ENDOCRINE DISEASES OF PANCREAS

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DIABETES MELLITUS

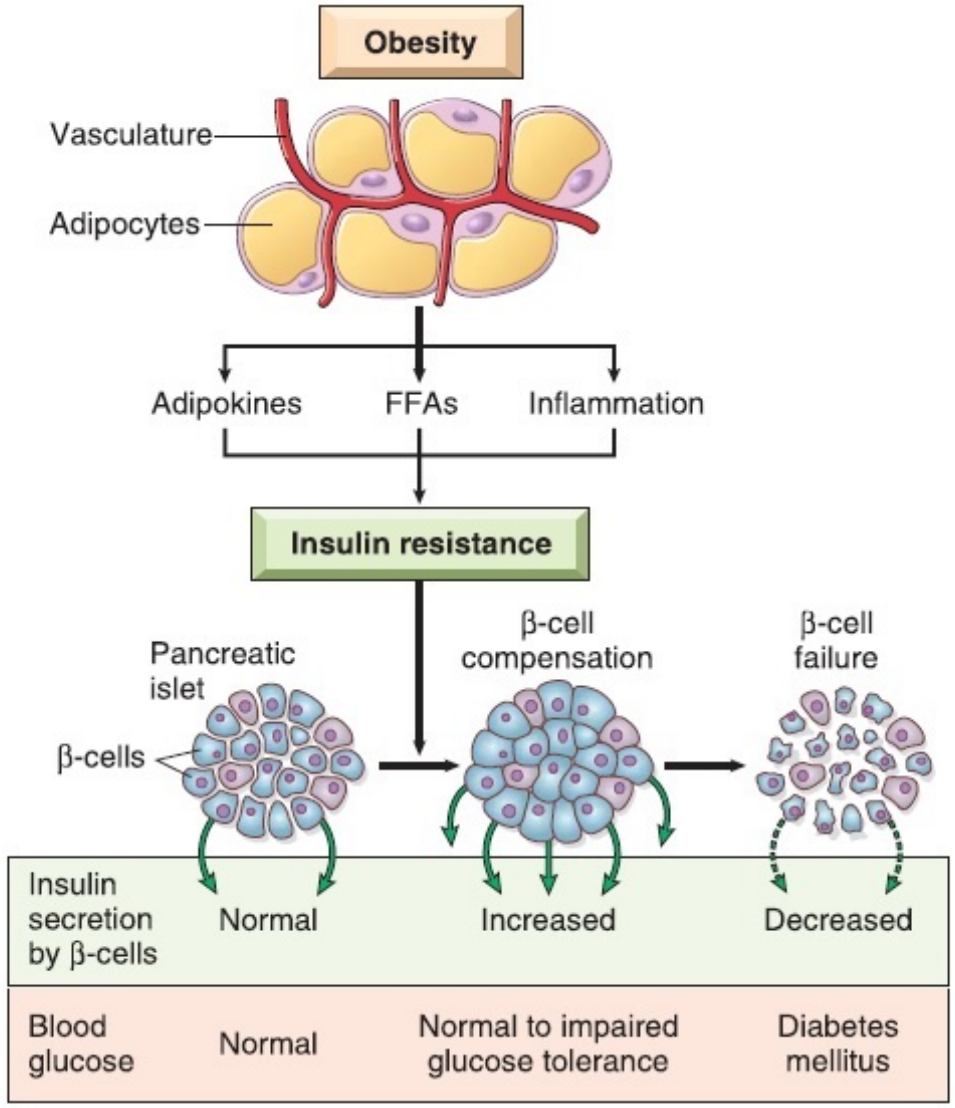
- Group of metabolic disorders results in chronic hyperglycemia
- Multi-organ damage (kidneys, retina, cardiovascular)
- Very common
- Increased morbidity and mortality
- Risk factors: family history, life-style, obesity

TYPE-1 DIABETES

- 5% of all DM cases
- Autoimmune destruction of pancreatic β-cells □ deficiency in insulin
- Commonly affects children and adolescents
- Symptoms tend to appear rapidly, although the cell damage takes time
- Associated with HLA-DR3, DR-4, DQ8
- Polymorphism in CTLA4 and PTPN22 genes (similar to autoimmune thyroiditis)
- Environmental factor: virus epitopes, only 50% of monozygotic twins share DM-1
- Failure of self-tolerance in T-cells for islet antigens
- Other less common causes DM: chronic pancreatitis, pancreatic carcinoma, cystic fibrosis, hemochromatosis, infections by cytomegalovirus, coxsackie virus, congenital rubella, systemic amyloidosis

TYPE-2 DIABETES

- >90% of DM cases
- Peripheral resistance to insulin
- Inadequate response by β-cells to overcome this resistance
- Patients are commonly obese, adults, insidious onset
- Impaired function of incretins (peptides secreted form small intestine following glucose feeding, promotes secretion of insulin from B-cells)
- Genetic factors: 90% concordance rate in identical twins, 10x risk in first degree relative. Genes related to adipose-tissue distribution in body, B-cell function and obesity
- Environmental factors: central obesity is most important, then sedentary life-style, circadian-disruption (sleep disorder)



Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids *(FFAs)*, 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.

- B-cell dysfunction results from:
- Excess free fatty acids (due to increased activity of lipase enzyme in adipose tissue)
- Hyperglycemia: toxic effect
- Amyloid deposition in B-cells: seen in 90% of long-standing DM-2
- Genetic susceptibility

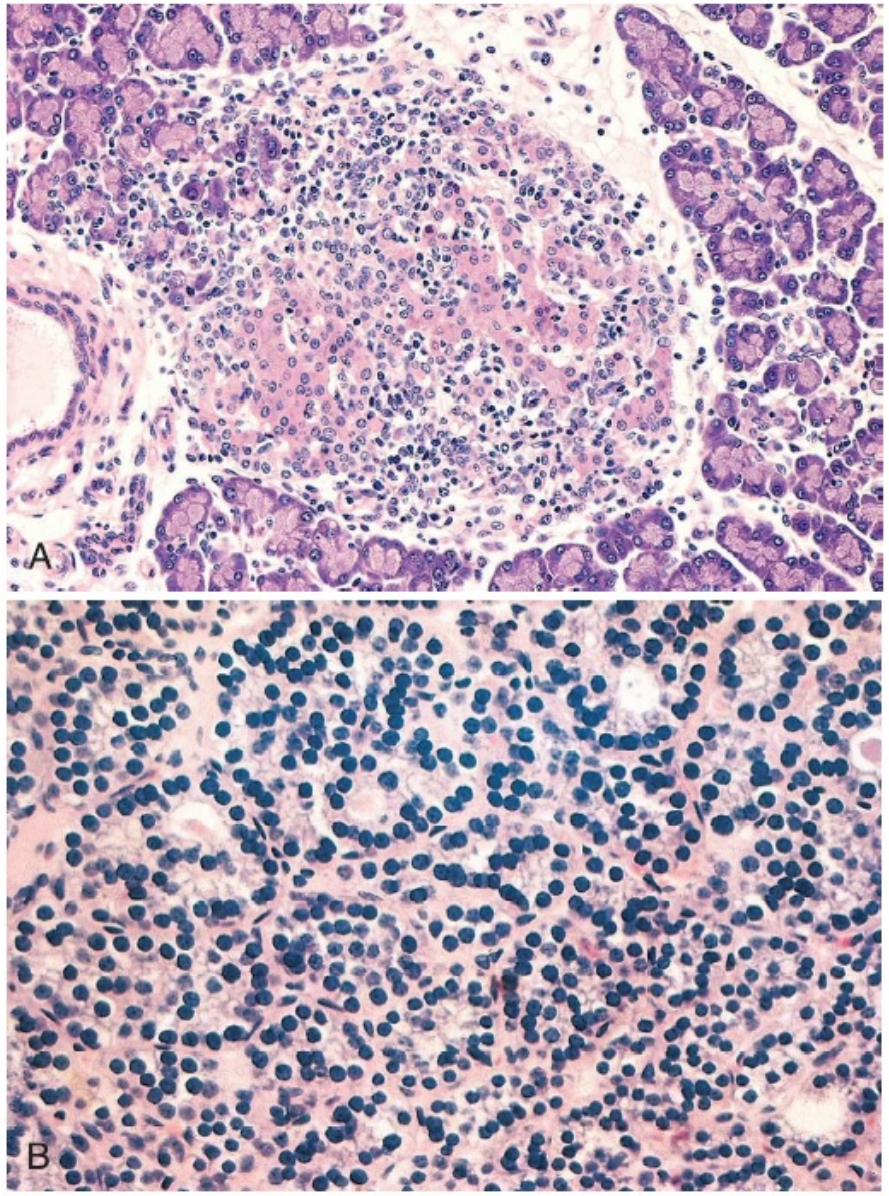


Figure 24.35 (A) Insulitis, shown here from a rat (BB) model of autoimmune diabetes, also seen in type 1 human diabetes. (B) Amyloidosis of a pancreatic islet in type 2 diabetes.

OTHER CAUSES OF TYPE-2 DIABETES

- Endocrinopathies: Cushing syndrome, acromegaly, hyperthyroidism, pheochromocytoma, glucagonoma
- Drugs: steroids, β-agonists, phenytoin, thiazide
- Certain syndromes: Down, Turner
- Gestational diabetes (5% of pregnant women, due to increased steroid hormones)

MONOGENIC FORMS OF DM

- Maturity-onset diabetes of the young (MODY)
- Resemble DM-2
- Results from germline loss of function mutation in glucokinase (GCK) genes, affects glucose metabolism and insulin secretion
- Rarely: mutation is insulin-receptor synthesis, binding or activity, associated with hyperinsulinemia and skin pigmentation

HYPERGLYCEMIA EFFECT ON TISSUE

- (1) **Advanced glycation end products (AGE):** non-enzymatic glucose addition to molecules results in activation of AGE signaling, resulting in cytokines and growth factors release causing vascular proliferation (retinopathy) and basement membrane deposition (nephropathy), release of reactive oxygen species, procoagulant activity and proliferation of vascular smooth muscle cells
- (2) **Activation of protein kinase C:** results in activation of plasminogen activator inhibitor-1 (procoagulant effect)
- (3) **Oxidative stress and disturbance in polyol pathways**: occurs in tissues that do not require insulin to take glucose (nerves, lenses, kidneys, blood vessels): hyperglycemia results in increased intracellular glucose that ends up with depletion of NADPH, making these cells susceptible to oxidative stress

CLINICAL PRESENTATION

- Polyurea, polydipsia (osmotic effect), polyphagia, weight loss (catabolic effect)
- Chronic systemic complications results from chronic hyperglycemia
- Macrovascular: myocardial infarction, stroke, lower limb ischemia
- Microvascular: retinopathy, nephropathy, neuropathy
- Varies among patients
- Tight control of blood glucose level prevents complications

DIABETIC KETOACIDOSIS

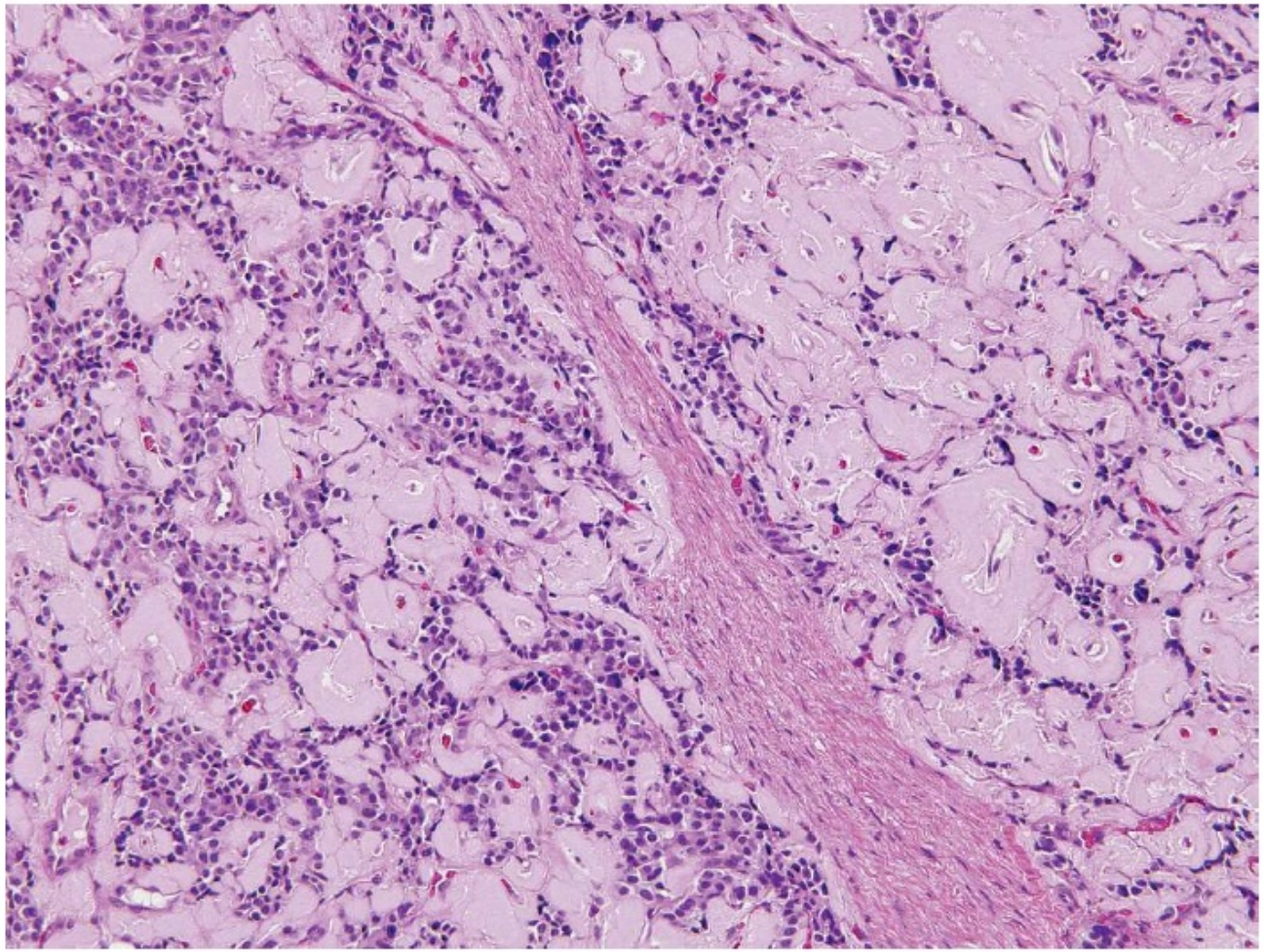
- Mostly seen in type-1 DM
- Failure to take insulin, stress, infections, trauma
- May occur in type-2 DM with severe stress (release of epinephrin which blocks residual insulin and stimulates release of glucagon).
- Severe hyperglycemia causes osmotic diuresis and dehydration
- Insulin deficiency promotes ketone body synthesis, when severe and accompanied by dehydration, results in metabolic acidosis (fatigue, nausea, vomiting, abdominal pain, difficult breathing, fruity odor, loss of consciousness, coma.

HYPEROSMOLAR HYPERGLYCEMIC STATE

- Affects DM-2
- Osmotic diuresis results in dehydration, if not corrected (stroke, infections, no enough water drinking), results in mental status dysfunction and coma. No ketons are produced.

HYPERINSULINISM (INSULINOMA)

- Most common pancreatic endocrine neoplasm
- Hyperinsulinemia results in hypoglycemic episodes (usually mild)
- In severe forms causes confusion and loss of consciousness
- Mostly single tumor, benign behavior (90%)
- Microscopically appears as giant islets, contain amyloid
- Islet-cell hyperplasia is seen in newborns of diabetic mothers (cause serious hypoglycemia after birth, transient)



Pancreatic endocrine neoplasm ("islet cell tumor"). The neoplastic cells are monotonous and demonstrate minimal pleomorphism or mitotic activity. There is abundant amyloid deposition, characteristic of an insulinoma. Clinically, the patient had episodic hypoglycemia.

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

- Arises in pancreas or duodenum
- Causes severe peptic ulcer, jejunal ulcer
- 50% are malignant
- 25% of cases appear as a part of MEN-1 syndrome (multifocal)