate in the blood, where it accounts for 12–20% of the circulating immunoreactive "insulin" in the basal state in humans. Human proinsulin has about 7–8% of the biologic activity of insulin. The kidney is the principal site of proinsulin degradation.

C peptide, the 31-amino-acid residue (MW 3000) formed during cleavage of insulin from proinsulin, has no known biologic activity. It is released from the β cells in equimolar amounts

with insulin. It is not removed by the liver but is degraded or excreted chiefly by the kidney. It has a half-life three to four times that of insulin.

Insulin is a protein consisting of 51 amino acids contained within two peptide chains: an A chain, with 21 amino acids; and a B chain, with 30 amino acids. The chains are connected by two disulfide bridges as shown in Figure 18–3. In addition, there is an intrachain disulfide bridge that links positions 6 and 11 in the A chain. The molecular weight of human insulin is 5808.

Endogenous insulin has a circulatory half-life of 3–5 minutes. It is catabolized chiefly by insulinases in liver, kidney, and placenta. Approximately 50% of insulin is removed in a single pass through the liver.

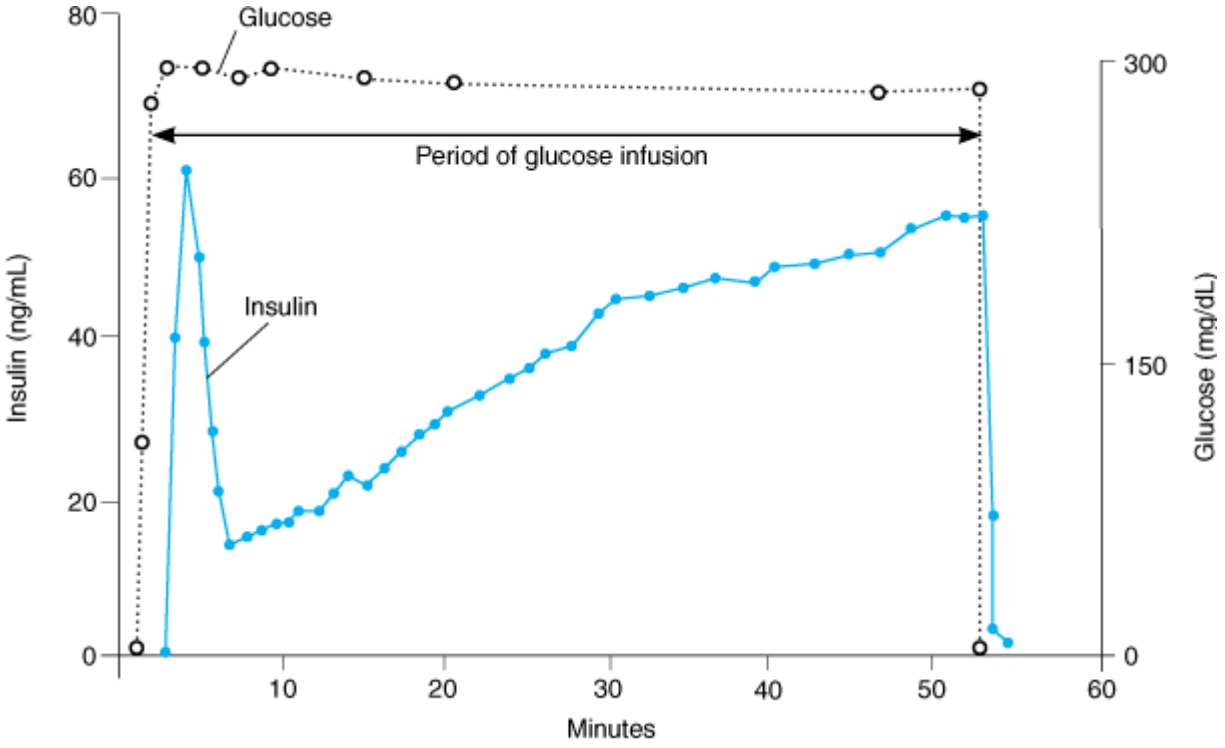
Secretion

The human pancreas secretes about 30 units of insulin per day in normal adults. The basal concentration of insulin in the blood of fasting humans averages 10 μU/mL (0.4 ng/mL, or 61 pmol/L). In normal control subjects, insulin seldom rises above 100 μU/mL (610 pmol/L) after standard meals. There is an increase in peripheral insulin concentration beginning 8–10 minutes after ingestion of food and reaching peak concentrations in peripheral blood by 30–45 minutes. This is followed by a rapid decline in postprandial plasma glucose concentration, which returns to baseline values by 90–120 minutes.

Basal insulin secretion, which occurs in the absence of exogenous stimuli, is the quantity of insulin secreted in the fasting state. Although it is known that plasma glucose levels below 80–100 mg/dL (4.4–5.6 mmol/L) do not stimulate insulin release, it has also been demonstrated that the presence of glucose is necessary (in in vitro systems) for most other known regulators of insulin secretion to be effective.

Stimulated insulin secretion is that which occurs in response to exogenous stimuli. In vivo, this is the response of the β cell to ingested meals. Glucose is the most potent stimulant of insulin release. The perfused rat pancreas has demonstrated a biphasic release of insulin in response to glucose (Figure 18–4). When the glucose concentration in the system is increased suddenly, an initial short-lived burst of insulin release occurs (the **first phase**); if the glucose concentration is held at this level, the insulin release gradually falls off and then begins to rise again to a steady level (the **second phase**). However, sustained levels of high glucose stimulation (~ 4 hours in vitro or > 24 hours in vivo) result in a reversible desensitization of the β cell response to glucose but not to other stimuli.

Figure 18-4. Multiphasic response of the in vitro perfused pancreas during constant stimulation with glucose.

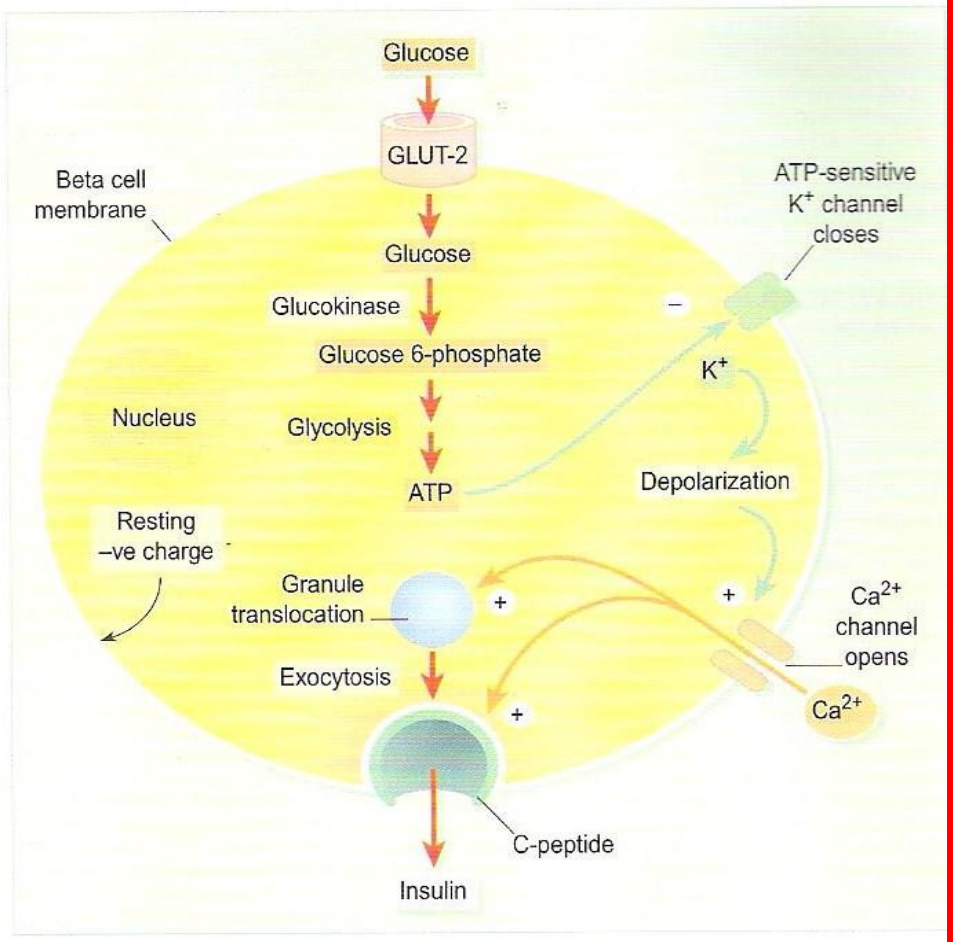


Glucose is known to enter the pancreatic β cell by passive diffusion, which is facilitated by a specific membrane proteins termed glucose transporters. Because the transporters function in both directions and the β cell has an excess of glucose transporters, the glucose concentration inside the β cell is in equilibrium with the extracellular glucose concentration. A body of data suggests that *metabolism* of glucose is essential in stimulating insulin release. Indeed, agents such as 2-deoxyglucose that inhibit the metabolism of glucose interfere with release of insulin. The rate-limiting step in glucose metabolism by the pancreatic β cell is the phosphorylation of glucose by the low-affinity enzyme glucokinase. The catabolism of glucose in the β cell results in a rise in the intracellular ATP/ADP ratio. This rise causes the ATP-sensitive potassium channels on the surface of the β cell to close, thereby depolarizing the cell and activating the voltage-sensitive calcium channel.

Insulin release has been shown to require calcium. The following effects of glucose on calcium ion movement have been demonstrated: (1) calcium uptake is increased by glucose stimulation of the β cell, (2) calcium efflux from the cell is retarded by some action of glucose, and (3) mobilization of calcium from intracellular compartments occurs secondary to cyclic adenosine monophosphate (cAMP) induction by glucose.

cAMP is another important modulator of insulin release. As mentioned above, glucose directly induces cAMP formation. Furthermore, many nonglucose stimuli of insulin release increase

intracellular cAMP. Elevations of cAMP alone, however, do not stimulate insulin release in the absence of glucose.



Insulin synthesis is coupled to its secretion. GLUT is a glucose transporter.

Other factors involved in the regulation of insulin secretion are summarized in Table 18–2. These factors can be divided into three categories: **direct stimulants,** which are known to stimulate insulin release directly; **amplifiers,** which appear to potentiate the response of the β cell to glucose; and **inhibitors.** The action of the amplifier substances, many of which are gastrointestinal hormones released in response to the ingestion of meals, explains the observation that the insulin secretory response to an ingested meal is greater than the response to intravenously administered substrates.

Table 18–2. Regulation of Insulin Release in Humans.

Stimulants of insulin release
Glucose, mannose
Leucine
Vagal stimulation
Sulfonylureas
Amplifiers of glucose-induced insulin release
1. Enteric hormones:
Glucagon-like peptide I (7–37)
Gastric inhibitory peptide
Cholecystokinin
Secretin, gastrin
2. Neural amplifiers: beta-adrenergic stimulation
3. Amino acids: arginine
Inhibitors of insulin release
Neural: alpha-adrenergic effect of catecholamines
Humoral: somatostatin
Drugs: diazoxide, phenytoin, vinblastine, colchicine

Insulin Receptors & Insulin Action

Insulin action begins with the binding of insulin to a receptor on the surface of the target cell membrane. Most cells of the body have specific cell surface insulin receptors. In fat, liver, and muscle cells, binding of insulin to these receptors is associated with the biologic response of these tissues to the hormone. These receptors bind insulin rapidly, with high specificity and with an affinity high enough to bind picomolar amounts.

Insulin receptors, members of the growth factor receptor family, are membrane glycoproteins composed of two protein subunits encoded by a single gene. The larger alpha subunit (MW 135,000) resides entirely extracellularly, where it binds the insulin molecule. The alpha subunit is tethered by disulfide linkage to the smaller beta subunit (MW 95,000). The beta subunit crosses the membrane, and its cytoplasmic domain contains a ***tyrosine kinase*** activity that initiates specific intracellular signaling pathways.

On binding of insulin to the alpha subunit, the beta subunit activates itself by ***autophosphorylation***. The activated beta subunit then recruits additional proteins to the complex and phosphorylates a network of intracellular substrates, including insulin receptor substrate-1 (IRS-1), insulin receptor substrate-2 (IRS-2), and others (Figure 18–5). These activated substrates each lead to subsequent recruitment and activation of additional kinases, phosphatases, and other signaling molecules in a complex pathway that generally contains two arms: the ***mitogenic*** pathway, which mediates the growth effects of insulin; and the ***metabolic*** pathway, which regulates nutrient metabolism.

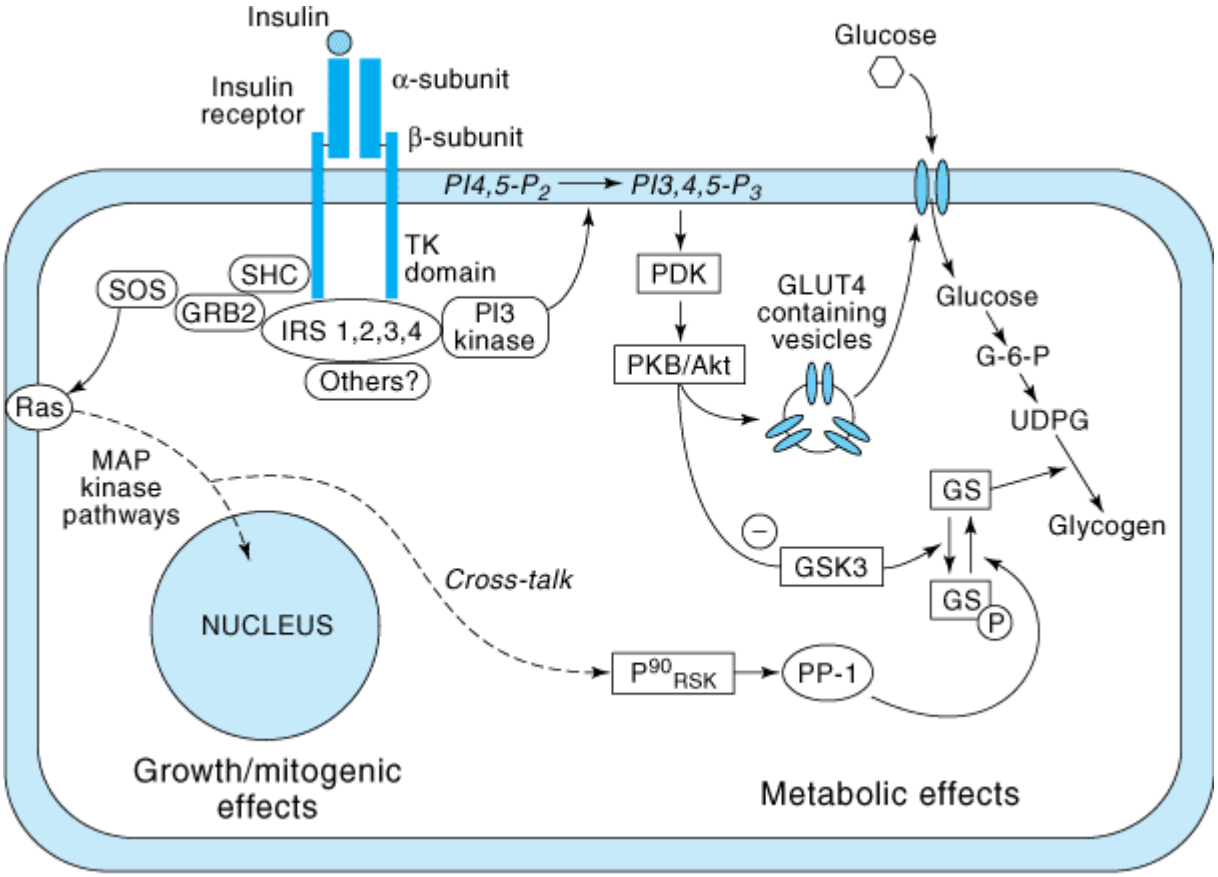


Figure 18-5. A simplified outline of insulin signaling. A minimal diagram of the mitogenic and metabolic arms of the insulin signaling pathway is shown (GLUT 4, glucose transporter 4; Grb-2, growth factor receptor binding protein 2; GS, glycogen synthase [P indicates the inactive phosphorylated form]; GSK-3, glycogen synthase kinase 3; IRS, insulin receptor substrate [four different proteins]; MAP kinase, mitogen-activated protein kinase; PDK, phospholipid-dependent kinase; PI3 kinase, phosphatidylinositol 3 kinase; PKB, protein kinase B; PP-1, glycogen-associated protein phosphatase-1; Ras, rat sarcoma protein; SHC, Src and collagen homology protein; SOS, son-of-sevenless related protein; TK, tyrosine kinase).

In the metabolic signaling pathway, activation of phosphatidylinositol-3-kinase leads to the movement of glucose transporter (GLUT) 4-containing vesicles to the cell membrane, increased glycogen and lipid synthesis, and stimulation of other metabolic pathways. After insulin is bound to its receptor, a number of insulin-receptor complexes are internalized. However, it remains controversial whether these internalized complexes contribute to further action of insulin or whether they limit continued insulin action by exposing insulin to intracellular scavenger lysosomes.

Abnormalities of insulin receptors—in concentration, affinity, or both—affect insulin action. **"Down-regulation"** is a phenomenon in which the number of insulin receptors is decreased in response to chronically elevated circulating insulin levels, probably by increased intracellular

degradation. When insulin levels are low, on the other hand, receptor binding is up-regulated. Conditions associated with high insulin levels and lowered insulin binding to the receptor include obesity, high intake of carbohydrates, and chronic exogenous overinsulinization. Conditions associated with low insulin levels and increased insulin binding include exercise and fasting. The presence of excess amounts of cortisol decreases insulin binding to the receptor, although it is not clear if this is a direct effect of the hormone itself or one that is mediated through accompanying increases in the insulin level.

The insulin receptor itself is probably not the major determinant of insulin sensitivity under most circumstances, however. Clinically relevant insulin resistance most commonly results from defects in postreceptor intracellular signaling pathways.

Metabolic Effects of Insulin

The major function of insulin is to promote **storage of ingested nutrients.** Although insulin directly or indirectly affects the function of almost every tissue in the body, the discussion here will be limited to a brief overview of the effects of insulin on the three major tissues specialized for energy storage: liver, muscle, and adipose tissue. In addition, the **paracrine effects** of insulin will be discussed briefly. The section on hormonal control of nutrient metabolism (see below) presents a detailed discussion of the effects of insulin and glucagon on the regulation of intermediary metabolism.

Paracrine Effects

The effects of the products of endocrine cells on surrounding cells are termed "paracrine" effects, in contrast to actions that take place at sites distant from the secreting cells, which are termed "endocrine" effects. Paracrine effects of the β and δ cells on the close-lying α cells (Figure 18–1) are of considerable importance in the endocrine pancreas. The first target cells reached by insulin are the pancreatic α cells at the periphery of the pancreatic islets. In the presence of insulin, α cell secretion of glucagon is reduced. In addition, somatostatin, which is released from δ cells in response to most of the same stimuli that provoke insulin release, also acts to inhibit glucagon secretion.

Because glucose stimulates only β and δ cells (whose products then inhibit α cells) whereas amino acids stimulate glucagon as well as insulin, the type and amounts of islet hormones released during a meal depend on the ratio of ingested carbohydrate to protein. The higher the carbohydrate content of a meal, the lower the amount of glucagon released by any amino acids absorbed. In contrast, a predominantly protein meal results in relatively greater glucagon secretion, because amino acids are less effective at stimulating insulin release in the absence of concurrent hyperglycemia but are potent stimulators of α cells.

Endocrine Effects

See Table 18-3.

Table 18–3. Endocrine Effects of Insulin.
Effect on liver:
Reversal of catabolic features of insulin deficiency
Inhibits glycogenolysis
Inhibits conversion of fatty acids and amino acids to keto acids
Inhibits conversion of amino acids to glucose
Anabolic action
Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
Increases triglyceride synthesis and very low density lipoprotein formation
Effect on muscle:
Increased protein synthesis
Increases amino acid transport
Increases ribosomal protein synthesis
Increased glycogen synthesis
Increases glucose transport
Induces glycogen synthetase and inhibits phosphorylase
Effect on adipose tissue:
Increased triglyceride storage
Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
Intracellular lipase is inhibited by insulin

Liver

The first major organ reached by insulin via the bloodstream is the liver. Insulin exerts its action on the liver in two major ways:

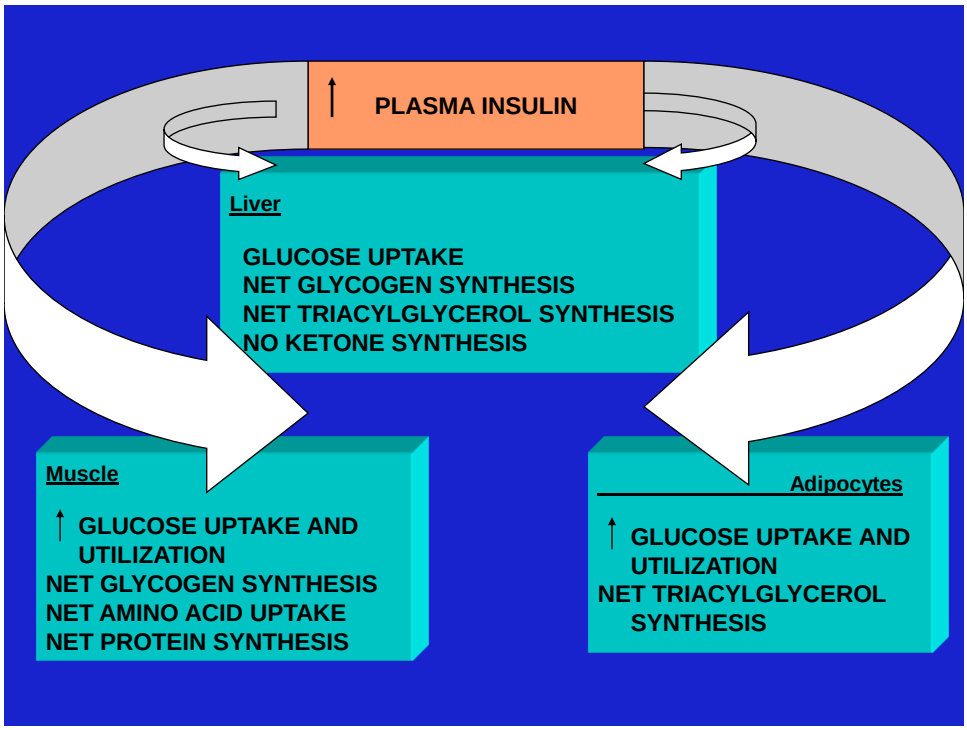
Insulin Promotes Anabolism

Insulin promotes glycogen synthesis and storage while inhibiting glycogen breakdown. These effects are mediated by changes in the activity of enzymes in the glycogen synthesis pathway. The liver has a maximum storage capacity of 100–110 g of glycogen, or approximately 440 kcal of energy.

Insulin increases both protein and triglyceride synthesis and very low density lipoprotein (VLDL) formation by the liver. It also inhibits gluconeogenesis and promotes glycolysis through its effects on enzymes of the glycolytic pathway.

Insulin Inhibits Catabolism

Insulin acts to reverse the catabolic events of the postabsorptive state by inhibiting hepatic glycogenolysis, ketogenesis, and gluconeogenesis.



Muscle

Insulin promotes protein synthesis in muscle by increasing amino acid transport as well as by stimulating ribosomal protein synthesis. In addition, insulin promotes glycogen synthesis to replace glycogen stores expended by muscle activity. This is accomplished by increasing glucose transport into the muscle cell, enhancing the activity of glycogen synthase, and inhibiting the activity of glycogen phosphorylase. Approximately 500–600 g of glycogen are stored in the muscle tissue of a 70-kg man, but because of the lack of glucose 6-phosphatase in this tissue, it cannot be used as a source of blood glucose, except for a small amount produced when the debranching enzyme releases unphosphorylated glucose from branch points in the glycogen polymer, and the glucose indirectly produced by the liver from lactate generated by muscle.

Adipose Tissue

Fat, in the form of triglyceride, is the most efficient means of storing energy. It provides 9 kcal per gram of stored substrate, as opposed to the 4 kcal/g generally provided by protein or carbohydrate. In the typical 70-kg man, the energy content of adipose tissue is about 100,000 kcal.

Insulin acts to promote triglyceride storage in adipocytes by a number of mechanisms: (1) It induces the production of lipoprotein lipase in adipose tissue (this is the lipoprotein lipase that is bound to endothelial cells in adipose tissue and other vascular beds), which leads to hydrolysis of triglycerides from circulating lipoproteins, thereby yielding fatty acids for uptake by adipocytes. (2) By increasing glucose transport into fat cells, insulin increases the availability of α-glycerol phosphate, a substance used in the esterification of free fatty acids into triglycerides. (3) Insulin inhibits intracellular lipolysis of stored triglyceride by inhibiting intracellular lipase (also called

"hormone-sensitive lipase"). This reduction of fatty acid flux to the liver appears to be a key regulatory factor in the action of insulin to lower hepatic gluconeogenesis and ketogenesis.

Glucose Transporter (GLUT) Proteins

Glucose oxidation is a major source of energy for many cells and is critical for brain function. Because cell membranes are impermeable to hydrophilic molecules such as glucose, all cells require carrier proteins to transport glucose across the lipid bilayers into the cytosol. Whereas the intestine and kidney have an energy dependent Na^+-glucose cotransporter, all other cells have non-energy-dependent transporters that facilitate diffusion of glucose from a higher concentration to a lower concentration across cell membranes. Facilitative glucose transporters comprise a large family including at least 13 members, although some of the recently identified members of the family have not yet been shown to transport glucose. The first four members of the family are the ones that have been best-characterized, and they have distinct affinities for glucose and distinct patterns of expression.

GLUT 1 is present in all human tissues. It appears to mediate basal glucose uptake, because it has a very high affinity for glucose and therefore is able to transport glucose at relatively low concentrations as found in the basal state. For this reason, it is an important component of the brain vascular system (blood-brain barrier) to ensure adequate transport of plasma glucose into the central nervous system.

GLUT 3, which is also found in all tissues, is the major glucose transporter on the neuronal surface. It also has a very high affinity for glucose and is responsible for transferring glucose into neuronal cells.

In contrast, GLUT 2 has a very low affinity for glucose and seems to act as a transporter only when plasma glucose levels are relatively high, such as postprandially. It is a major transporter of glucose in hepatic, intestinal, and renal tubular cells, so that diffusion of glucose across these cells increases as glucose levels rise. The low affinity of GLUT 2 for glucose reduces hepatic uptake of glucose during the basal state or during fasting. GLUT 2 is also expressed on the surface of the β cells in rodents, but it is not detected at significant levels on human β cells.

GLUT 4 is found in two major insulin target tissues: skeletal muscle and adipose tissue. It appears to be sequestered mainly within an intracellular compartment of these cells and thus is not able to function as a glucose transporter until a signal from insulin results in translocation of GLUT 4 to the cell membrane, where it facilitates glucose entry into these storage tissues after a meal.

Glucagon

Biochemistry

Pancreatic glucagon, along with several other biologically active peptides, is derived from the large proglucagon peptide encoded by the preproglucagon gene located on human chromosome 2. Tissue-specific proteases (the prohormone convertases) cleave a different set of peptide products from the proglucagon molecule in the endocrine L-cells of the gut and the α cells in the islet (Figure 18–6). The activity of prohormone convertase 2 in α cells generates the glucagon peptide, along with the amino-terminal glicentin-related peptide, a small central hexapeptide and a large carboxyl-terminal fragment.

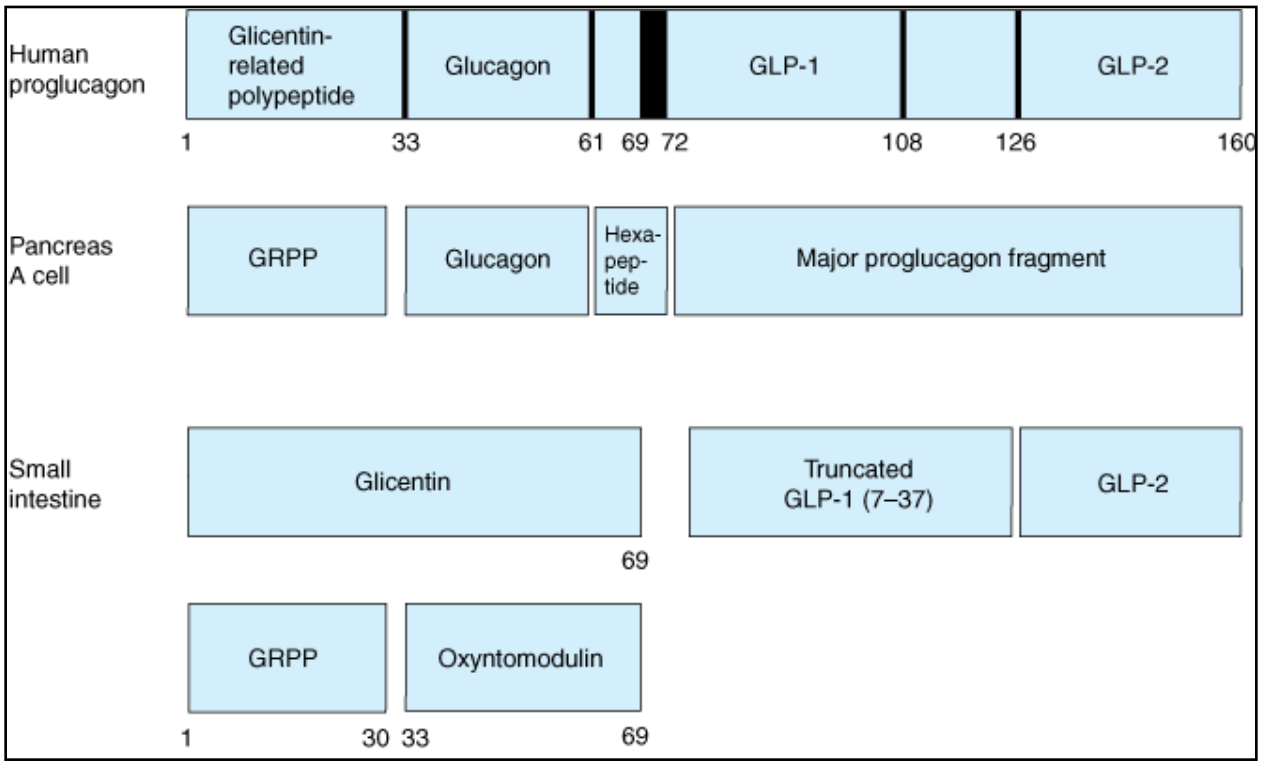


Figure 18-6. Tissue-specific secretory products of human proglucagon (GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; GRPP, glicentin-related polypeptide).

Glucagon is a single-chain polypeptide consisting of 29 amino acids with a molecular weight of 3485. In healthy humans, the average fasting plasma immunoreactive glucagon level is 75 pg/mL (25 pmol/L). Only 30–40% of this is actually pancreatic glucagon, the remainder being a heterogeneous composite of higher-molecular-weight molecules with glucagon immunoreactivity such as proglucagon, glicentin, and oxyntomodulin. The circulation half-life of glucagon is 3–6 minutes. Glucagon is mainly removed by the liver and kidney.

Secretion

Glucagon secretion is inhibited by glucose—in contrast to the effect of glucose on insulin secretion. There are conflicting data about whether the effect of glucose is a direct one on the α cell or whether it is mediated via release of insulin or somatostatin, both of which are known to inhibit the α cell directly. In addition, because gamma-aminobutyric acid (GABA) is released by β cells and its receptors have recently been detected on α cells, GABA may participate in the inhibition of α cells during β cell stimulation.

Many amino acids stimulate glucagon release, although there are differences in their ability to do so. Some, such as arginine, release both glucagon and insulin; others (e.g., alanine) stimulate primarily glucagon release. Leucine, a good stimulant for insulin release, does not stimulate glucagon. Other substances that promote glucagon release are catecholamines, the gastrointestinal hormones (cholecystokinin [CCK], gastrin, and gastric inhibitory polypeptide [GIP]), and glucocorticoids. Both sympathetic and parasympathetic (vagal) stimulation promote glucagon release; this is especially important in augmenting the response of the α cell to hypoglycemia. High levels of circulating fatty acid are associated with suppression of glucagon secretion.

Action of Glucagon

In contrast to insulin, which promotes energy storage in a variety of tissues, glucagon provides a humoral mechanism for making energy available to the tissues between meals, when ingested food is not available for absorption. The ratio of insulin to glucagon affects key target tissues by mediating phosphorylation or dephosphorylation (either or both) of key enzymes affecting nutrient metabolism. In addition, this ratio increases or decreases actual quantities of certain enzymes, thereby controlling the flux of these nutrients into or out of storage.

The liver, because of its geographic proximity to the pancreas, represents the major target organ for glucagon, with portal vein glucagon concentrations reaching as high as 300–500 pg/mL (100–166 pmol/L). Glucagon signals through the glucagon receptor, a G protein-coupled receptor (GPCR) found predominantly on the surface of hepatocytes. Binding of glucagon to its receptor in the liver activates adenylyl cyclase and the generation of cAMP, which in turn stimulates the breakdown of stored glycogen, maintains hepatic output of glucose from amino acid precursors (gluconeogenesis), and promotes hepatic output of ketone bodies from fatty acid precursors (ketogenesis). Uptake of alanine by liver cells is facilitated by glucagon, and fatty acids are directed away from reesterification to triglycerides and toward ketogenic pathways. The net result of glucagon signaling is the release of readily available energy stores from the liver in the form of glucose and ketones. It is unclear whether physiologic levels of glucagon affect tissues other than the liver.

Glucagon-Related Peptides

In the intestinal L-cells, prohormone convertase 1/3 generates a different set of peptides from the proglucagon molecule, including glicentin, glicentin-related polypeptide (GRPP), oxyntomodulin, and the two glucagon-like peptides GLP-1 and GLP-2 (Figure 18–6). Several

biological activities have been attributed to glicentin and oxyntomodulin based on studies using high concentrations of the peptides, but all these actions can be explained by low-affinity interactions with the receptors for glucagon, GLP-1, and GLP-2. Specific receptors for glicentin and oxyntomodulin have not been identified, and it remains uncertain whether these peptides play any biological role at physiologic concentrations. GRPP has no clearly established biological activity. The other two gut-derived glucagon related peptides, GLP-1 and GLP-2, however, play important roles in nutrient metabolism (Table 18–4).

Table 18–4. Biologic Roles of Glucagon-Related Peptides.

Target Tissue	Glucagon	GLP-1	GLP-2
Islet	**Stimulates** insulin secretion	**Stimulates** insulin and somatostatin secretion	
		Inhibits glucagon secretion	
		Increases beta cell mass by inhibiting beta cell death and inducing beta cell proliferation	
Liver	**Stimulates** glycogenolysis, glucogenesis, fatty acid oxidation, and ketogenesis		
	Inhibits glycogen synthesis and fatty acid synthesis		
Stomach		**Stimulates** gastric acid secretion	
		Inhibits gastric emptying	
Intestine			**Stimulates** mucosal growth and nutrient absorption
			Inhibits motility
Brain (hypothalamus)		**Inhibits** appetite	

There are two active forms of GLP-1: GLP-1(7–36) amide, and GLP-1(7–37). GLP-1 is secreted from the intestinal L-cells in response to meals, and binds to the GLP-1 receptor, a GPCR similar to the glucagon receptor. Circulating GLP-1 is rapidly inactivated (half-life < 2 min) by the ubiquitous protease dipeptidyl peptidase IV (DPP-IV), which removes the two amino-terminal amino acids. Pancreatic islets are a major target of GLP-1 action. GLP-1 stimulates the production and secretion of insulin and somatostatin, and it inhibits the secretion of glucagon. In addition, GLP-1 protects the β cells from destruction and stimulates β cell growth. Other targets of GLP-1 include the stomach, where the peptide inhibits gastric emptying and stimulates gastric acid secretion; the brain, where it inhibits appetite and induces weight loss; and the heart, where it has some protective effects.

GLP-2 is secreted with GLP-1 in response to eating, binds to a specific GPCR that is closely related to the glucagon and GLP-1 receptors, and is also inactivated by DPP-IV. The major target of GLP-2 signaling appears to be the intestine, where it stimulates mucosal growth and nutrient absorption and inhibits motility.

Somatostatin

The gene for somatostatin is on the long arm of chromosome 3. It codes for a 116-amino-acid peptide, preprosomatostatin, from whose carboxyl end is cleaved the hormone somatostatin, a 14-amino-acid cyclic polypeptide with a molecular weight of 1640 (Figure 18–7). It is present in δ cells at the periphery of the human islet (Figure 18–1). It was first identified in the hypothalamus and owes its name to its ability to inhibit release of growth hormone (GH; pituitary somatotropin). Since that time, somatostatin has been identified in a number of tissues, including many areas of the brain, the gastrointestinal tract, and the pancreas. In the central nervous system and the pancreas, somatostatin-14 predominates, but approximately 5–10% of the somatostatin-like immunoreactivity in the brain is due to a 28-amino-acid peptide, somatostatin-28. This consists of an amino terminal region of 14 amino acids and a carboxyl terminal segment containing somatostatin-14. In small intestine, the larger molecule is more prevalent, with 70–75% of the hormone having 28 amino acids and only 25–30% being somatostatin-14. The larger peptide somatostatin-28 is ten times more potent than somatostatin-14 in inhibiting growth hormone and insulin, whereas somatostatin-14 is more effective in inhibition of glucagon release.

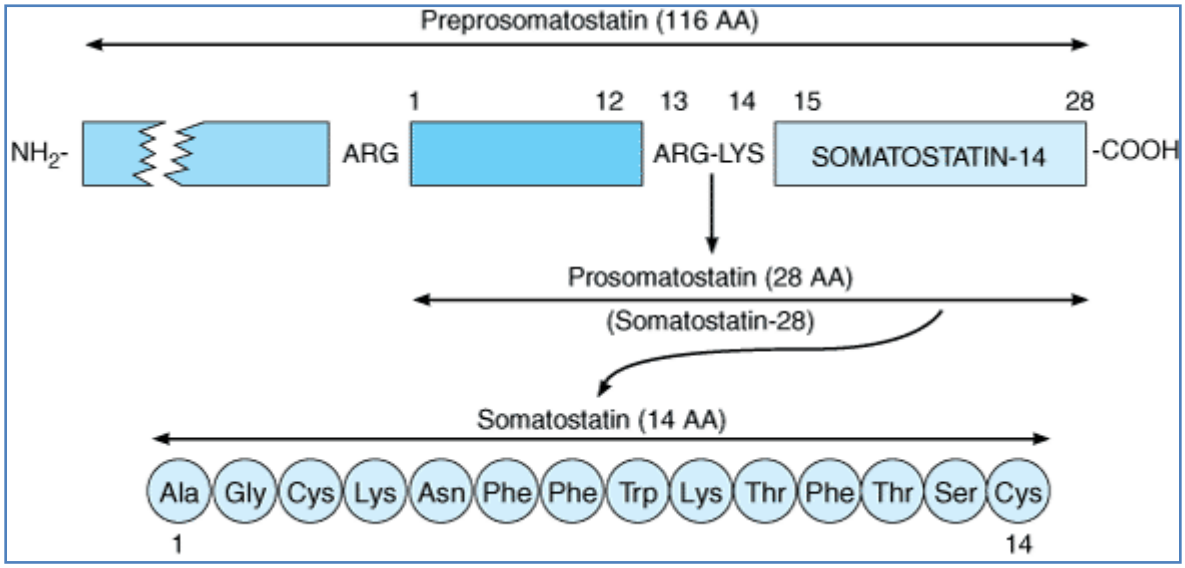


Figure 18-7. Amino acid sequence of somatostatin and its cleavage from dibasic amino acid residue in prosomatostatin and preprosomatostatin.

Most known stimulators of insulin release also promote somatostatin release from δ cells. This includes glucose, arginine, gastrointestinal hormones, and tolbutamide. The importance of circulating somatostatin is unclear; a major role of this peptide may be as a paracrine regulator of the pancreatic islet and the tissues of the gastrointestinal tract. Physiologic levels of somatostatin in humans seldom exceed 80 pg/mL (49 pmol/L). The metabolic clearance of exogenously

infused somatostatin in humans is extremely rapid; the half-life of the hormone is less than 3 minutes.

Recently, molecular cloning has demonstrated the existence of at least five somatostatin receptors (SSTR1–5), all of which are GPCRs. They are found in the central nervous system and in a wide variety of peripheral tissues, including the pituitary gland, the small intestine, and the pancreas. These receptors activate tyrosine phosphatases that interfere with the secretory process by dephosphorylating proteins. Inhibition of insulin secretion is due to binding of ligand to SSTR5, whereas inhibition of GH release as well as glucagon release by α cells of the pancreas works through SSTR2. This explains why an analog of somatostatin, octreotide, which has a much greater affinity for SSTR2 than for SSTR5, is effective in correcting GH excess without much of an effect on carbohydrate tolerance when used to treat acromegaly.

Somatostatin acts in several ways to restrain the movement of nutrients from the intestinal tract into the circulation. It prolongs gastric emptying time, decreases gastric acid and gastrin production, and diminishes pancreatic exocrine secretion.

Pancreatic Polypeptide

PP is found in PP cells located chiefly in islets in the posterior portion of the head of the pancreas. PP is a 36-amino-acid peptide with a molecular weight of 4200. Little is known about its biosynthesis. Circulating levels of the peptide increase in response to a mixed meal; however, intravenous infusion of glucose or triglyceride does not produce such a rise, and intravenous amino acids cause only a small increase.

In healthy subjects, basal levels of PP average 24 ± 4 pmol/L and may become elevated owing to a variety of factors including old age, alcohol abuse, diarrhea, chronic renal failure, hypoglycemia, or inflammatory disorders. Values above 300 pmol/L are found in most patients with pancreatic endocrine tumors such as glucagonoma or vasoactive intestinal polypeptide-secreting tumor and in all patients with tumors of the pancreatic PP cell. As many as 20% of patients with insulinoma and one-third of those with gastrinomas also have plasma concentrations of PP that are greater than 300 pmol/L.

The physiologic action of PP is unknown.

DIABETES MELLITUS

Introduction

Clinical diabetes mellitus is a syndrome of disordered metabolism with inappropriate hyperglycemia due either to an absolute deficiency of insulin secretion or a reduction in the biologic effectiveness of insulin (or both).

Classification

Traditionally, diabetes was classified according to the patient's age at onset of symptoms (juvenile-onset versus adult-onset). In 1979, the NIH Diabetes Data Group proposed a classification that divided diabetes into two main types—insulin-dependent and non-insulin-dependent—but this "therapeutic classification" proved unsatisfactory as more information on the pathogenesis and etiology of diabetes mellitus accumulated. In 1997, an international committee of diabetologists recommended several changes in the classification of diabetes that have been endorsed by the American Diabetes Association and the World Health Organization (Table 18–5). They include the following:

Table 18–5. Etiologic Classification of Diabetes Mellitus.[1]

I. Type 1 diabetes[2] (B cell destruction, usually leading to absolute insulin deficiency)
A. Immune-mediated
B. Idiopathic
II. Type 2 diabetes[2] (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
A. Genetic defects of B cell function
1. Chromosome 12, HNF-1α (MODY 3)
2. Chromosome 7, glucokinase (MODY 2)
3. Chromosome 20, HNF-4α (MODY 1)
4. Chromosome 13, IPF1 (MODY 4)
5. Chromosome 17, HNF-1β (MODY 5)
6. Chromosome 2, Neuro D1 (MODY 6)
7. Mitochrondrial DNA
8. Others
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma, pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis

6. Fibrocalculous pancreatopathy
7. Others
D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others
E. Drug- or chemical-induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. Beta-adrenergic agonists
8. Thiazides
9. Phenytoin
10. Alpha-interferon
11. Others
F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others
G. Uncommon forms of immune-mediated diabetes
1. Stiff-man syndrome
2. Anti-insulin receptor antibodies
3. Others
H. Other genetic syndromes sometimes associated with diabetes
1. Down's syndrome
2. Klinefelter's syndrome
3. Turner's syndrome
4. Wolfram's syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others
IV. Gestational diabetes mellitus (GDM)

[1]Modified from American Diabetes Association: Diabetes Care 1999;22(Suppl 1):1185.

[2]Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

HNF = hepatic nuclear factor.

1. The terms "insulin-independent diabetes mellitus" and "non-insulin-dependent diabetes mellitus" and their acronyms IDDM and NIDDM were eliminated because they are based on pharmacologic rather than etiologic considerations.

2. The terms "type 1 diabetes" and "type 2 diabetes" are retained, with arabic rather than roman numerals. Type 1 diabetes is due to pancreatic islet β cell destruction, which is caused by an autoimmune process in more than 95% of cases, whereas the cause of β cell destruction is idiopathic in less than 5% of cases. Patients with type 1 diabetes are generally prone to ketoacidosis and require insulin replacement therapy. Type 2 diabetes, the much more prevalent form, is a heterogeneous disorder encompassing a spectrum of defects consisting in some cases of defects in β cell function alone but most commonly associated with insulin resistance in the presence of an associated impairment in compensatory insulin secretion.

Type 1 Diabetes Mellitus

This form of diabetes is immune-mediated in more than 90% of cases and idiopathic in less than 10%. The rate of pancreatic β cell destruction is quite variable, being rapid in some individuals and slow in others. It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic β cells fail to respond to all known insulinogenic stimuli. In the absence of insulin, the three main target tissues of insulin (liver, muscle, and fat) not only fail to appropriately take up absorbed nutrients but continue to deliver glucose, amino acids, and fatty acids into the bloodstream from their respective storage depots. Furthermore, alterations in fat metabolism lead to the production and accumulation of ketones. This inappropriate persistence of the fasted state postprandially can be reversed by the administration of insulin. The highest incidence of immune-mediated type 1 diabetes is in Scandinavia and northern Europe, where the yearly incidence per 100,000 youngsters 14 years of age or less is as high as 37 in Finland, 27 in Sweden, 22 in Norway, and 19 in the United Kingdom. The incidence of type 1 diabetes generally decreases across the rest of Europe to 10 in Greece and 8 in France. Surprisingly, the island of Sardinia has as high an incidence as Finland, even though in the rest of Italy, including the island of Sicily, it is only 10 per 100,000 per year. The United States averages 15 per 100,000, with higher incidences in states more densely populated with persons of Scandinavian descent (eg, Minnesota). The lowest incidence of type 1 diabetes worldwide was found to be less than 1 per 100,000 per year in China and parts of South America.

Diabetes mellitus type 1 occurs at any age but most commonly arises in children and young adults with a peak incidence before school age and again at around puberty. Family members of diabetics have an increased lifetime risk of developing type 1 diabetes. The offspring of a mother with type 1 diabetes have a risk of 3%, whereas the risk is 6% if the father is affected. The risk in

siblings is related to the number of human leukocyte antigen (HLA) haplotypes that the sibling shares with the diabetic. If one haplotype is shared, the risk is 6% and if two haplotypes are shared, the risk increases to 12–25%. The highest risk is for identical twins, where the concordance rate is 25 to 50%.

Certain unrecognized patients with a milder expression of type 1 diabetes initially retain enough β cell function to avoid ketosis but develop increasing dependency on insulin therapy later in life as their β cell mass diminishes. Islet cell antibody surveys among northern Europeans indicate that up to 15% of patients who supposedly have type 2 diabetes may actually have this mild form of type 1 diabetes (latent autoimmune diabetes of adulthood [LADA]).

Genetics of Type 1 Diabetes

Studies in monozygotic twins suggest that genetic influences are less marked in type 1 diabetes than in type 2 diabetes. Only 30–40% of identical twins of type 1 diabetic patients develop the disease. This also suggests that an environmental factor is required for induction of diabetes in these cases. In contrast, the identical twin of a type 2 diabetic is much more prone to develop diabetes, often with onset within a year after onset of the disease in the sibling.

Type 1 diabetes is believed to result from an infectious or toxic environmental insult to genetically predisposed persons whose aggressive immune system destroys pancreatic β cells while overcoming the invasive agent. Environmental factors that have been associated with altered pancreatic islet cell function include viruses (mumps, rubella, coxsackievirus B4), toxic chemical agents such as vacor (a nitrophenylurea rat poison), and other destructive cytotoxins such as hydrogen cyanide.

At least half of the familial aggregation of type 1 diabetes is accounted for by genes in the major histocompatibility locus on the short arm of chromosome 6. The most important of these are the HLA class II molecules DQ and DR, which code for antigens expressed on the surface of macrophages and B lymphocytes. The class II molecules bind to peptide antigens and present them to T cells by binding to the T cell receptor. Of approximately 21 known DR genes, only DR3 and DR4 are major susceptibility risk factors for type 1 diabetes. As many as 95% of type 1 diabetic patients have a DR3 or a DR4 or both.

DQ alleles are associated not only with risk for type 1 diabetes but also with dominant protection, often in linkage with HLA-DR2. The most protective of these—and a quite common allele—is DQA1*0102, DQB1*0602.

It remains a mystery why people with certain HLA types are predisposed to type 1 diabetes. The concept of an autoimmune destruction of pancreatic β cells due to selective loss of immune tolerance is supported by evidence that immune suppression therapy interrupts progression to insulin deficiency in a number of newly diagnosed patients with type 1 diabetes. Moreover, extensive infiltration with both helper and cytotoxic T lymphocytes is present in the islets of children who have just developed type 1 diabetes, and their serum contains autoantibodies against structural and secretory proteins of the pancreatic β cells before the onset of type 1 diabetes and for some time after diagnosis.

On the strength of the above evidence, a theory for autoimmune β cell destruction has been proposed based on molecular mimicry, wherein the immune system mistakenly targets β cell proteins that share homologies with certain viral or other foreign peptides (e.g., partially digested cow's milk dietary proteins). The efficiency of presenting certain proteins depends on the composition of the class II HLA proteins on the surface of the antigen-presenting cells (macrophages). Efficiency of antigen presentation by the class II HLA proteins could play a role during the deletion of self-reactive T cells in the thymus. Failure to properly delete T cells that recognize β cell antigens would predispose to later development of type 1 diabetes. Alternatively, efficiency of antigen presentation could play a role later during the peripheral development of an autoimmune response.

Most patients with type 1 diabetes at diagnosis have circulating antibodies: islet cell antibody (ICA), insulin autoantibody (IAA), antibody to glutamic acid decarboxylase (GAD) 65, and antibody to tyrosine phosphatases (IA-2 and IA2-β).

Type 2 Diabetes

Type 2 diabetes—previously classified as non-insulin-dependent diabetes—afflicts individuals with insulin resistance who generally have relative rather than absolute insulin deficiency. It accounts for 80–90% of cases of diabetes in the United States. These patients are usually adults over age 40 with some degree of obesity. They do not require insulin to survive, although over time their insulin secretory capacity tends to deteriorate, and many need insulin treatment to achieve optimal glucose control. Ketosis seldom occurs spontaneously, and if present, it is a consequence of severe stress from trauma or infection.

The nature of the primary defect in type 2 diabetes is obscure. Tissue insensitivity to insulin has been noted in most patients with type 2 disease irrespective of weight and has been attributed to several interrelated factors (Table 18–7). These include a putative (as yet undefined) genetic factor, which is aggravated in time by further enhancers of insulin resistance such as aging, a sedentary lifestyle, and abdominal visceral obesity. In addition, there is an accompanying deficiency in the response of pancreatic β cells to glucose, a genetic disorder that may be aggravated by gradual displacement of β cells due to deposition of intraislet amyloid with aging. Furthermore, both the tissue resistance to insulin and the impaired β cell response to glucose appear to be further aggravated by sustained hyperglycemia, which may impede both insulin signaling and β cell function. Treatment that reduces the hyperglycemia toward normal reduces this acquired defect in insulin resistance and also improves glucose-induced insulin release to some degree. Type 2 diabetes frequently goes undiagnosed for many years, because the hyperglycemia develops quite gradually and is generally asymptomatic initially. Despite this mild presentation, these patients are at increased risk of developing macrovascular and microvascular complications.

Table 18–7. Factors Reducing Response to Insulin.

Prereceptor inhibitors: Insulin antibodies
Receptor inhibitors:
Insulin receptor autoantibodies
"Down-regulation" of receptors by hyperinsulinism:
Primary hyperinsulinism (B cell adenoma)
Hyperinsulinism, secondary to a postreceptor defect (obesity, Cushing's syndrome, acromegaly, pregnancy) or prolonged hyperglycemia (diabetes mellitus, post-glucose tolerance test)
Postreceptor influences:
Poor responsiveness of principal target organs: obesity, hepatic disease, muscle inactivity
Hormonal excess: glucocorticoids, growth hormone, oral contraceptive agents, progesterone, human chorionic somatomammotropin, catecholamines, thyroxine

The genetics of type 2 diabetes is complex and poorly defined despite the strong genetic predisposition in these patients. This is probably because of the heterogeneous nature of this disorder as well as the difficulty in sorting out the contribution of acquired factors affecting insulin action and glycemic control.

Subgroups of Type 2 Diabetes

Two subgroups of patients with type 2 diabetes are currently distinguished by the absence or presence of obesity. It is at present impossible to identify diagnostic characteristics that allow further clear-cut separation into more specific subtypes. Circulating insulin levels vary with the prevailing degree of hyperglycemia and are considered too unreliable to be of use in classifying type 2 diabetes.

Obese Type 2 Diabetes

The prevalence of obesity varies among different racial groups. Although obesity is apparent in no more than 30% of Chinese and Japanese patients with type 2 diabetes, it is present in 60–80% of North Americans, Europeans, or Africans with type 2 diabetes and approaches 100% of individuals with type 2 disease among Pima Indians or Pacific Islanders from Nauru or Samoa. Patients with type 2 diabetes have an insensitivity to endogenous insulin that is correlated with the presence of a predominantly abdominal distribution of fat, producing an abnormally high waist to hip ratio. In addition, distended adipocytes and overnourished liver and muscle cells may also resist the deposition of additional glycogen and triglycerides in their storage depots. Hyperplasia of pancreatic β cells is often present and probably accounts for the normal or exaggerated insulin responses to glucose and other stimuli seen in the milder forms of this disease. In more severe cases, secondary (but potentially reversible) failure of pancreatic β cell secretion may result after exposure to prolonged fasting hyperglycemia. This phenomenon has been called "desensitization" or "glucose toxicity." It is selective for glucose, and the β cell can recover some degree of sensitivity to glucose stimulation once the sustained hyperglycemia is corrected by any form of therapy, including diet therapy, sulfonylureas, and insulin.

Not all patients with obesity and insulin resistance develop hyperglycemia, however. An underlying defect in the ability of the β cells to compensate for the increased demand may determine which patients will develop diabetes in the setting of insulin resistance. Furthermore, as noted above, patients with type 2 diabetes suffer from a progressive decline in β cell function that results in worsening hyperglycemia even when the degree of insulin resistance remains stable.

Metabolic Syndrome (Syndrome X)

When obese type 2 patients predominantly present with insulin resistance, the diabetes may be associated with a cluster of abnormalities commonly termed the metabolic syndrome. **Hyperglycemia** in these patients is frequently associated with **hyperinsulinemia, dyslipidemia,** and **hypertension,** which together lead to **coronary artery disease** and **stroke.** It has been suggested that this aggregation results from a genetic defect producing insulin resistance, particularly when obesity aggravates the degree of insulin resistance. In this model, impaired action of insulin predisposes to hyperglycemia, which in turn induces hyperinsulinemia. If this hyperinsulinemia is of insufficient magnitude to correct the hyperglycemia, type 2 diabetes is manifested. The excessive insulin level could also increase sodium retention by renal tubules, thereby contributing to or causing hypertension. Increased VLDL production in the liver, leading to hypertriglyceridemia (and consequently a low high-density lipoprotein [HDL] cholesterol level), has also been attributed to hyperinsulinism. Moreover, it has been proposed that high insulin levels can stimulate endothelial and vascular smooth muscle cell proliferation—by virtue of the hormone's action on growth factor receptors—to initiate atherosclerosis.

Although there is full agreement on an association of these disorders, the mechanism of their interrelationship remains speculative and open to experimental investigation. Controversy persists about whether or not hypertension is caused by the hyperinsulinism that results from insulin resistance..

An alternative unifying hypothesis could be that visceral obesity directly induces the other components of this syndrome. Visceral obesity is an independent risk factor for all of the other components of metabolic syndrome. In addition to the metabolic effects of visceral obesity, adipocytes produce a number of secreted products, including tumor necrosis factor-α (TNF-α), leptin, adiponectin, and resistin. Although the full details of the role of these molecules in causation of the metabolic syndrome are still under investigation, the adipocyte clearly plays an active role in the development of systemic insulin resistance, hypertension, and hyperlipidemia. Furthermore, thrombi in atheromatous vessels may be more hazardous in patients with visceral obesity because they also have an associated increase in plasminogen activator inhibitor-1 (PAI-1), a circulating factor produced by visceral adipocytes that inhibits clot lysis. This discussion emphasizes the importance of measures such as diet and exercise that reduce visceral adiposity in the management of patients with metabolic syndrome and obese type 2 diabetes.

Nonobese Type 2 Diabetes

Approximately 20–40% of patients with type 2 diabetes are nonobese. Among nonobese patients with type 2 diabetes, deficient insulin release by the pancreatic β cells seems to be the major defect, but some insulin resistance may also contribute.

Currently, type 2 diabetes is considered of idiopathic origin. However, with developments in biotechnology, a variety of etiologic genetic abnormalities have been documented within this heterogeneous group, particularly in those presenting with clinical and laboratory manifestations similar to those seen in the nonobese type 2 subgroup. When the genetic defect has been defined, these patients have recently been reclassified within a group designated "other specific types" (Table 18–5). In most of these patients, impaired insulin action at the postreceptor level and an absent or delayed early phase of insulin release in response to glucose can be demonstrated. However, other insulinogenic stimuli, such as acute infusion of amino acids, intravenous tolbutamide, or intramuscular glucagon, often remain partially effective in eliciting acute insulin release.

The hyperglycemia in patients with nonobese type 2 diabetes often responds to dietary therapy or to oral antidiabetic agents. Occasionally, insulin therapy is required to achieve satisfactory glycemic control even though it is not needed to prevent ketoacidosis.

Other Specific Types of Diabetes

Genetic Defects of Pancreatic β Cell Function

This subgroup of monogenic disorders is characterized by a diabetes that occurs in late childhood or before the age of 25 years as a result of a partial defect in glucose-induced insulin release and accounts for up to 5% of diabetes in North American and European populations. A strong family history of early-onset diabetes occurring in one parent and in one-half of the parent's offspring suggests autosomal dominant transmission. These patients are generally nonobese, and because they are not ketosis-prone and may initially achieve good glycemic control without insulin therapy, their disease has been called "maturity-onset diabetes of the young" (MODY). Six types have been described with single-gene defects, and all have been shown to produce a defect in glucose-induced insulin release. MODY 2 results from an abnormal glucokinase enzyme. Other forms of MODY are due to mutations of nuclear transcription factors that regulate b cell gene expression (Table 18–8).

Table 18–8. Genetic Defects of Pancreatic β Cell Function.

Syndrome	Mutation	Chromosome
MODY 1	Hepatocyte nuclear factor-4α	20q
MODY 2	Glucokinase gene	7p
MODY 3	Hepatocyte nuclear factor-1α	12q
MODY 4	Insulin promoter factor-1	13q
MODY 5	Hepatocyte nuclear factor-1β	17q
MODY 6	NeuroD1	2q
Mitochondrial dysfunction	Transfer RNAs (leucine or lysine tRNA)	Mitochondrial DNA
Mutant insulin or proinsulin	Insulin gene	11p

Mutant Insulins

Despite awareness of this disorder over the past 12 years, only eight families have been identified as having abnormal circulating forms of insulin. In three of these families, there is

impaired cleavage of the proinsulin molecule; in the other five families, abnormalities of the insulin molecule itself have been reported

Genetic Defects of Insulin Action

These are rare and unusual causes of diabetes that result from mutations of the insulin receptor (type A insulin resistance) or from other genetically determined postreceptor abnormalities of insulin action. Metabolic abnormalities associated with these disorders may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals have acanthosis nigricans, which seems to be a consequence of very high circulating insulin levels that cross over to bind to IGF receptors on epidermal and melanin-containing cutaneous cells.

Diabetes Due to Diseases of the Exocrine Pancreas

Any process that diffusely damages or displaces at least two-thirds of the pancreas can cause diabetes, although individuals with a predisposition to type 2 diabetes are probably more susceptible to developing diabetes with lesser degrees of pancreatic involvement. Acquired causes include pancreatitis, trauma, infection, pancreatic carcinoma, and pancreatectomy. When extensive enough, hemochromatosis and cystic fibrosis can also displace β cells and cause deficiency in insulin secretion. Because glucagon-secreting α cells are also damaged or removed by these processes, less insulin is usually required for replacement—as compared with most other forms of diabetes, where α cells are intact.

Endocrinopathies

Excess production of certain hormones—GH (acromegaly), glucocorticoids (Cushing's syndrome or disease), catecholamines (pheochromocytoma), thyroid hormone (thyrotoxicosis), glucagon (glucagonoma), or pancreatic somatostatin (somatostatinoma)—can produce the syndrome of type 2 diabetes by a number of mechanisms. In all but the last instance (somatostatinoma), peripheral responsiveness to insulin is impaired. In addition, excess of catecholamines or somatostatin decreases insulin release from β cells. Diabetes mainly occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is corrected.

Drug- or Chemical-Induced Diabetes

Many drugs are associated with carbohydrate intolerance or frank diabetes mellitus. Some act by interfering with insulin release from the β cells (thiazides, phenytoin), some by inducing insulin resistance (glucocorticoids, oral contraceptive pills), and some by causing β cell destruction such as vacor (a rat poison) and intravenous pentamidine. Patients receiving alpha interferon have been reported to develop diabetes associated with ICAs and in certain instances severe insulin deficiency.

Infections Causing Diabetes

Certain viruses have been associated with direct pancreatic β cell destruction in animals. Diabetes is also known to develop frequently in humans who had congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of diabetes.

Uncommon Forms of Immune-Mediated Diabetes

These include two rare conditions associated with autoantibodies implicated in causing diabetes. Stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness and painful spasm of skeletal muscle. Many patients have high titers of autoantibodies that react with GAD in the central nervous system and also in pancreatic β cells. Approximately one-third of patients develop severe β cell destruction and diabetes.

A severe form of insulin resistance has been reported in patients who developed high titers of antibodies that bind to the insulin receptor and block the action of insulin in its target tissues. As in other states of extreme insulin resistance, these patients often have acanthosis nigricans. In the past, this form of immune-mediated diabetes was termed type B insulin resistance.

Other Genetic Syndromes Sometimes Associated with Diabetes

A number of genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. **Wolfram's syndrome** is an autosomal recessive neurodegenerative disorder first evident in childhood. It consists of **d**iabetes **i**nsipidus, **d**iabetes **m**ellitus, **o**ptic **a**trophy, and **d**eafness—hence the acronym DIDMOAD.

Clinical Features of Diabetes Mellitus

The principal clinical features of the two major types of diabetes mellitus are listed for comparison in Table 18–10.

Table 18–10. Clinical Features of Diabetes at Diagnosis.

	Diabetes Type 1	**Diabetes Type 2**
Polyuria and thirst	++	+
Weakness or fatigue	++	+
Polyphagia with weight loss	++	–
Recurrent blurred vision	+	++
Vulvovaginitis or pruritis	+	++
Peripheral neuropathy	+	++
Nocturnal enuresis	++	–
Often asymptomatic	–	++

Type 1 Diabetes

Patients with type 1 diabetes present with a characteristic symptom complex, as outlined below. An absolute deficiency of insulin results in excessive accumulation of circulating glucose and fatty acids, with consequent hyperosmolality and hyperketonemia. The severity of the insulin deficiency and the acuteness with which the catabolic state develops determine the intensity of the osmotic and ketotic excess.

Clinical Features

Symptoms

Increased urination is a consequence of osmotic diuresis secondary to sustained hyperglycemia. This results in a loss of glucose as well as free water and electrolytes in the urine. Nocturnal enuresis (involuntary passing of urine) due to polyuria may signal the onset of diabetes in very young children. Thirst is a consequence of the hyperosmolar state, as is blurred vision, which often develops as the lenses and retinas are exposed to hyperosmolar fluids.

Weight loss, despite normal or increased appetite, is a common feature of type 1 diabetes when it develops subacutely over a period of weeks. The weight loss is initially due to depletion of water, glycogen, and triglyceride stores. Chronic weight loss due to reduced muscle mass occurs as amino acids are diverted to form glucose and ketone bodies.

Lowered plasma volume produces dizziness and weakness due to postural hypotension when sitting or standing. Total body potassium loss and the general catabolism of muscle protein contribute to the weakness.

Paresthesias (abnormal neurological sensation –numbness, tingling, burning) may be present at the time of diagnosis of type 1 diabetes, particularly when the onset is subacute. They reflect a temporary dysfunction of peripheral sensory nerves and usually clear as insulin replacement restores glycemic levels closer to normal; thus, their presence suggests neurotoxicity from sustained hyperglycemia.

When insulin deficiency is severe and of acute onset, the above symptoms progress in an accelerated manner. Ketoacidosis exacerbates (worsens) the dehydration and hyperosmolality by producing anorexia, nausea, and vomiting, thus interfering with oral fluid replacement. As plasma osmolality exceeds 330 mosm/kg (normal, 285–295 mosm/kg), impaired consciousness ensues. With progression of acidosis to a pH of 7.1 or less, deep breathing with a rapid ventilatory rate occurs as the body attempts to eliminate carbonic acid. With worsening acidosis (to pH 7.0 or less), the cardiovascular system may be unable to maintain compensatory vasoconstriction; severe circulatory collapse may result.

Signs

The patient's level of consciousness can vary depending on the degree of hyperosmolality. When insulin deficiency develops relatively slowly and sufficient water intake is maintained to permit renal excretion of glucose and appropriate dilution of extracellular sodium chloride concentration, patients remain relatively alert and physical findings may be minimal. When

vomiting occurs in response to worsening ketoacidosis, dehydration progresses and compensatory mechanisms become inadequate to keep plasma osmolality below 330 mosm/kg. Under these circumstances, coma may occur. Evidence of dehydration, with rapid deep breathing and the fruity breath odor of acetone, suggests the diagnosis of diabetic ketoacidosis.

Postural hypotension indicates a depleted plasma volume. Loss of subcutaneous fat and muscle wasting are features of more slowly developing insulin deficiency. In occasional patients with slow, insidious onset of insulin deficiency, subcutaneous fat may be considerably depleted. An enlarged liver, eruptive xanthomas, and lipemia retinalis indicate that chronic insulin deficiency has resulted in chylomicronemia, with circulating triglycerides elevated usually to over 2000 mg/dL.

Type 2 Diabetes

Patients with type 2 diabetes also present with characteristic signs and symptoms. The presence of obesity or a strongly positive family history of mild diabetes also suggests a high risk for the development of type 2 diabetes.

Clinical Features

Symptoms

The classic symptoms of polyuria, thirst, recurrent blurred vision, paresthesias, and fatigue are manifestations of hyperglycemia and osmotic diuresis and are therefore common to both forms of diabetes. However, many patients with type 2 diabetes have an insidious onset of hyperglycemia and may be relatively asymptomatic initially. This is particularly true in obese patients, whose diabetes may be detected only after glycosuria or hyperglycemia is noted during routine laboratory studies. Chronic skin infections are common.

Signs

Nonobese patients with this mild form of diabetes often have no characteristic physical findings at the time of diagnosis. Obese patients with type 2 diabetes may have any variety of fat distribution; however, diabetes seems to be more often associated in both men and women with localization of fat deposits on the upper part of the body (particularly the abdomen, chest, neck, and face) and relatively less fat on the appendages, which may be quite muscular. This centripetal fat distribution has been termed "android" and is characterized by a high waist to hip ratio. It differs from the more centrifugal "gynecoid" form of obesity, in which fat is localized more in the hips and thighs and less in the upper parts of the trunk. Refined radiographic techniques of assessing abdominal fat distribution with computed tomography or magnetic resonance imaging scans has documented that a "visceral" obesity, due to accumulation of fat in the mesenteric regions, correlates with insulin resistance, whereas fat predominantly in subcutaneous tissues of the abdomen has little, if any, association with insulin insensitivity. Mild hypertension may be present in obese patients with type 2 diabetes, particularly when the "android" form of obesity is predominant.

Laboratory Findings in Diabetes Mellitus

Tests of urine glucose and ketone bodies as well as whole blood or plasma glucose measured in samples obtained under basal conditions and after glucose administration are very important in evaluation of the patient with diabetes. Tests for glycosylated hemoglobin have proved useful in both initial evaluation and in assessment of the effectiveness of therapeutic management. In certain circumstances, measurements of insulin or C peptide levels and levels of other hormones involved in carbohydrate homeostasis (e.g., glucagon, GH) may be useful. In view of the increased risk of atherosclerosis in patients with diabetes, determination of serum cholesterol (including its beneficial HDL fraction) and triglycerides may be helpful. From these three measurements, an estimate of LDL-cholesterol can be made.

Urinalysis

Glycosuria

Several problems are associated with using urine glucose as an index of blood glucose, regardless of the method employed. First of all, the glucose concentration in bladder urine reflects the blood glucose at the time the urine was formed. Therefore, the first voided specimen in the morning contains glucose that was excreted throughout the night and does not reflect the morning blood glucose at all. Some improvement in the correlation of urine glucose to blood glucose can be obtained if the patient "double voids"—that is, empties the bladder completely, discards that sample, and then urinates again about one-half hour later, testing only the second specimen for glucose content. However, difficulty in completely emptying the bladder (large residual volumes), problems in understanding the instructions, and the inconvenience impair the usefulness of this test. Self-monitoring of blood glucose has replaced urine glucose testing in most patients with diabetes (particularly those receiving insulin therapy).

Differential Diagnosis of Glycosuria

Although glycosuria reflects hyperglycemia in more than 90% of patients, two major classes of nondiabetic glycosuria must be considered:

Nondiabetic Glycosuria Due to Glucose

This occurs when glucose appears in the urine despite a normal amount of glucose in the blood as in disorders associated with abnormalities in renal glucose handling.

In addition, glycosuria is relatively common in pregnancy as a consequence of the increased load of glucose presented to the tubules by the elevated glomerular filtration rate during pregnancy. As many as 50% of pregnant women normally have demonstrable sugar in the urine, especially after the first trimester. This sugar is almost always glucose except during the late weeks of pregnancy, when lactose may be present.

Nondiabetic Glycosuria Due to Sugars Other Than Glucose

Occasionally, a sugar other than glucose is excreted in the urine. Lactosuria during the late stages of pregnancy and the period of lactation is the most common example. Much rarer are other conditions in which inborn errors of metabolism allow fructose, galactose, or a pentose to be

excreted in the urine. Testing the urine with glucose-specific strips helps differentiate true glucosuria from other glycosurias.

Ketonuria
In the absence of adequate insulin, three major "ketone bodies" are formed and excreted into the urine: β-hydroxybutyric acid, acetoacetic acid, and acetone. Other conditions besides diabetic ketoacidosis may cause ketone bodies to appear in the urine; these include starvation, high-fat diets, alcoholic ketoacidosis, fever, and other conditions in which metabolic requirements are increased.

Proteinuria
Proteinuria is often the first sign of renal complications of diabetes. If proteinuria is detected, a 24-hour urine collection should be analyzed to quantify the degree of proteinuria (normal individuals excrete < 30 mg of protein per day) and the rate of urinary creatinine excretion; at the same time, serum creatinine levels should be determined so that the creatinine clearance (an estimate of the glomerular filtration rate) can be calculated. In some cases, heavy proteinuria (3–5 g/d) develops later, along with other features of the nephrotic syndrome such as edema, hypoalbuminemia, and hypercholesterolemia.

Microalbuminuria
Urinary albumin can now be detected in microgram concentrations using high-performance liquid chromatography or immunoassay methodology. Conventional 24-hour urine collections, in addition to being inconvenient for patients, also show wide variability of albumin excretion,. For these reasons, many clinics prefer to screen patients by measuring the albumin-creatinine ratio in an early morning spot urine collected on awakening—prior to breakfast or exercise—and brought in by the patient for laboratory analysis. A ratio of albumin (μg/L) to creatinine (mg/L) of less than 30 is normal, and a ratio of 30–300 indicates abnormal microalbuminuria.

Blood Glucose Testing

Normal Values
The range of normal fasting plasma or serum glucose is 70–110 mg/dL (3.9–6.1 mmol/L). Plasma or serum from venous blood samples has the advantage over whole blood of providing values for glucose that are independent of hematocrit and reflect levels in the interstitial spaces to which body tissues are exposed. For these reasons—and because plasma and serum lend themselves to automated analytic procedures—they are used in most laboratories. The glucose concentration is 10–15% higher in plasma or serum than in whole blood because structural components of blood cells are absent. Whole blood glucose determinations are seldom used in clinical laboratories but have been used by patients with diabetes during self-monitoring of capillary blood glucose, a technique widely accepted in the management of diabetes mellitus. Recently, however, many new reflectance meters have been modified to directly record serum glucose rather than to calculate whole blood glucose concentrations.

Venous Blood Samples
Samples should be collected in tubes containing sodium fluoride, which prevents glycolysis in the blood sample that would artifactually lower the measured glucose level. If such tubes are not

available, samples must be centrifuged within 30 minutes of collection and the plasma or serum stored at 4 °C. The laboratory methods regularly used for determining plasma glucose utilize enzymatic methods (such as glucose oxidase or hexokinase), colorimetric methods (such as *o*-toluidine), or automated methods.

Serum Ketone Determinations

As noted above in the section on ketonuria, there are three major ketone bodies: β-hydroxybutyrate (often the most prevalent in diabetic ketoacidosis), acetoacetate, and acetone. The same testing materials used for determining urine ketones may be used to measure serum (or plasma) ketones.

Glycated Hemoglobin Assays

Ketoamine reactions between glucose and other sugars and free amino groups on the alpha and beta chain lead to glycated forms of hemoglobin. Only glycation of the N-terminal valine of the beta chain imparts sufficient negative charge to the hemoglobin molecule to allow separation by charge-dependent techniques. The charge-separated hemoglobins are collectively referred to as hemoglobin A_1 (HbA_1). The major form of HbA_1 is hemoglobin A_{1c} (HbA_{1c}), where glucose is the carbohydrate. This form comprises 4–6% of total hemoglobin. The remaining HbA_1 species contain fructose 1,6-diphosphate (HbA_{1a1}), glucose 6-phosphate (HbA_{1a2}), and an unknown carbohydrate moiety (HbA_{1b}). The hemoglobin A_{1C} fraction is abnormally elevated in diabetic patients with chronic hyperglycemia. Some laboratories measure the sum of these glycohemoglobins (GHbs) and report the total as hemoglobin A_1, but more laboratories are converting to the more intricate but highly specific HbA_{1c} assay. Methods for measuring Hb_{A1c} include electrophoresis, cation exchange chromatography, affinity chromatography, and immunoassays.

Office-based immunoassays using capillary blood give a result in about 9 minutes, and this allows for immediate feedback to the patients regarding their glycemic control. Because GHbs circulate within red blood cells whose life span lasts up to 120 days, they generally reflect the state of glycemia over the preceding 8–12 weeks, thereby providing an improved method of assessing diabetic control. The HbA_{1c} value, however, is weighted to more recent glucose levels (previous month) and this explains why significant changes in HbA_{1c} are observed with short term (1 month) changes in mean plasma glucose levels. Measurements should be made in patients with either type of diabetes mellitus at 3- to 4-month intervals so that adjustments in therapy can be made if GHb is either subnormal or if it is more than 1% above the upper limits of normal for a particular laboratory. In patients monitoring their own blood glucose levels, GHb values provide a valuable check on the accuracy of monitoring. In patients who do not monitor their own blood glucose levels, GHb values are essential for adjusting therapy.

Lipoproteins in Diabetes

Levels of circulating lipoproteins are dependent on normal levels and action of insulin, just as is the plasma glucose. In type 1 diabetes, moderately deficient control of hyperglycemia is associated with only a slight elevation of low-density lipoprotein (LDL) cholesterol and serum

triglycerides and little if any changes in HDL cholesterol. Once the hyperglycemia is corrected, lipoprotein levels are generally normal. However, in obese patients with type 2 diabetes, a distinct "diabetic dyslipidemia" is characteristic of the insulin resistance syndrome. Its features are a high serum triglyceride level (300–400 mg/dL), a low HDL cholesterol (< 30 mg/dL), and a qualitative change in LDL particles producing a smaller dense LDL whose membrane carries supranormal amounts of free cholesterol. Because a *low* HDL cholesterol is a major feature predisposing to macrovascular disease, the term "dyslipidemia" is used instead of the previous label of "hyperlipidemia," which mainly described the elevated triglycerides. Measures designed to correct obesity and hyperglycemia, such as exercise, diet, and hypoglycemic therapy, are the treatment of choice for diabetic dyslipidemia. In occasional patients in whom normal weight is achieved, all features of the lipoprotein abnormalities clear. Because primary disorders of lipid metabolism may coexist with diabetes, persistence of lipid abnormalities after restoration of normal weight and blood glucose should prompt a diagnostic workup and possible pharmacotherapy of the lipid disorder.

Diagnosis of Diabetes Mellitus

Diagnostic Criteria

The following three criteria are the most recent recommendations of an international committee of diabetes experts who have revised previous diagnostic criteria. The diagnosis of diabetes can be based on any one of these criteria but should be confirmed on a later day with one of the three methods listed.

1. Symptoms of diabetes (thirst, increased urination, unexplained weight loss) plus a random plasma glucose concentration greater than 200 mg/dL (11.1 mmol/L).
2. Fasting plasma glucose greater than 126 mg/dL (7.0 mmol/L) after an overnight (at least 8-hour) fast
3. Two-hour plasma glucose greater than 200 mg/dL (11.1 mmol/L) during a standard 75-g oral glucose tolerance test.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) refer to a stage intermediate between normal glucose homeostasis and diabetes. IFG refers to a level of plasma glucose after an overnight fast that is greater than 100 mg/dL (> normal upper limit of 100 mg/dL [5.6 mmol/L]) but less than the level of 126 mg/dL (7.0 mmol /L), which indicates diabetes.

The corresponding category for the IGT when the oral glucose tolerance test is used is as follows: two-hour plasma glucose greater than 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L).

Many individuals with IGT are euglycemic (have normal glucose levels) in their daily lives and may have normal or near-normal glycosylated hemoglobin levels. These subjects may also have fasting plasma glucose levels in the normal range (< 100 mg/dL [6.1 mmol/L]) and often manifest their impaired glucose metabolism only when challenged with a standardized oral glucose tolerance test.

Oral Glucose Tolerance Test

An oral glucose tolerance test is only rarely indicated, as there is a preference in clinical situations to use fasting plasma glucose levels for diagnosis because they are easier and faster to perform, more convenient and acceptable to patients, more reproducible, and less expensive. Recently, an international committee of diabetologists has recommended simplifying the glucose tolerance test to require only an overnight fasting measurement and one 2 hours after a standard 75-g oral glucose load. Samples at 30, 60, and 90 minutes are no longer required.

If the fasting plasma glucose is between 110 and 126 mg/dL ("impaired fasting glucose"), an oral glucose tolerance test may be considered.

Table 18–12. The Diabetes Expert Committee Criteria for Evaluating the Standard Oral Glucose Tolerance Test.[1]

	Normal Glucose Tolerance	**Impaired Glucose Tolerance**	**Diabetes Mellitus[2]**
Fasting plasma glucose (mg/dL)	< 100	⩾ 100–125	⩾ 126
Two hours after glucose load (mg/dL)	< 140	⩾ 140–199	⩾ 200

[1]Give 75 g of glucose dissolved in 300 mL of water after an overnight fast in subjects who have been receiving at least 150–200 g of carbohydrate daily for 3 days before the test.

[2]A fasting plasma glucose ⩾126 mg/dL is diagnostic of diabetes if confirmed on a subsequent day to be in the diabetic range after either an overnight fast or 2 hours after a standard glucose load.

Insulin Levels

To measure insulin levels during the glucose tolerance test, serum or plasma must be separated within 30 minutes after collection of the specimen and frozen prior to assay. Normal immunoreactive insulin levels range from 5–20 μU/mL in the fasting state, reach 50–130 μU/mL at 1 hour, and usually return to levels below 30 μU/mL by 2 hours. Insulin levels are rarely of clinical usefulness during glucose tolerance testing for the following reasons: When fasting glucose levels exceed 120 mg/dL (6.7 mmol/L), β cells generally have reduced responsiveness to further degrees of hyperglycemia regardless of the type of diabetes. When fasting glucose levels are below 120 mg/dL (6.7 mmol/L), late hyperinsulinism may occur as a result of insulin resistance in type 2 diabetes; however, it also may occur even in mild forms or in the early phases of type 1 diabetes when sluggish early insulin release results in late hyperglycemia that may stimulate excessive insulin secretion at 2 hours.

Treatment of Diabetes Mellitus

Diet

A well-balanced, nutritious diet remains a fundamental element of therapy for diabetes. However, in more than half of cases, patients with diabetes fail to follow their diet. In

prescribing a diet, it is important to relate dietary objectives to the type of diabetes. In obese patients with mild hyperglycemia, the major goal of diet therapy is weight reduction by caloric restriction. This type of patient represents the most frequent challenge for the clinician. Weight reduction is an elusive goal that can only be achieved by close supervision and education of the obese patient.

ADA Recommendations

The American Diabetes Association releases an annual position statement on medical nutrition therapy that replaces the calculated ADA diet formula of the past with suggestions for an individually tailored dietary prescription based on metabolic, nutritional, and lifestyle requirements. They contend that the concept of one diet for "diabetes" and prescription for an "ADA diet" no longer can apply to both major types of diabetes. In their medical nutrition therapy recommendations for persons with type 2 diabetes, the 55–60% carbohydrate content of previous "ADA" diets has been reduced considerably because of the tendency of high carbohydrate intake to cause hyperglycemia, hypertriglyceridemia, and a lowered HDL cholesterol. In obese patients with type 2 disease, glucose and lipid goals join weight loss as the focus for therapy. These patients are advised to limit their carbohydrate intake by substituting noncholesterologenic monounsaturated oils such as olive oil, or the oils in nuts and avocados. This maneuver is also indicated in patients with type 1 diabetes on intensive insulin regimens in whom near-normoglycemic control is less achievable on diets higher in carbohydrate content. The current recommendations for both types of diabetes continue to limit cholesterol to 300 mg daily and advise a daily protein intake of 10–20% total calories. They suggest that saturated fat be no higher than 8–9% of total calories, with a similar proportion of polyunsaturated fat, and that the remainder of the caloric needs be made up of an individualized ratio of monounsaturated fat and of carbohydrate containing 20–35 g dietary fiber. Previous recommendations of polyunsaturated fat supplements have been revised because of their potential hazards. Polyunsaturated fatty acids appear to promote oxidation of LDL and lower HDL cholesterol, both of which may contribute to atherogenesis; furthermore, in large quantities during supplementation, they may promote carcinogenesis. Poultry, veal, and fish continue to be recommended as a substitute for red meats for keeping saturated fat content low. Stearic acid is the least cholesterologenic saturated fatty acid, because it is rapidly converted to oleic acid—in contrast to palmitic acid (found in animal fat as well as in coconut oil), which is a major substrate for cholesterol formation. In contrast to previous recommendations, the present ADA position statement that there is no evidence that reducing protein intake below 10% of total caloric intake (~ 0.8 g/kg/d) is of any benefit in patients with nephropathy with renal impairment, and in fact the investigators believe it may be detrimental.

Exchange lists for meal planning can be obtained from the ADA. Their Internet address is http://www.eatright.org.

Special Considerations in Dietary Control

Dietary Fiber

Plant components such as cellulose, gum, and pectin are indigestible by humans and are termed dietary "fiber." **Insoluble fibers** such as cellulose or hemicellulose, as found in bran, tend to

increase intestinal transit time and may have beneficial effects on colonic function. In contrast, **soluble fibers** such as gums and pectins, as found in beans, oatmeal, or apple skin, tend to decrease gastric and intestinal transit so that glucose absorption is slower and hyperglycemia is diminished. Although the ADA diet does not require insoluble fiber supplements such as added bran, it recommends foods such as oatmeal, cereals, and beans with relatively high soluble fiber content as stable components of the diet in patients with diabetes. High soluble fiber content in the diet may also have a favorable effect on blood cholesterol levels.

Sweeteners

The nonnutritive sweetener **saccharin** is widely used as a sugar substitute (Sweet 'N Low) and continues to be available in certain foods and beverages despite warnings by the Food and Drug Administration (FDA) about its potential long-term bladder carcinogenicity. The latest position statement of the ADA concludes that all non-nutritive sweeteners that have been approved by the FDA are safe for consumption by all people with diabetes.

Aspartame (NutraSweet) may prove to be the safest sweetener for use in diabetic patients; it consists of two major amino acids, aspartic acid and phenylalanine, which combine to produce a nutritive sweetener 180 times as sweet as sucrose. A major limitation is its heat lability, which precludes its use in baking or cooking. Sucralose (Splenda) and acesulfame potassium (Sunett, Sweet One, DiabetiSweet) are two other nonnutritive sweeteners approved by the FDA as safe for general use. They are both highly stable and, in contrast to aspartame, can be used in cooking and baking.

Other sweeteners such as sorbitol and fructose have recently gained popularity. Except for acute diarrhea induced by ingestion of large amounts of sorbitol-containing foods, their relative risk has yet to be established. **Fructose** represents a "natural" sugar substance that is a highly effective sweetener. It induces only slight increases in plasma glucose levels and does not require insulin for its utilization. However, because of potential adverse effects of large amounts of fructose (up to 20% of total calories) on raising serum cholesterol and LDL cholesterol, the ADA believes that it may have no overall advantage as a sweetening agent in the diabetic diet. This does not preclude, however, ingestion of fructose-containing fruits and vegetables or fructose-sweetened foods in moderation.

Agents for the Treatment of Hyperglycemia

The drugs for treating type 2 diabetes, other than insulin, fall into five categories: (1) Drugs that act on the sulfonylurea receptor complex of the beta cell. Sulfonylureas remain the most widely prescribed drugs for treating hyperglycemia. The meglitinide analog repaglinide and the D-phenylalanine derivative nateglinide also bind the sulfonylurea receptor and stimulate insulin secretion. (2) Drugs that principally lower glucose levels by their actions on liver, skeletal muscle or adipose tissue. Metformin works primarily in the liver. The peroxisome proliferator-activated receptor agonists (PPARs) rosiglitazone and pioglitazone appear to have their main effects on skeletal muscle and adipose tissue. (3) Drugs that principally affect absorption of glucose. The α-glucosidase inhibitors acarbose and miglitol are currently available drugs in this class. (4) Drugs that mimic incretin effects or prolong incretin action. Exenatide and the DPP-IV

inhibitors fall into this category. (5) Other drugs include pramlintide, which lowers glucose by suppressing glucagon and slowing gastric emptying.

Drugs that Stimulate Insulin Secretion

These drugs bind to the sulfonylurea receptor complex of the beta cell.

Sulfonylureas

The primary mechanism of action of the sulfonylureas is to stimulate insulin release from pancreatic β cells.

Mechanism of Action

Specific receptors on the surface of pancreatic β cells bind sulfonylureas (glyburide with the greatest affinity and tolbutamide with the least). It has been shown that activation of these receptors closes potassium channels, resulting in depolarization of the β cell. This depolarized state permits calcium to enter the cell and actively promote insulin release (Figure 18–8).

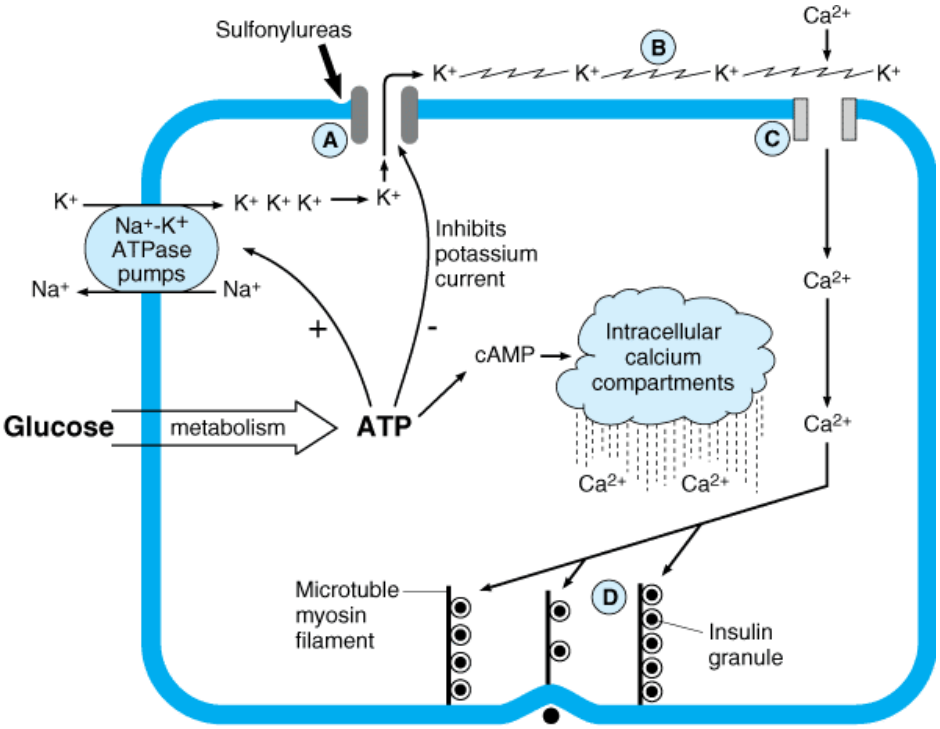


Figure 18-8. Proposed mechanism for sulfonylurea stimulation of insulin release by the pancreatic β cell. Energy-dependent pumps maintain a high intracellular concentration of potassium (K^+). In the resting β cell, K^+ diffuses from the cell through non-energy-dependent K^+ channels (A). This current of K^+ ions generates an electrical potential that polarizes the resting cell membrane (B) and closes a voltage-gated calcium channel (C), thereby preventing extracellular calcium from entering the cell. When sulfonylureas bind to a specific receptor on the K^+ channel (or when glucose metabolism generates ATP), the K^+ channel closes. This depolarizes the cell, allowing calcium to enter and cause microtubules to contract (D), moving insulin granules to the cell surface for exocytosis.

Sulfonylureas

See Table 18–13.

Table 18–13. Drugs for Treatment of Type 2 Diabetes.

Drug	Tablet Size	Daily Dose	Duration of Action (h)
Sulfonylureas			
Tolbutamide (Orinase)	250 and 500 mg	0.5–2 g in 2 or 3 divided doses	6–12
Tolazamide (Tolinase)	100, 250, and 500 mg	0.1–1 g as single dose or in 2 divided doses	Up to 24
Acetohexamide (Dymelor)	250 and 500 mg	0.25–1.5 g as single dose or in 2 divided doses	8–24
Chlorpropamide (Diabinese)	100 and 250 mg	0.1–0.5 g as single dose	24–72
Glyburide			
(DiaBeta, Micronase)	1.25, 2.5, and 5 mg	1.25–20 mg as single dose or in 2 divided doses	Up to 24
(Glynase)	1.5, 3, and 6 mg	1.5–18 mg as single dose or in 2 divided doses	Up to 24
Glipizide			
(Glucotrol)	5 and 10 mg	2.5–40 mg as single dose or in 2 divided doses on an empty stomach	6–12
(Glucotrol XL)	5 and 10 mg	Up to 20 or 30 mg daily as a single dose	Up to 24
Gliclazide (not available in US)	80 mg	40–80 mg as single dose; 160–320 mg as divided dose	12
Glimepiride (Amaryl)	1, 2, and 4 mg	1–4 mg as single dose	Up to 24
Meglitinide analogs			
Repaglinide (Prandin)	0.5, 1, and 2 mg	4 mg in two divided doses given 15 minutes before breakfast and dinner	3
D-Phenylalanine			
Nateglinide (Starlix)	60 and 120 mg	60 or 120 mg 2 times a day before meals	1.5
Biguanides			
Metformin (Glucophage)	500, 850, and 1000 mg	1–2.5 g; one tablet with meals 2 or 3 times daily	7–12
Extended-release metformin (Glucophage XR)	500 mg	500–2000 mg once a day	Up to 24
Thiazolidinediones			

Rosiglitazone (Avandia)	2, 4, and 8 mg	4–8 mg daily (can be divided)	Up to 24
Pioglitazone (Actos)	15, 30, and 45 mg	15–45 mg daily	Up to 24
α-Glucosidase inhibitors			
Acarbose (Precose)	50 and 100 mg	75–300 mg in 3 divided doses with first bite of food	4
Miglitol (Glyset)	25, 50, and 100 mg	75–300 mg in 3 divided doses with first bite of food	4
Incretins			
Exenatide	5 and 10 g	5 µg by injection within 1 hour of breakfast and dinner. Increase to 10 µg twice a day after about a month. Refrigerate between uses.	6
Sitagliptin	25, 50, and 100 mg	100 mg orally once a day either alone or in combination with metformin or a thiazolidinedione. Reduce dose to 50 mg if calculated creatinine clearance is 30 to 50 mL/min. Give 25 mg daily if creatinine clearance less than 30.	24
Others			
Pramlintide	5-mL vial containing 0.6 mg/mL	For insulin-treated type 2 patients, start at 60-µg dose three times a day (10 units on U100 insulin syringe) and increase to 120 µg three times a day (20 units) if patient has no nausea for 3 to 7 days. Give immediately before meal. For type 1 patients, start at 15 µg three times a day (2.5 units on U100 insulin syringe) and increase by increments of 15 µg to a maximum of 60 µg three times a day as tolerated. Lower insulin dose by 50% on initiation of therapy to avoid hypoglycemia.	3

Drugs that Principally Lower Glucose Levels

Biguanides

Unlike sulfonylureas, the biguanides (Table 18–13) do not require functioning pancreatic β cells for reduction of hyperglycemia. **Metformin,** a biguanide that is much less likely to produce lactic acidosis, has replaced phenformin in the treatment of diabetic patients.

Clinical Pharmacology

Metformin's primary action is on the liver, reducing hepatic gluconeogenesis by activating adenosine monophosphate-activated protein kinase (AMPK), which acts as an intracellular energy sensor and in the liver has a critical role regulating gluconeogenesis. LKB1 is a protein threonine kinase that phosphorylates and activates AMPK. It was recently reported that deletion of LKB1 function in the liver results in hyperglycemia with increased gluconeogenic and lipogenic gene expression. The deletion of LKB1 also eliminated the glucose lowering effect of metformin, providing genetic support for the hypothesis that metformin lowers glucose levels by AMP kinase activation. Metformin has a half-life of 1.5–3 hours, is not bound to plasma proteins, and is not metabolized in humans, being excreted unchanged by the kidneys.

Metformin is dispensed as 500 mg, 850 mg, and 1000 mg tablets. A 500 mg extended-release preparation is also available. The dosage range is from 500 mg to a maximum of 2550 mg daily, with the lowest possible effective dose being recommended. Eighty-five percent of the maximal glucose-lowering effect is achieved by a daily dose of 1500 mg, and there is little benefit from giving more than 2000 mg daily. It is important to begin with a low dose and increase the dosage very gradually in divided doses—taken with meals—to reduce minor gastrointestinal upsets. A common schedule would be one 500 mg tablet three times a day with meals or one 850 mg or 1000 mg tablet twice daily at breakfast and dinner. The maximum recommended dose is 850 mg three times a day. One to four tablets of the extended-release preparation can be given once a day.

Adverse Reactions

The most frequent side effects of metformin are gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal discomfort, diarrhea), which occur in up to 20% of patients. These effects are dose-related, tend to occur at onset of therapy, and often are transient. However, in 3–5% of patients, therapy may have to be discontinued because of persistent diarrheal discomfort. Absorption of vitamin B_{12} appears to be reduced during chronic metformin therapy, and annual screening of serum vitamin B_{12} levels and red blood cell parameters has been encouraged by the manufacturer.

Hypoglycemia does not occur with therapeutic doses of metformin, which permits its description as a "euglycemic" or "antihyperglycemic" drug rather than an oral hypoglycemic agent. Dermatologic or hematologic toxicity is rare.

Drugs that Affect Glucose Absorption

Alpha-Glucosidase Inhibitors

Drugs of this family are competitive inhibitors of intestinal brush border α-glucosidases. Two of these drugs, acarbose and miglitol, are available for clinical use. Both are potent inhibitors of glucoamylase, α-amylase, and sucrase. They are less effective on isomaltase and are ineffective on trehalase or lactase. Acarbose binds 1000 times more strongly to the intestinal disaccharidases than do products of carbohydrate digestion or sucrose.

Acarbose

Acarbose is available as 50 and 100 mg tablets. The recommended starting dose is 50 mg twice daily, gradually increasing to 100 mg three times daily. For maximal benefit on postprandial hyperglycemia, acarbose should be given with the first mouthful of food ingested. In diabetic patients it reduces postprandial hyperglycemia by 30–50%, and its overall effect is to lower the HbA_{1c} by 0.5–1%. The principal adverse effect, seen in 20–30% of patients, is flatulence. This is caused by undigested carbohydrate reaching the lower bowel, where gases are produced by bacterial flora. In 3% of cases, troublesome diarrhea occurs. This gastrointestinal discomfort tends to discourage excessive carbohydrate consumption and promotes improved compliance of patients with type 2 diabetes with their diet prescriptions.

Miglitol

Miglitol is similar to acarbose in terms of its clinical effects. It is indicated for use in diet- or sulfonylurea-treated patients with type 2 diabetes. Therapy is initiated at the lowest effective dosage of 25 mg three times a day. The usual maintenance dose is 50 mg three times a day, although some patients may benefit from increasing the dose to 100 mg three times a day. Gastrointestinal side effects occur as with acarbose.

Incretins

Oral glucose provokes a 3- to 4-fold higher insulin response than an equivalent dose of glucose given intravenously. This is because the oral glucose causes a release of gut hormones, principally GLP-1 and glucose-dependent insulinotropic polypeptide (GIP1), that amplify the glucose-induced insulin release. This "incretin effect" is reduced in patients with type 2 diabetes. GLP-1 secretion (but not GIP1) is impaired in patients with type 2 diabetes, and when GLP1 is infused in patients with type 2 diabetes, it stimulates insulin secretion and lowers glucose levels. GLP-1, unlike the sulfonylureas, has only a modest insulin stimulatory effect at normoglycemic concentrations. This means that GLP-1 administration has a lower risk of causing hypoglycemia than the sulfonylureas.

GLP-1, in addition to its insulin stimulatory effect, also has a number of other pancreatic and extrapancreatic effects. It suppresses glucagon secretion. GLP-1 acts on the stomach delaying gastric emptying.

Insulin

Insulin is indicated for individuals with type 1 diabetes as well as for those with type 2 diabetes whose hyperglycemia does not respond to diet therapy and oral hypoglycemic drugs.

Insulin replacement in patients with type 1 diabetes has been less than optimal because subcutaneous injections cannot completely reproduce the normal physiologic pattern of insulin secretion into the portal vein. With the help of appropriate modifications of diet and exercise and careful monitoring of capillary blood glucose levels at home, however, it is possible to achieve acceptable control of blood glucose by using multiple injections of short-acting and longer-acting insulins. In some patients, a portable insulin infusion pump may be required for optimal control.

With the development of highly purified human insulin preparations, immunogenicity has been markedly reduced, thereby decreasing the incidence of therapeutic complications such as insulin allergy, immune insulin resistance, and localized lipoatrophy at the injection site.

Transplantation

Pancreas transplantation at the time of renal transplantation is becoming more widely accepted. Patients undergoing simultaneous pancreas and kidney transplantation have an 85% chance of pancreatic graft survival and a 92% chance of renal graft survival after 1 year. Pancreatic transplantation in the absence of a need for renal transplantation should be considered only in those rare patients who fail all other insulin therapeutic approaches and who have frequent severe hypoglycemia or who have life-threatening complications related to their lack of metabolic control.

Islet cell transplantation is a minimally invasive procedure, and investigators in Edmonton, Canada, have reported initial insulin independence in a small number of patients with type 1 diabetes who underwent this procedure. Using islets from multiple donors and steroid-free immunosuppression, percutaneous transhepatic portal vein transplantation of islets was achieved in more than 20 subjects. Although all of the initial subjects were able to achieve insulin independence post-transplantation, some for more than 2 years of follow-up, a decline in insulin secretion has occurred with time, and the subjects have again required supplemental insulin. All patients had complete correction of severe hypoglycemic reactions, leading to a marked improvement in overall quality of life. Even if long-term insulin independence is demonstrated, wide application of this procedure for the treatment of type 1 diabetes is limited by the dependence on multiple donors and the requirement for potent long-term immunotherapy.

Acute Complications of Diabetes Mellitus

Hypoglycemia

Hypoglycemic reactions are the most common complications that occur in patients with diabetes who are treated with insulin. They may also occur in patients who take oral sulfonylureas, especially older patients or those with impaired liver or kidney function. Hypoglycemia may result from delay in taking a meal or from unusual physical exertion without supplemental calories or a decrease in insulin dose.

Clinical Features
Signs and symptoms of hypoglycemia may be divided into those resulting from neuroglycopenia (insufficient glucose for normal central nervous system function leading to confusion and coma) and those resulting from stimulation of the autonomic nervous system. There is great variation in the pattern of hypoglycemic signs and symptoms from patient to patient; however, individual patients tend to experience the same pattern from episode to episode. In older diabetic patients, in patients with frequent hypoglycemic episodes, and in those with diabetic autonomic neuropathy, autonomic responses may be blunted or absent, so that hypoglycemia may be manifested only by signs and symptoms of neuroglycopenia. The gradual onset of hypoglycemia with intermediate-acting or long-acting insulin also makes recognition more difficult in older patients.

Neuroglycopenia
Signs and symptoms of neuroglycopenia include mental confusion; this may be followed by bizarre antagonistic behavior. dizziness, coma, and even death may occur with profound hypoglycemia. Full recovery of central nervous system function does not always occur if treatment is delayed.

Autonomic Hyperactivity
Signs and symptoms of autonomic hyperactivity can be both adrenergic (tachycardia, palpitations, sweating) and parasympathetic (nausea, hunger). Except for sweating, most of the sympathetic symptoms of hypoglycemia are blunted in patients receiving beta-adrenergic receptor blocking agents for angina or hypertension.

Coma

Coma is a *medical emergency* calling for immediate evaluation to determine its cause so that proper therapy can be started. There are several causes of coma that result directly from diabetes mellitus or its treatment. When evaluating a comatose diabetic patient, these must be considered *in addition* to the numerous causes included in the differential diagnosis of coma (e.g., cerebrovascular accidents, head trauma, intoxication with alcohol or other drugs).

Etiologic Classification of Diabetic Coma
The causes of coma resulting directly from diabetes mellitus or its treatment include the following:

Hyperglycemic Coma

Hyperglycemic Coma may be associated with either severe insulin deficiency (diabetic ketoacidosis) or with mild to moderate insulin deficiency (hyperglycemic, hyperosmolar, nonketotic coma).

Hypoglycemic Coma results from excessive doses of insulin or certain oral hypoglycemic agents (see above).

Lactic Acidosis in diabetic patients is particularly apt to occur in association with severe tissue anoxia, sepsis, or cardiovascular collapse.

Diabetic Ketoacidosis

This acute complication of diabetes mellitus may be the first manifestation of previously undiagnosed type 1 diabetes or may result from increased insulin requirements in type 1 diabetes patients during the course of infection, trauma, myocardial infarction, or surgery. It is a life-threatening medical emergency with a mortality rate just under 5% in individuals under 40 years of age but with a more threatening prognosis in the elderly, who have mortality rates over 20%.

Diabetic ketoacidosis has been found to be one of the more common serious complications of insulin pump therapy. Many patients who monitor capillary blood glucose regularly ignore urine ketone measurements, which would signal the possibility of insulin leakage or pump failure, before serious illness develops.

Patients with type 2 diabetes may also develop ketoacidosis under severe stress such as sepsis, trauma, or major surgery.

Chronic Complications of Diabetes Mellitus

In most patients with diabetes, a number of pathologic changes occur at variable intervals during the course of the disease. These changes involve the vascular system for the most part; however, they also occur in the nerves, the skin, and the lens. In addition to these complications, patients with diabetes have an increased incidence of certain types of infections and may handle their infections less well than the general population.

Classifications of Diabetic Vascular Disease

Diabetic vascular disease is conveniently divided into two main categories: microvascular disease and macrovascular disease.

Microvascular Disease

Disease of the smallest blood vessels, the capillary and the precapillary arterioles, is manifested mainly by thickening of the capillary basement membrane. Microvascular disease involving the retina leads to diabetic retinopathy, and disease involving the kidney causes diabetic

nephropathy. Small vessel disease may also involve the heart, and cardiomegaly with heart failure has been described in diabetic patients.

Macrovascular Disease

Large vessel disease in diabetes is essentially an accelerated form of atherosclerosis. It accounts for the increased incidence of myocardial infarction, stroke, and peripheral gangrene in diabetic patients. Just as in the case of atherosclerosis in the general population, the exact cause of accelerated atherosclerosis in the diabetic population remains unclear. Abnormalities in vessel walls, platelets and other components of the clotting system, red blood cells, and lipid metabolism have all been postulated to play a role. In addition, there is evidence that coexistent risk factors such as cigarette smoking and hypertension may be important in determining the course of the disease.

Gestational Diabetes

Impaired glucose tolerance develops in 2–8% of pregnant women, usually during the second half of gestation. The frequency depends on ethnic group and is increased in those with central obesity or a family history of diabetes. The mechanism of glucose intolerance in lean women results from sluggish first-phase insulin release coupled with excessive insulin resistance. In overweight women with gestational diabetes, insulin resistance increases more than in overweight controls, despite increased circulating insulin levels, so that insulin secretion is actually inadequate in relation to the hyperglycemia.