

Acute Pancreatitis: Pancreatitis = inflammation of exocrine pancreas

→ acute pancreatitis ⇒ acute inflammation of exocrine pancreas due to injury to parenchyma of pancreas

Etiology:

① Metabolic:

- Alcoholism
- hyperlipoproteinemia
- Hyperparathyroidism
- Hypercalcemia

② Mechanical:

- Gallstones
- Blunt abdominal trauma
- Ischaemic injury: during surgery (eg: endoscopy with die infection)
- Periapillary neoplasms
- Parasites (Ascariasis, Clonorchis)

③ Drugs & toxins:

- Furosemide, azathioprine
- Insecticides, methanol, OPs

④ Vascular:

- Shock
- Atheroembolism
- Thromboembolism
- Vasculitis

⑤ Genetic: mutation in cationic trypsinogen (PRSS1) & trypsin inhibitor (SPINK1) gene.

⑦ Idiopathic

⑥ Infectious:

- Viral: mumps, coxsackie virus

Alcohol: polymorphism in detoxifying enzyme uridine 5-diphosphate (UDP) glucuronyl transferase increases the risk for alcoholic induced pancreatitis.

Gallstones: frequency of acute pancreatitis is inversely proportional to size of gallstones

Genetic factors: mutations in gene PRSS1, SPINK1, CFTR

Morphological Types of Acute Pancreatitis:

→ interstitial
→ necrotizing
→ haemorrhagic

① Acute Interstitial/Edematous Pancreatitis: mild & reversible

Microscopy: interstitial edema & mild infiltration by polymorphonuclear leukocytes, no necrosis/haemorrhage.

② Acute Necrotizing Pancreatitis:

Gross: ① Pancreas: enlarged & swollen; shows red-black areas of haemorrhage with foci of yellow-white chalky fat necrosis (fat necrosis is due to action of lipase on triglycerides which release fatty acids from the fat cells)

- fatty acids combine with calcium to form insoluble salts (calcium soaps) by a process called saponification
∴ blood Ca^{2+} levels may reduce (sometimes causing neuromuscular irritability)

② Extrapancratic lesions: foci of fat necrosis may be seen in the omentum & mesentery of bowel

- peripancratic tissue / peritoneal cavity may contain a serous, slightly-turbid, brown-tinged fluid & the fluid may show necrotic fat globules (produced by the action of enzymes on adipose tissues)
- ∴ necrotic tissue appears putty-like / like canned dog food.

Microscopy: • edema of interstitial tissue (due to leakage of fluid from microvasculature)

- acute inflammation in interstitial tissue
- enzymatic fat necrosis $\Rightarrow$ granular blue with ghost outlines of necrotic cells
- destruction of pancreatic parenchyma (due to proteolytic digestion)
- destruction of blood vessels (by activated elastase) leading to interstitial haemorrhage.

③ Acute Haemorrhagic Pancreatitis: (peak incidence at 60 years)

Gross: • extensive necrosis, haemorrhage & fat necrosis within pancreatic parenchyma

Pathogenesis:

{ Safety mechanism in pancreas to prevent autoactivation of trypsin: pancreatic secretory trypsin inhibitor (PSTI) (binds with active trypsin & inhibits its activity)

→ Pancreatitis develops due to premature (inappropriate) activation of proteolytic pancreatic enzymes leading to autodigestion.

→ pancreatic enzymes are synthesized in an inactive proenzyme form (trypsinogen, chymotrypsinogen, proelastase) & become active later

→ premature activation (before their secretion from acinar cells) of pancreatic enzymes $\Rightarrow$ pancreatitis

→ Factors activating trypsinogen to trypsin: endotoxins, exotoxins, viral infections, ischemia, anoxia

→ activated trypsin causes many proenzymes to convert to their active form • proelastase $\rightarrow$ elastase (damages elastic fibres of blood vessels) • prophospholipase $\rightarrow$ phospholipase (degrades fat cells).

→ prekallikrein $\xrightarrow{\text{Trypsin}}$ kallikrein $\rightarrow$ activate Hageman factor (XII), clotting & complement systems.

Mechanism of Premature Activation of Pancreatic Enzymes:

① Pancreatic duct obstruction: pancreatic duct obstruction $\rightarrow$ rise in intraductal pressure $\rightarrow$ exacerbation of back-diffusion across ducts $\rightarrow$ rupture of ductules & acini $\rightarrow$ liberation of enzyme-rich fluid in interstitium $\rightarrow$ inappropriate activation of proenzymes $\rightarrow$ injury $\rightarrow$ local inflammation & interstitial edema

→ exacerbation of ischaemic injury to acinar cells

② Primary acinar cell injury: due to viruses (mumps), drugs, alcohol, direct trauma, ischaemia/shock

→ acinar cell injury → inflammation → pancreatic edema, haemorrhage → necrosis

③ Defective Intracellular transport of Proenzymes within Acinar cells: due to metabolic injury, alcohol, duct obstruction (normally digestive enzymes & lysosomal hydrolases are transported in separate pathways)

→ Fusion of lysosome & digestive enzymes within large vacuoles → activation of pancreatic proenzymes → injury

Mechanism of Alcohol-induced Pancreatitis:

① Small ductule obstruction by proteinaceous plugs

② Abnormal sphincter of Oddi

③ Direct toxic effects on acinar cells

④ Increased proteases

Clinical Features: • constant & intense abdominal pain, referred to the upper back • anorexia • nausea, vomiting

Laboratory Findings: • leukocytosis • marked elevation of serum amylase (in first 24 hours) • raised serum lipase (72-96 hours)

• glycosuria • hypocalcaemia • CRP > 130 mg/mL → severe pancreatitis.

[Lipase is a more specific marker than amylase]

Complications:

Local Complications

- sterile pancreatic abscess
- pancreatic pseudocyst
- infection by gram negative organism from alimentary tract.

Systemic Complications

- shock with acute renal tubular necrosis (in first week)
- Acute RDS
- ARF
- diffuse fat necrosis
- hemolysis
- DIC

Chronic Pancreatitis: irreversible damage to pancreatic parenchyma & scar formation.

Definition: chronic inflammation of pancreas $\Rightarrow$ permanent morphologic or functional damage

Etiology: most common cause = alcohol abuse (usually develops in middle-aged males)

- obstruction of pancreatic duct by pseudocysts, calculi, trauma or carcinoma
- hyperparathyroidism (hypercalcemia)
- CFTR gene mutation $\Rightarrow$ decreases bicarbonate secretion by pancreatic ductal cells & promotes protein plugging
 - hereditary pancreatitis
 - idiopathic (20%)
- tropical pancreatitis in Africa & Asia
- autoimmune pancreatitis

Pathogenesis: not clear

$\rightarrow$ repeated attacks of acute pancreatitis may lead to chronic pancreatitis

4 theories:

① Obstruction theory: $\uparrow$ protein concentration $\rightarrow$ precipitation of proteins $\rightarrow$ form ductal plugs $\rightarrow$ calcification of ductal plugs to form calculi $\rightarrow$ further obstruction of pancreatic ducts

② Necrosis-Fibrosis theory: bouts of acute pancreatitis $\rightarrow$ inflammation & scarring $\rightarrow$ obstruction & stasis within ducts $\rightarrow$ stone formation in ducts.

③ Toxic-metabolic theory: toxins $\rightarrow$ direct toxic damage to acinar cells $\rightarrow$ necrosis of cells $\rightarrow$ eventual fibrosis

④ Oxidative Stress theory: oxidative stress either through systemic circulation or through reflux of bile into pancreatic duct $\rightarrow$ generation of free radicals in acinar cells $\rightarrow$

- membrane lipid oxidation & acinar cell necrosis
- recurrent inflammation, tissue damage & fibrosis, fusion of lysosomes & proenzymes
- alcohol abuse

Profibrogenic Chemokines: transforming growth factor β (TGF- β) & platelet derived growth factor (PDGF) are found in chronic pancreatitis

→ They cause activation & proliferation of periacinar myofibroblasts (pancreatic stellate cells) which deposit collagen & ultimately cause fibrosis

Gross:

① Non-obstructive Chronic Pancreatitis: most common form (95%)

- hard, nodular pancreas
- pancreas is enlarged or atrophic
- cut-section shows dilated ducts & calcified concretions (in case of extensive calcification $\Rightarrow$ chronic calcifying pancreatitis)

② Obstructive Chronic Pancreatitis: (due to narrowing/occlusion of pancreatic ducts)

- commonly due to carcinoma & stones in ductal system.

Microscopy:

① Parenchymal fibrosis: large irregular areas of fibrosis

② Atrophy of acini: reduction in number & size of acini (islets of Langerhans are relatively resistant to chronic pancreatitis)

③ Dilation of pancreatic ducts: dilation of interlobular & intralobular ducts & lumen showing protein plugs

④ Alteration in duct epithelium: atrophy / hyperplasia / squamous metaplasia

⑤ Chronic inflammatory infiltrate: infiltration by lymphocytes, plasma cells, macrophages.

Clinical Features: • repeated attacks of abdominal pain / persistent abdominal & back pain • steatorrhoea

• silent until severe functional damage develops:

- pancreatic exocrine insufficiency $\Rightarrow$ weight loss & hypoalbuminaemic edema

- pancreatic endocrine insufficiency $\Rightarrow$ diabetes mellitus

Complications: • Pancreatic pseudocysts • malabsorption, steatorrhoea • secondary diabetes

• risk of developing pancreatic cancer

Pseudocyst of Pancreas: pseudocyst $\Rightarrow$ not true cyst, does not have any epithelial lining

Causes: • complication of acute & chronic pancreatitis • traumatic injury to pancreas

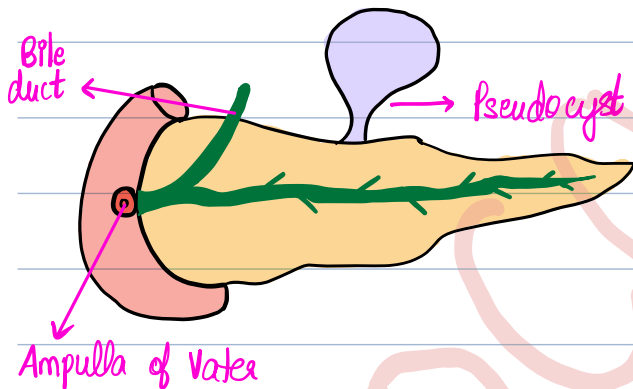
Cysts: • usually single • 2-30 cm diameter • Site: within the substance of pancreas / lesser omental sac / retroperitoneum between stomach & transverse colon or between stomach & liver

• lumen: contains necrotic-haemorrhagic material rich in pancreatic amylase

Microscopy: wall of pseudocysts show non-epithelial-lined fibrous connective tissue & necrotic pancreatic debris

Complications: majority pseudocysts resolve spontaneously

- enlarge & compress/obstruct duodenum or perforate into adjacent structures
- secondary infection $\Rightarrow$ abscess formation
- rarely, may rupture $\Rightarrow$ chemical &/or septic peritonitis



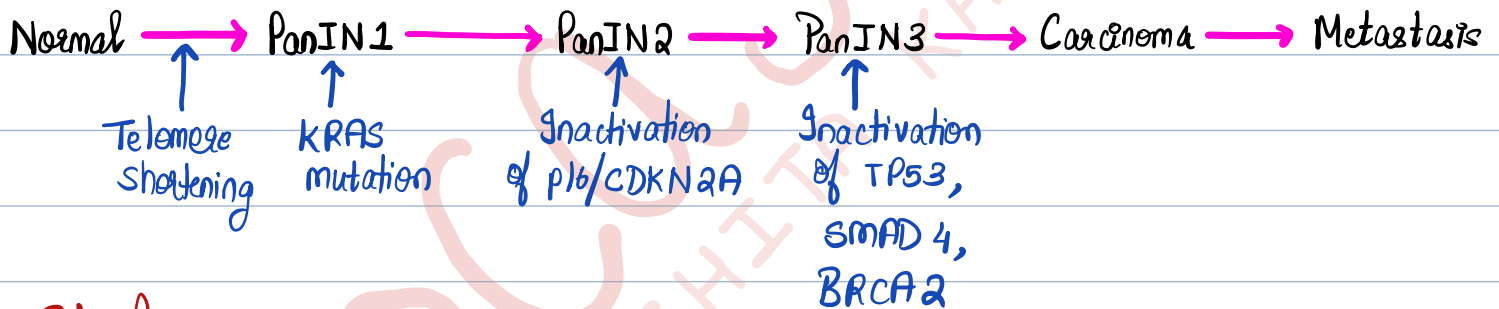
Pancreatic Carcinoma: infiltrating ductal adenocarcinoma of exocrine pancreas is most common

Precursor to Pancreatic Cancer (Pancreatic Intraepithelial Neoplasias - PanINs):

→ progression from non-neoplastic epithelium to well-defined non-invasive lesions in small ducts & ductules to invasive carcinomas

Molecular Carcinogenesis:

- ① Telomere Shortening: in epithelial cells in PanINs
- ② Oncogene KRAS mutation (chromosome 12p)
- ③ Tumor Suppressor gene: inactivating mutations of p16/CDKN2A, mutational inactivation of SMAD4, mutations of TP53.



Etiology:

→ usually found in elderly patients; mostly between 60 - 80 years

- Risk factors:
- Cigarette smoking
 - Alcohol use
 - Consumption of a diet rich in fats
 - Chronic pancreatitis
 - Diabetes mellitus
 - Inherited genetic defects — BRCA2 mutations
 - Mutations in CDKN2A (p16)
 - Mutations in PALLD gene

Morphology:

Location: • Head (60%) • Body (15%) • Tail (5%) • Diffuse (20%)

Gross: hard, stellate, gray-white, poorly delineated, firm masses

Microscopy: • tumor cells form abortive tubular structures or cell clusters & show infiltration

Spread:

① **Local spread (Perineural invasion):** grow along nerves & invade into retroperitoneum

② **Lymphatic spread:** to peripancreatic, gastric, mesenteric, omental lymph nodes

③ **Blood spread:** to liver, lung, bones, adrenals

Clinical Features: • carcinoma of head of pancreas presents

with obstructive jaundice

• pain (usually first symptom)

• advanced stage: weight loss, anorexia, malaise, weakness

• Trousseau's sign (migratory thrombophlebitis):

spontaneously appearing & disappearing thrombosis

— associated malignancies:

1) carcinoma of pancreas

4) Prostatic cancer

2) carcinoma of lung

5) Ovarian cancer

3) GI tract malignancies

6) Lymphoma

Perineural invasion:

• Pancreatic cancer

• Prostate cancer

• Adenocystic carcinoma

• Carcinoma of gallbladder

• Cholangiocarcinoma.

Laboratory Findings:

• raised serum levels of CEA (carcinoembryonic antigen) & CA19-9 antigen

• CT scan

Diabetes Mellitus: group of metabolic disorders having features of hyperglycemia

Normal fasting blood glucose: 70-120 mg/dL

	Euglycemic	Prediabetes	Diabetes
Fasting glucose	< 100 mg/dL	100 - 126 mg/dL	> 126 mg/dL
OGTT	< 140 mg/dL	140 - 200 mg/dL	> 200 mg/dL
HbA _{1c}	< 5.7 %	5.7 - 6.4 %	> 6.5 %

(Prediabetes $\Rightarrow$ impaired glucose tolerance)

Classification:

- Type 1 Diabetes: Juvenile-onset DM / Insulin-Dependent DM (IDDM)
- Type 2 Diabetes: Maturity-onset DM / Non-Insulin-Dependent DM (NIDDM)
- Genetic defects of β -cell function: - Maturity-onset diabetes of young (MODY)
 - neonatal diabetes
- Genetic defects in insulin action
- Exocrine pancreatic defects: - chronic pancreatitis - haematochromatosis
- Endocrinopathies: - Acromegaly - Cushing syndrome - hyperthyroidism
 - pheochromocytoma
- Infections: - Cytomegalovirus - coxsackie B virus
- Drugs: - glucocorticoids - thyroid hormone
- Genetic syndrome: - Down syndrome - Klinefelter syndrome - Turner syndrome
- Gestational diabetes mellitus.

Cause: • Autoimmune disease - pancreatic β -cell destruction

- Absolute insulin deficiency

- Idiopathic

Pathogenesis of Type 1 DM:

- Genetic Factors: increased incidence in twins of affected individuals (monozygotic > dizygotic twins)

- HLA-DR3, HLA-DR4 or both

- polymorphism in gene coding insulin, CTLA4 & PTPN22 genes, CD25

- Environmental factors:

- Viral infections: may trigger islet cell destruction (mumps, rubella, coxsackie B, cytomegalovirus)

- Mechanism:

- * Release of hidden or sequestered antigens: activates auto-reactive T-cells

- * Molecular mimicry: viruses produce proteins that mimic β -cell antigens

- * Sharing of antigen epitopes: first infection (predisposing virus) during early life might persist in β -cells; subsequent re-infection with a related virus (precipitating virus) that shares antigenic epitopes may lead to an immune response against β -cells.

Mechanism of β -cell Destruction: autoimmune damage starts many years before the disease becomes clinically evident (hyperglycemia & ketosis occur after >90% of the β -cells have been destroyed)

① Failure of self-tolerance in T-cells: basic abnormality in Type 1 DM

- failure of self tolerance may be due to: - defective clonal deletion of self-reactive T-cells in thymus

- defects in functions of regulatory T-cells

- resistance of effector T-cells to suppression by regulatory cells

② Through cytokines: T_H1 cells may destroy β -cells by secreting cytokines including IFN- γ & TNF.

③ Directly by cytotoxic T-cells: CD8+ CTLs may directly kill β -cells

④ Autoantibodies against β -cell antigens (eg: islet antigens β -cell enzymes): anti-insulin, anti-GAD, anti-ICA512

Pathogenesis of Type 2 DM: multifactorial disease

- Environmental factors: • sedentary lifestyle • dietary habits • obesity
- Genetic factors: • monozygotic twins > dizygotic twins • lifetime risk in an offspring if both parents are affected
- diabetogenic genes present (no evidence of autoimmune basis)

Metabolic Defects in Type II DM: • Insulin resistance • β -cell dysfunction

- Insulin Resistance: decrease/failure of target (peripheral) tissues to insulin action

- Insulin resistance is found even in simple obesity but without hyperglycemia; risk for diabetes increases as BMI increases
- distribution of body fat has an effect on insulin sensitivity $\Rightarrow$ central obesity (abdominal fat) is more associated with insulin resistance than peripheral (gluteal/subcutaneous) fat.
- Causes of insulin resistance in obesity: • nonesterified free fatty acids • adipokines • chronic inflammation in adipose tissue • activation of PPAR γ .

(i) Excess of Free Fatty Acids (FFAs): inverse relation between fasting plasma FFAs & insulin sensitivity

- excess circulating FFAs $\rightarrow$ deposited as triglycerides in liver & muscle $\rightarrow$ $\uparrow$ level of intracellular triglycerides
- excess intracellular FFAs $\rightarrow$ $\uparrow$ fatty acid oxidation $\rightarrow$ accumulation of cytoplasmic toxic intermediates such as diacylglycerol (DAG) & ceramide $\rightarrow$ $\downarrow$ insulin signalling $\rightarrow$ $\uparrow$ gluconeogenesis (insulin normally inhibits hepatic gluconeogenesis)

(ii) Adipokines: adipose tissue acts as a functional endocrine organ & secretes variety of proteins into systemic circulation called adipokines

- Prohyperglycemic adipokines: resistin, retinol binding protein (RBP4)
- Antihyperglycemic adipokines: leptin, adiponectin

(iii) Inflammation: excess FFAs & glucose $\rightarrow$ release of proinflammatory cytokines $\rightarrow$ $\uparrow$ insulin resistance & β -cell dysfunction

- excess FFAs within macrophages & β -cells $\rightarrow$ activation of inflammasome $\rightarrow$ release of cytokine IL-1 β $\rightarrow$ secretion of additional proinflammatory cytokines $\rightarrow$ $\uparrow$ insulin resistance

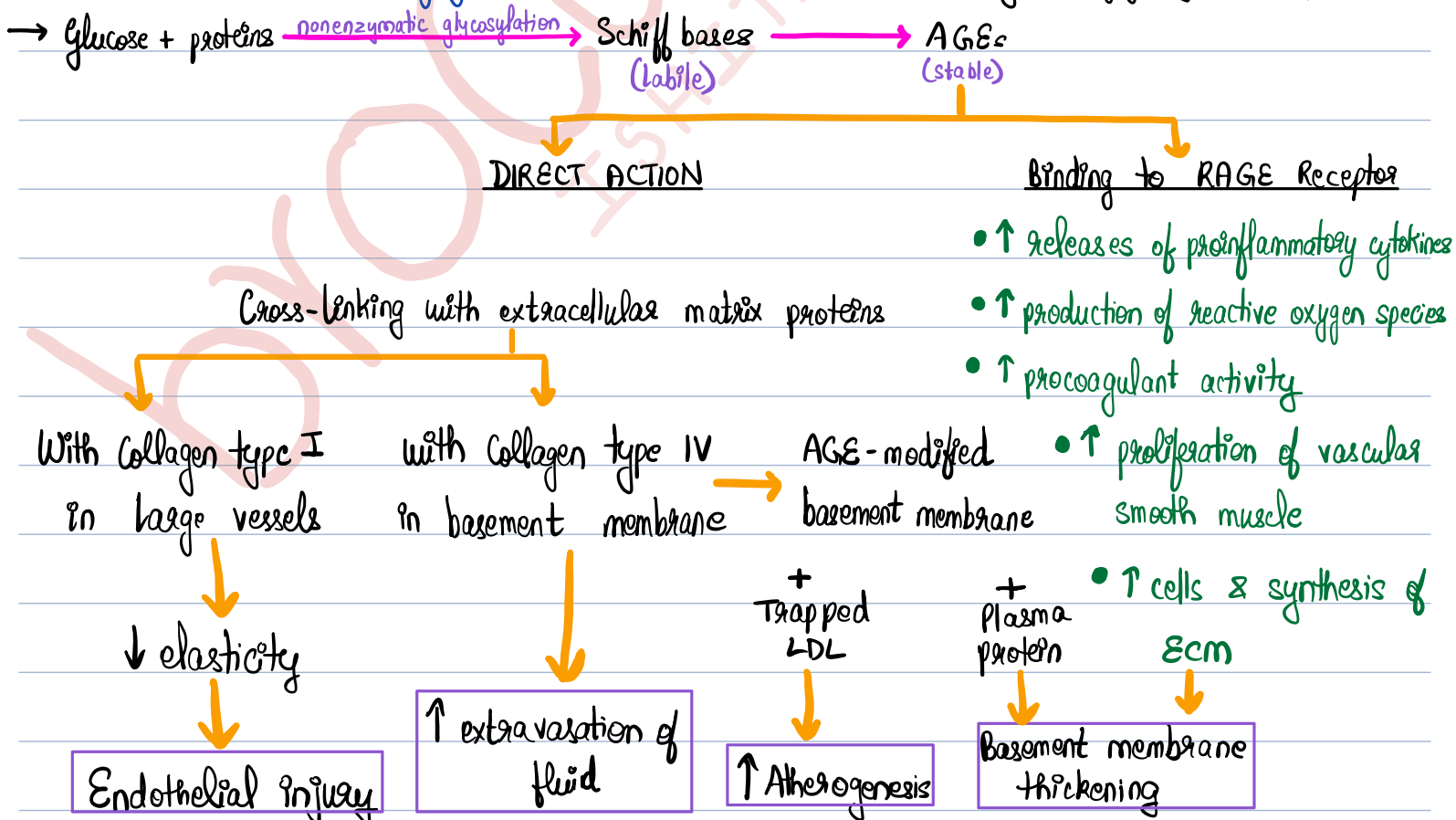
• β -cell Dysfunction: inadequate insulin secretion by pancreatic β -cells (relative insulin deficiency)

- pancreatic β -cells initially respond to long-term demands of peripheral insulin resistance by undergoing compensatory β -cell hyperplasia leading to hypersecretion of insulin
- at some point, β -cells exhaust their capacity to adapt & normal blood sugar cannot be maintained
∴ impaired glucose tolerance ⇒ Early stage of β -cell Failure.
- Insulin secretion decreases leading to hyperglycemia ∴ diabetes develops ⇒ Late stage of β -cell Failure.
- Molecular Mechanisms of β -cell dysfunction:
 - Excess FFAs & decreased insulin signalling (lipotoxicity)
 - Chronic hyperglycemia (glucotoxicity)
 - abnormal incretin effect ⇒ ↓ secretion of hormones that increase insulin release (GIP, GLP-1)
 - direct toxicity by amyloid deposits in islets

Pathogenesis of Complications of Diabetes:

- glycemic control is assessed by estimation of glycosylated hemoglobin Hb_{A1c}
- chronic hyperglycemia secondary multiple organ damage (kidneys, eyes, nerves, blood vessels)

Formation of Advanced Glycation End-products (AGEs): nonenzymatic glycosylation of proteins



Activation of Protein Kinase C (PKC): intracellular hyperglycemia stimulates synthesis of diacylglycerol (DAG) from glycolytic intermediates → DAG activates intracellular PKC → consequences:

- production of proangiogenic molecules like vascular endothelial growth factor (VEGF) → neovascularization characteristic of diabetic retinopathy
- production of profibrogenic factors (eg: TGF- β) → increased production of ECM & basement membrane material
- production of plasminogen activator inhibitor (PAI-1) → reduces fibrinolysis & favours vascular occlusion (due to atherosclerotic plaque/thrombus formation)

Disturbance in Polyol Pathways: (some tissues do not require insulin for glucose transport eg: nerves, lenses, kidneys, blood vessels)

→ persistent hyperglycemia → ↑ intracellular glucose in these tissues → glucose metabolism by aldose reductase to sorbitol → converted to fructose
↳ utilizes NADPH as a cofactor → NADPH is also needed for regeneration of reduced glutathione (GSH) which protects against injury by free radicals → decrease in GSH → increased cell susceptibility to oxidative stress

Morphology:

Pancreas: lesions of pancreas are not diagnostic

- Reduced number & size of islets
- Infiltration of islets (insulitis) mainly by T-lymphocytes (predominant in type 1 DM)
- amyloid deposition within islets
- increase in the number & size of islets may be seen in nondiabetic newborns of diabetic mothers as a hyperplastic response to maternal hyperglycemia

Blood vessels:

- Hyaline arteriosclerosis: related to the duration of diabetes & level of BP
 - characterized by amorphous, hyaline thickening of wall of arterioles which may narrow the lumen of vessels

→ Diabetic microangiopathy: diffuse thickening of basement membrane (mostly seen in capillaries of skin, skeletal muscle, retina, renal glomeruli, renal medulla)

- capillaries become leakier to plasma proteins than normal
- microangiopathy results in diabetic nephropathy, retinopathy, neuropathy

Clinical Features: Classical Triad • Polydipsia • Polyphagia • Polyuria

Type 1 DM: → Classical triad + ketoacidosis (in severe cases)

→ in the initial 1 or 2 years, exogenous insulin requirement may be minimal; later, its requirement suddenly increases

Consequences of insulin deficiency: (catabolism)

① Carbohydrate metabolism:

- diminished glucose transport into muscle cells & adipose tissue
- reduction of stored glycogen in liver & muscle due to glycogenolysis → further aggravates hyperglycemia
- when hyperglycemia exceeds renal threshold level → glycosuria → osmotic diuresis → polyuria
- water loss through urine + hyperosmolarity due to hyperglycemia → depletion of intracellular water → stimulates osmoreceptors of thirst centers of brain → polydipsia

② Protein & fat Metabolism: catabolism of proteins & fats → negative energy balance → polyphagia

- catabolic effects of insulin cause a paradoxical loss of weight & muscle weakness

③ Diabetic ketoacidosis:

- Diuresis & dehydration: masked insulin deficiency + epinephrine release → ↑ secretion of glucagon → decreased peripheral utilization of glucose + ↑ gluconeogenesis → severe hyperglycemia (500-700 mg/dL) → osmotic diuresis & dehydration

- Activation of ketogenic machinery: insulin deficiency → stimulates lipoprotein lipase → breaks down fat stores → ↑ FFAs → FFAs are esterified to fatty acyl coenzyme A in liver → in mitochondria of liver cells, fatty acyl coA is oxidized to ketone bodies (acetoacetic acid & β -hydroxybutyric acid)

- when rate of production of ketone bodies exceeds the rate of utilization by peripheral tissues → ketonemia, ketonuria
- if excretion of ketone bodies in urine is compromised by dehydration → systemic metabolic ketoacidosis

Type 2 DM: usually occurs above 40 years & frequently in obese individuals

→ Presentation: polyuria, polydipsia, unexplained weakness / weight loss (ketoacidosis is infrequent)

	Type 1 DM	Type 2 DM
Age of onset	Childhood & adolescence	Adult (also seen in childhood)
Weight	Normal / weight loss	Majority are obese
Insulin levels	Progressive decrease	Increased (early); decrease (late)
Circulating islet autoantibodies	Detected (anti-insulin, anti-GAD, anti-ICA512)	Not found
Diabetic Ketoacidosis	Develops in absence of insulin therapy	Nonketotic hyperosmolar coma
HLA association	Major linkage to MHC class I & II genes HLA-DR3 & DR4	No HLA association
Non-HLA genes	Polymorphisms in CTLA4 & PTPN22	Diabetogenic & obesity-related genes
Mode of development	Autoimmune	Multifactorial
Mechanism	Breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, β -cell dysfunction
Insulinitis	Inflammatory infiltrate of T-cells & macrophages in islets	No insulinitis; amyloid deposition in islets
β -cell depletion	Moderate to severe	Mild

Complications: long-term complications of diabetes usually develop 15-20 years after onset of hyperglycemia

Diabetic Macrovascular Disease: lesions of large & medium-sized muscular arteries

- Atherosclerosis: increased levels of PAI-1 in diabetics inhibits fibrinolysis & favors formation of atherosclerotic plaques
- Myocardial infarction: due to atherosclerosis of coronary arteries
- Gangrene of lower extremities
- Renal vascular insufficiency
- Cerebrovascular accidents (stroke)

Microvascular Disease (Microangiopathy): involves small vessels, capillary dysfunction in target organs

- Diabetic nephropathy: leading cause of end-stage renal disease; different stages:
 - (i) Microalbuminuria $\Rightarrow$ earliest manifestation (Urine albumin: 30-300 mg/day)
 - (ii) Nephropathy with macro albuminuria (Urine albumin > 300 mg/day)
 - (iii) End-stage renal disease
 - Diabetic retinopathy: lesion $\Rightarrow$ neovascularization caused by hypoxia-induced overexpression of VEGF in retina
 - $\rightarrow$ increased risk for glaucoma & cataract formation
 - Diabetic neuropathy: involving central & peripheral nervous system
 - $\rightarrow$ Distal symmetric polyneuropathy $\Rightarrow$ affects both motor & sensory function of lower extremities; later may involve the upper extremities leading to "glove & stocking" pattern
 - $\rightarrow$ Autonomic neuropathy $\Rightarrow$ produces disturbances in bowel & bladder function & sometimes, sexual impotence
 - $\rightarrow$ Diabetic mononeuropathy $\Rightarrow$ manifests as sudden footdrop, wristdrop or isolated cranial nerve palsies
- Diabetic Dyslipidemia: increased blood level of triglycerides & LDL & decreased levels of HDL
- Increased Susceptibility to Infections: due to defective neutrophil functions & impaired cytokine production by macrophages
- $\rightarrow$ susceptibility to skin infections, tuberculosis, pneumonia, pyelonephritis.

Zollinger-Ellison Syndrome:

Triad: • Hypergastrinemia

- Increased acid production
- Severe peptic ulcer disease

Hypergastrinemia: gastrinomas in small intestine/pancreas → ↑ gastrin secretion → ↑ acid & pepsin secretion.

(Fasting serum gastrin > 1000 pg/mL)

Increased acid secretion: → inactivation of pancreatic enzymes & bile salts → malabsorption & diarrhoea

(↑ number of parietal cells in stomach)

Peptic Ulcers: multiple & recurrent.