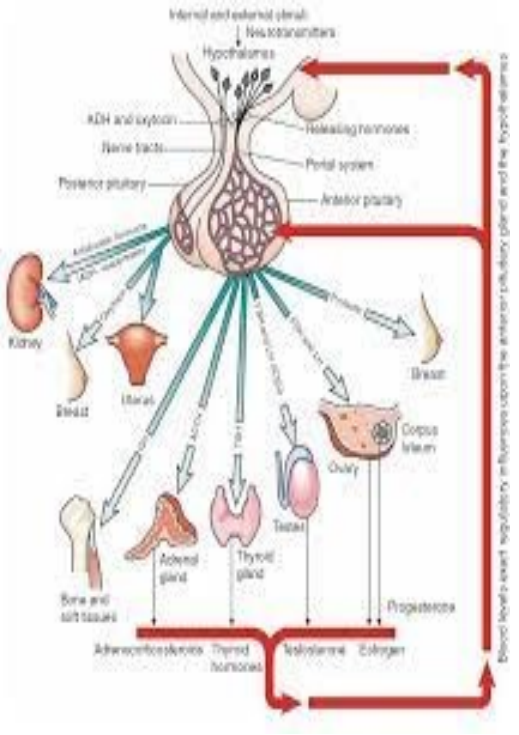
PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM



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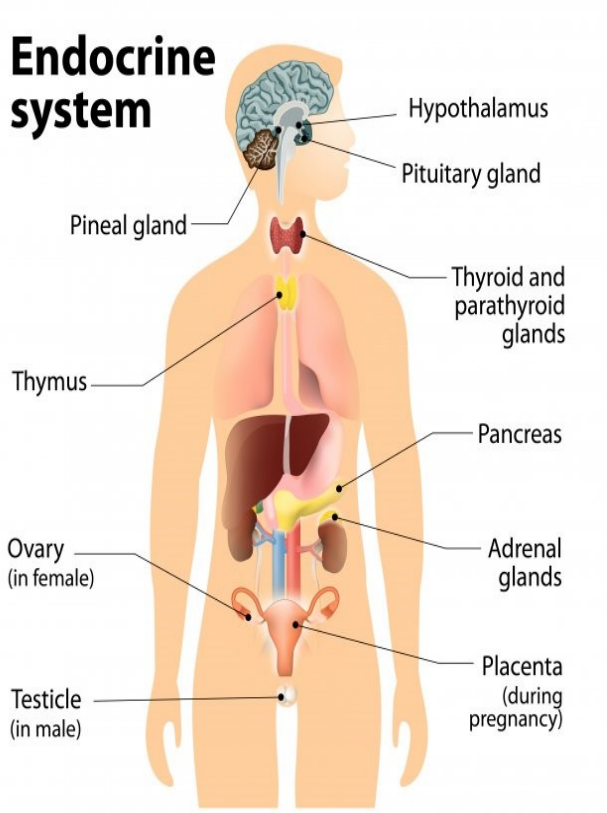
THE ENDOCRINE SYSTEM

- The ENDOCRINE SYSTEM works via chemical messengers (HORMONES) that are secreted directly into the circulatory system to regulate target organ function. The feedback loop works to control the release of these hormones and maintain homeostasis i.e the state of steady conditions vital for life.
- The diagram shows the glands of the endocrine system (Pineal gland, Thalamus/Hypothalamus, Pituitary gland, Thyroid and Parathyroid, Thymus, Adrenal gland, Pancreas, Uterus, Ovaries and Testes)



Endocrine Disorders

- Glands of the endocrine system secrete various hormones that play a key role in maintaining normal homeostasis as well as allowing the body to deal with periods of physiologic stress.

Abnormalities of endocrine glands generally fall into one of the several categories:

1- Hypersecretion

- Excess activity of a specific hormone or hormones
- May be due to overproduction of a hormone due to abnormal glandular function, glandular hypertrophy/hyperplasia or the presence of tumors that secrete hormone

Endocrine Disorders (continued)

2- Hyposecretion

- Reduced activity of a specific hormone or hormones
- May be due to atrophy of glandular tissue or damage from autoimmune attack, infection or neoplasia; may also occur as a result of reduced hormonal stimulation of a gland

3- Altered Responsiveness of a Tissue to a Specific Hormone

- Tissue no longer responds to a specific hormone
- May involve down-regulation of receptors or altered receptor/ secondary messenger function
- Circulating levels of hormone may be normal or even elevated (e.g., type 2 diabetes)

Pancreas

- The pancreas is both an exocrine gland and an endocrine gland.
- Endocrine cells referred to as the *islets of Langerhans are* small clusters scattered throughout the pancreas, surrounded by exocrine cells.
- These islets make up only 2%–3% of the mass of the pancreas. However, their blood supply has been modified so that they receive 5–10 times more blood than the exocrine pancreas.
- The most important hormones produced by the pancreas that regulate glucose metabolism are insulin and glucagon.

DIABETES MELLITUS - introduction

- Diabetes mellitus is the most common endocrine disorder.
- Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower-extremity amputations resulting from atherosclerosis of arteries.
- In the USA, approximately 800,000 new cases of diabetes are diagnosed each year.
- Some risk factors for diabetes mellitus are presented in the table below

Table 11.4 Risk factors for diabetes mellitus

• Obesity (risk for type 2 diabetes)
• Sedentary lifestyle (risk for type 2 diabetes)
• Familial history of diabetes mellitus
• Increasing age
• Ethnicity—high-risk groups include African Americans, Hispanics, and American Indians
• Dietary Factors

DIABETES MELLITUS- definitions

- **Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia.**
- Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both.
- The chronic hyperglycemia and attendant metabolic abnormalities of diabetes are often associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels.

- ***Prediabetes***, which is defined as *elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes* (discussed next); individuals with prediabetes have an elevated risk for development of frank diabetes.
- Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.
- The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

TABLE 77-4 Categorization of Glucose Status

Fasting plasma glucose (FPG)

Normal

- FPG <100 mg/dL (5.6 mmol/L)

Impaired fasting glucose (IFG)

- 100–125 mg/dL (5.6–6.9 mmol/L)

Diabetes mellitus[a]

- FPG ≥126 mg/dL (7.0 mmol/L)

2-Hour postload plasma glucose (oral glucose tolerance test)

Normal

- Postload glucose <140 mg/dL (7.8 mmol/L)

Impaired glucose tolerance (IGT)

- 2-hour postload glucose 140–199 mg/dL (7.8–11.1 mmol/L)

Diabetes mellitus[a]

- 2-hour postload glucose ≥200 mg/dL (11.1 mmol/L)

Simplified Classification of Diabetes

1. *Type 1 Diabetes*
   Beta cell destruction, usually leading to absolute insulin deficiency
2. *Type 2 Diabetes*
   Combination of insulin resistance and beta cell dysfunction
3. *Genetic Defects of Beta Cell Function*
   Maturity-onset diabetes of the young (MODY) (see text)
   Insulin gene mutations
4. *Genetic Defects in Insulin Action*
   Insulin receptor mutations
5. *Exocrine Pancreatic Defects*
   Chronic pancreatitis
   Pancreatectomy
   Cystic fibrosis
   Hemochromatosis
6. *Endocrinopathies*
   Growth hormone excess (acromegaly)
   Cushing syndrome
   Hyperthyroidism
   Pheochromocytoma
7. *Infections*
   Cytomegalovirus infection
   Coxsackievirus B infection
   Congenital rubella
8. *Drugs*
   Glucocorticoids
   Thyroid hormone
   β-Adrenergic agonists
9. *Gestational Diabetes*
   Diabetes associated with pregnancy

Modified from Diagnosis and classification of diabetes mellitus (American Diabetes Association). *Diabetes Care* 37:S81-S90; 2014.

Pathogenesis of Type 1 Diabetes

- **Type 1 diabetes is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous beta cell antigens.**
- **The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells specific for beta cell antigens.**
- This failure of tolerance may result from some combination of defective clonal deletion of self-reactive T cells in the thymus and abnormalities of regulatory T cells (Tregs) that normally dampen effector T-cell responses.
- One consequence of loss of self tolerance is the production of **autoantibodies** against a variety of beta cell antigens, including insulin and the beta cell enzyme glutamic acid decarboxylase, which are detected in the blood of 70% to 80% of patients.

Pathogenesis of Type 2 Diabetes

- Type 2 diabetes is a heterogeneous and multifactorial complex disease that involves interactions of genetics, environmental risk factors, and inflammation.
- Unlike type 1 diabetes, however, there is no evidence of an autoimmune basis.

The two defects that characterize type 2 diabetes are:

(1) A decreased ability of peripheral tissues to respond to insulin (insulin resistance)

(2) Beta cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and Hyperglycemia

- *Insulin resistance* predates the development of hyperglycemia and usually is accompanied by compensatory beta cell hyperfunction and hyperinsulinemia in the early stages of the evolution of diabetes.
- Environmental factors, such as a sedentary lifestyle and dietary habits, unequivocally play a role.
- **Genetic factors** also are involved, as evidenced by a concordance rate of 80% to 90% in monozygotic twins, which is even greater than that for type 1 diabetes (approximately 50% concordance rates in twins), suggesting perhaps an even larger genetic component in type 2 diabetes.
- Additional evidence for a genetic basis has emerged from recent large-scale genome-wide association studies, which have identified dozens of susceptibility loci called *diabetogenic genes*. Unlike type 1 diabetes, however, the disease is not linked to genes involved in immune tolerance and regulation.

Insulin Resistance

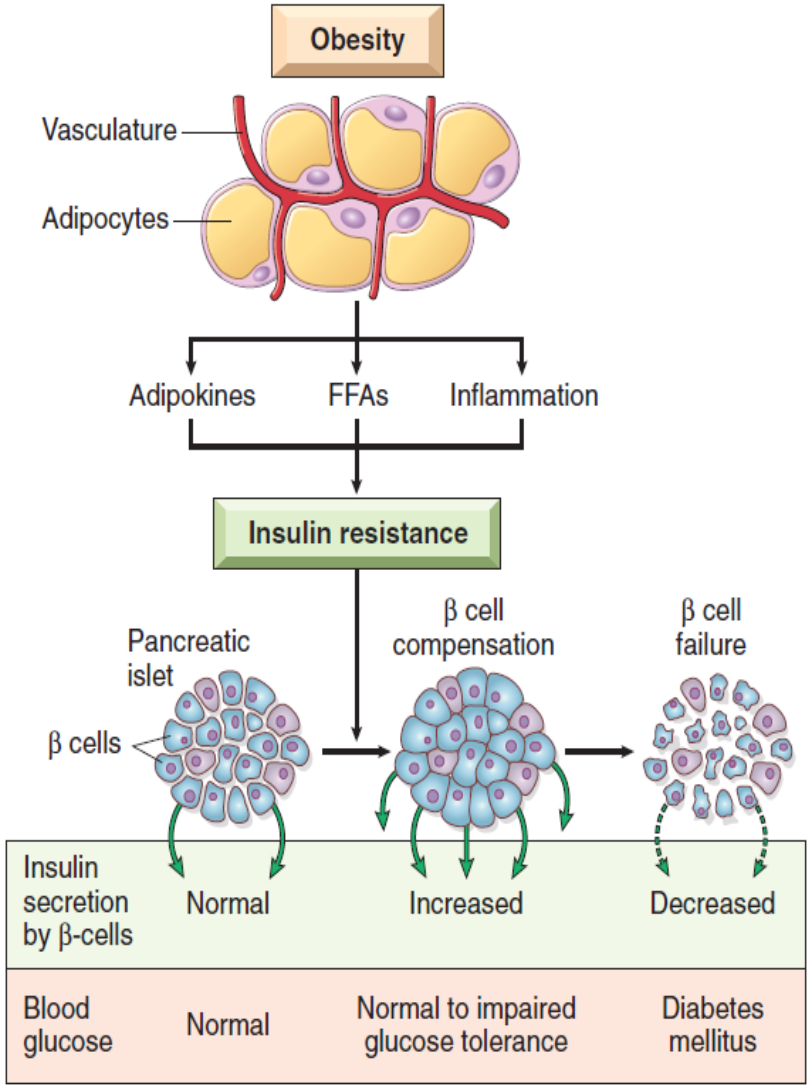
- ***Insulin resistance*** **is defined as the failure of target tissues to respond normally to insulin.**

The liver, skeletal muscle, and adipose tissue *are the major tissues where insulin resistance manifests as follows:*

- ✓ Failure to inhibit endogenous glucose production (gluconeogenesis) in the liver, which contributes to high fasting blood glucose levels
- ✓ Abnormally low glucose uptake and glycogen synthesis in skeletal muscle following a meal, which contributes to a high postprandial blood glucose level
- ✓ Failure to inhibit hormone-sensitive lipase in adipose tissue, leading to excess circulating free fatty acids (FFAs), which, exacerbates the state of insulin resistance

Development of type 2 diabetes.

- Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue.
- Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin.
- However, at some point, β cell compensation is followed by β cell failure, and diabetes ensues.
- *Insulin resistance and pancreatic β-cell failure*



ACUTE MANIFESTATIONS

- **3 P's** → **P**olydipsia, **P**olyuria, **P**olyphagia
- Weight loss
- Diabetic ketoacidosis DKA (type 1)
- Hyperosmolar hyperglycemic state (type 2)
- Rarely, can be caused by unopposed secretion of Growth hormone (GH) and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).
- General weakness
- Skin Sepsis (pruritis of external genitalia)
- Poor wound healing

CHRONIC COMPLICATIONS

- **Nonenzymatic glycation:**

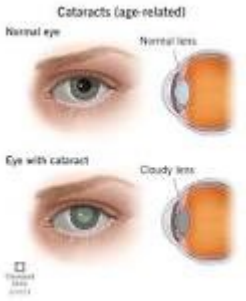
✓Small vessel disease (hyaline arteriolosclerosis: accumulation of various serum proteins in the subendothelial space often extending into the media), retinopathy, neuropathy, nephropathy.

✓Large vessel disease (atherosclerosis), CAD, cerebrovascular disease, peripheral vascular disease. MI is the most common cause of death.

- **Osmotic damage** (sorbitol accumulation in organs with aldose reductase and or absent sorbitol dehydrogenase):

✓Neuropathy: motor, sensory (glove and stocking distribution), autonomic degeneration (eg, GERD, gastroparesis, diabetic diarrhea).

✓Cataracts (a cloudy area in the lens of your eye).



Type 1 vs type 2 diabetes mellitus

	Type 1	Type 2
1° DEFECT	Autoimmune T-cell–mediated destruction of β cells	↑ resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMON)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes, HLA-DR4 and -DR3 (4 – 3 = type 1)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	↓	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	↓	↑ initially, but ↓ in advanced disease
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide deposits

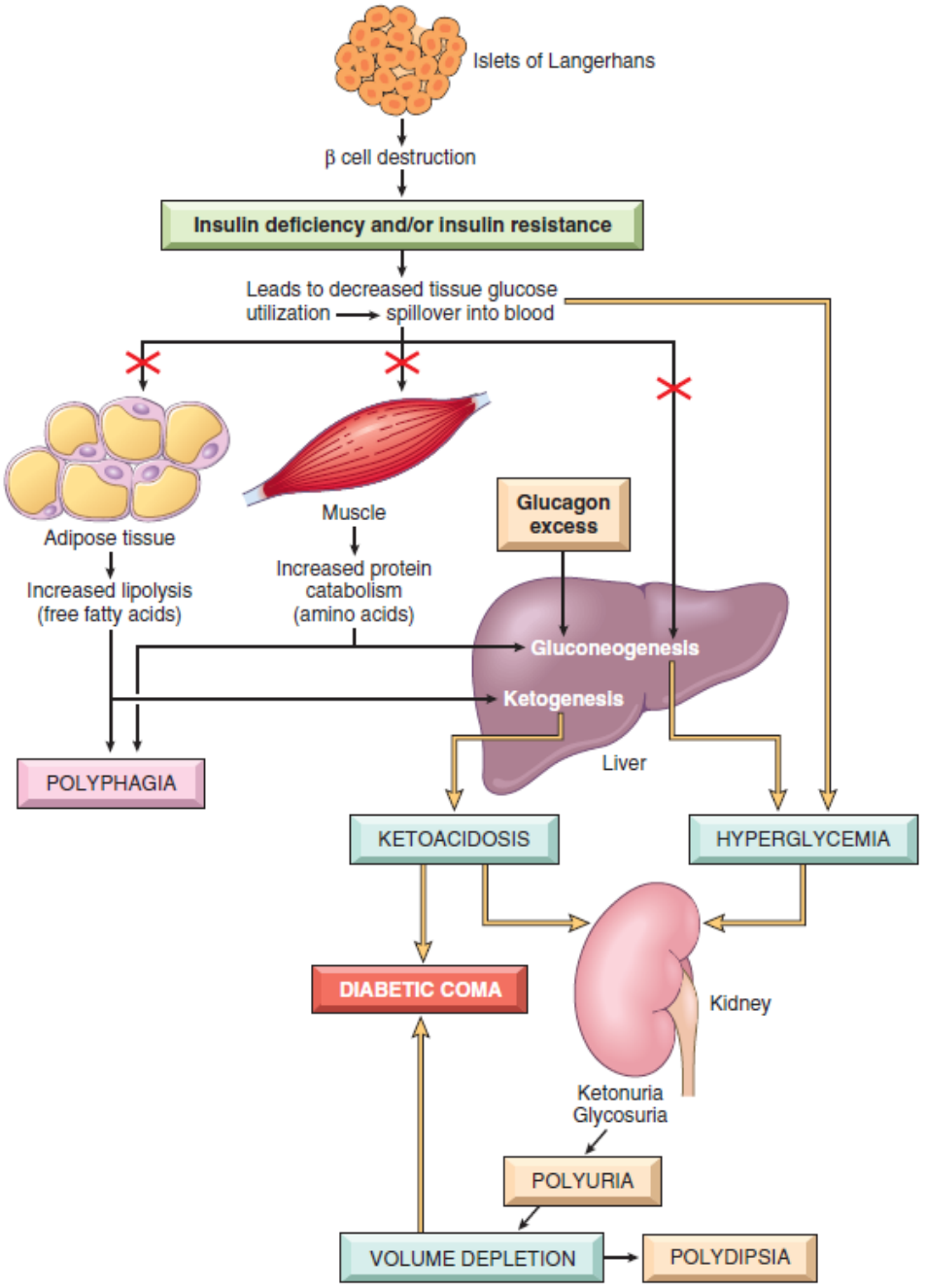
Hyperglycemic emergencies

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
PATHOGENESIS	Insulin noncompliance or ↑ requirements due to ↑ stress (eg, infection) → lipolysis and oxidation of free fatty acids → ↑ ketone bodies (β-hydroxybutyrate > acetoacetate). Insulin deficient, ketones present.	Profound hyperglycemia → excessive osmotic diuresis → dehydration and ↑ serum osmolality → HHS. Classically seen in older patients with type 2 DM and limited ability to drink. Insulin present, ketones deficient.
SIGNS/SYMPTOMS	DKA is Deadly: Delirium/psychosis, Kussmaul respirations (rapid, deep breathing), Abdominal pain/nausea/vomiting, Dehydration. Fruity breath odor due to exhaled acetone.	Thirst, polyuria, lethargy, focal neurologic deficits, seizures.
LABS	Hyperglycemia, ↑ H^+, ↓ HCO_3^- (↑ anion gap metabolic acidosis), ↑ urine and blood ketone levels, leukocytosis. Normal/↑ serum K^+, but depleted intracellular K^+ due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↑ K^+ loss in urine → total body K^+ depletion.	Hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), normal pH (no acidosis), no ketones. Normal/↑ serum K^+, ↓ intracellular K^+.
COMPLICATIONS	Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias.	Can progress to coma and death if untreated.
TREATMENT	IV fluids, IV insulin, and K^+ (to replete intracellular stores). Glucose may be required to prevent hypoglycemia from insulin therapy.	

→ Sequence of metabolic derangements leading to diabetic coma in type 1 diabetes mellitus.

→ An absolute insulin deficiency leads to a catabolic state, eventuating in ketoacidosis and severe volume depletion.

→These derangements bring about sufficient central nervous system compromise to cause coma and, eventually, death if left untreated.



Hypoglycemia in diabetes mellitus

- Hypoglycemia: is a blood sugar level below 70 milligrams per deciliter (mg/dL), or 3.9 millimoles per liter (mmol/L)
- Usually occurs in patients treated with insulin or insulin secretagogues (eg, sulfonylureas, meglitinides) in the setting of high-dose treatment, inadequate food intake, and/or exercise.

➢ **Neurogenic (autonomic- sympathetic activation) symptoms:** diaphoresis, tachycardia, tremor, anxiety, hunger. Allow perception of glucose (hypoglycemia awareness).

➢ **Neuroglycopenic symptoms:** altered mental status, seizures, death due to insufficient glucose in CNS. **Behavioral:** May occur in the absence of preceding neurogenic symptoms in patients with attenuated autonomic response (hypoglycemia unawareness).

Treatment: simple carbohydrates (eg, glucose tablets, fruit juice), IM glucagon, IV dextrose.

Classification of Hypoglycemia in Diabetes

Level	Glycemic criteria	
Hypoglycemia alert value (level 1)	≤70 mg/dl (3.9 mmol/L)	Sufficiently low for treatment with fast acting carbohydrate and dose adjustment of glucose lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dl (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery