

Endocrine

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islets of pancreas

major cell type

minor cell type

β cell

α cell

γ cell

PP cells

produce Insulin

secrete glucagon

secrete somatostatin

D cells

enteroendocrine cells

L.B.S

$\rightarrow$ T.B.S

both I & II

secrete VIP

secrete secretin

DM $\rightarrow$ Group of metabolic disorders sharing the common feature of

Hypoglycaemia

caused by

Defect in Insulin secretion

Defect in Insulin Action

Both

Chronic Hyperglycaemia

Metabolic decompensation

Secondary damage in multiple organ

system. Kidney, eye, nerves.

DIAGNOSIS:

A FBS > 126 mg/dl

PBS > 200 mg/dl

HbA1c $\geq 6.5\%$

$\rightarrow$ pancreatic β cell destruction.

DM

Type 1 DM (Autoimmune disease)

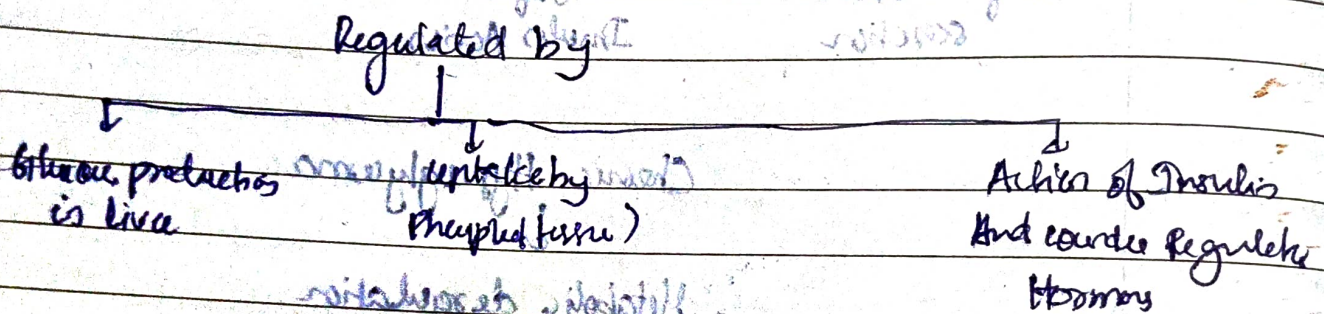
Type 2 DM $\rightarrow$ Peripheral Resistance to Insulin Action.

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→ Immune mediated β cell destruction, usually leading to Absolute Insulin deficiency

Type II DM - combination of Insulin Resistance And β cell dysfunction

- Genetic defect of β cell function → (MODY) (Maturity Onset Diabetes of the Young is MODY 1-6)
- Genetic defect in Insulin Action → Neonatal diabetes
- Exocrine pancreatic defect
- Endocrine pathis
- Defective Drugs



Fasting state ↓ Insulin ↑ Glucagon
 ↑ Glycogenolysis ↓ Glycogen synthesis } prevent hypoglycemia

After meal: ↑ Insulin ↓ Glucagon } Prevent Hyperglycemia

Insulin synthesis → Refu Phenylalanine

⇒ Other Hormone Responsible for promoting Insulin from pancreatic β cell.

• Incretins

GIP

GLP

↑ GIP & GLP → ↑ Insulin secretion
 ↓ Glucagon.

PATHOGENESIS

Insulin dependent.

→ juvenile onset.

Type 1: → Autoimmune disease.

Islet destruction.

Immune effector cell Reacting Against
endogenous β cell Antigens.

→ Manifest at puberty And progress with Age.

Occur due to imbalance → by
lymphocyte Activation And Mechanism of tolerance

why it fails

1. Genetic factors

Seen in monozygotic twins.

→ HLA gene (HLA DR3 & DR4) DR3

→ Family history

→ Mutation in AIRE gene

2) Autoimmune Mechanism:

• T cell Mediated Autoimmune disease.

• Loss of self tolerance to β cell Antigen

Environmental triggers

→ Viral infections.

→ molecular mimicry

production AutoAb
Against Islet of pancreas.

→ Polymorphism
C8orf48
PTPN 22

Initial Activation

→ In peripancratic lymph node

→ In Response to Antigens that released from damaged Islets.

Activated T cell

CD8+ T cell

CD4+ T cell

Cell Injury

NON-HODGKIN'S LYMPHOMA

Mechanism of β cell destruction

Three distinct stages

Stage 1	Stage 2	Stage 3
Autoimmunity +ve	Autoimm +ve	→ 11
Normoglycemia	Dysglycemia	→ 11
Presymptomatic	"	symptomatic T1D

→ Progressive loss of β cell mass → 90% β cell destroyed

Morphology

- Reduction in number And size of islet.
- most of them are small And inconspicuous.
- leukocyte infiltrate in the islet (insulitis)
- composed of T lymphocyte

PATHOGENESIS:

EF > Genetic

Type 2: No evidence of Autoimmune disease.

Interplay of genetic And environmental factors And proinflammatory state

RISK

1) Genetic factors:

1st degree Relative
twofold (high chance)

GWAS gene m-

2) Environmental factors:

→ Obesity (MRF)

→ sedentary lifestyle (↓ Insulin sensitivity → ↑ Risk of Insulin Res)

→ Metabolic syndrome

→ ethnicity → Asn, Afr

→ sleep disorder & circadian disruption.

Classification of diabetes - Related complication:

VASCULAR COMPLICATION:

NON VASCULAR COMPLICATION

Microvascular

- Retinopathy

- Neuropathy

- Nephropathy

• Glomerulopathy

• Infectious

• Cataracts

• Osteoporosis

Macrovascular

- Coronary heart disease

- peripheral Arterial disease

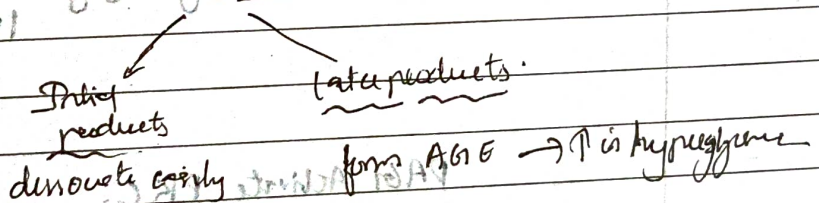
- cerebrovascular disease

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Pathway of Mechanism of complication in DM due chronic Hyperglycemia

1. Formation of Advanced glycation end products.

In DM, glucose-derived products bind to proteins nonenzymatically turned as nonenzymatic glycosylation.



Effects of AGEs

AGEs bind to specific receptor (RAGE for AGEs)

→ present on inflammatory cell (Mφ cell).

Their Actions

→ Release proinflammatory cytokines and growth factors.

→ lead to deposition of excess Basement

material of growth factors → is

Diabetic Retinopathy

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- ↑ proliferation of vascular smooth muscle cell And synthesis of extracellular Matrix
 - ↑ procoagulant Activity of endothelial cell And macrophages
 - Production of ROS in endothelial cell.
 - Trapping of low density LDL within AGE modified large vessel
 - ↓ Accumulation
 - Atherosclerosis
 - Trapping of Albumin within capillary wall.
 - ↓ thickness of basement membrane
 - Diabetic micro Angiopathy.

2) Activation of Protein kinase C (PKC)

Intracellular hyperglycemia → synthesis of (DAG) Diacylglycerol from glycolytic intermediates

DAG Activate PKC.

↓ lead to production of

→ proangiogenic molecule (eg: VEGF)

↳ which cause neovascularization in DR.

→ Pro fibrogenic factors (eg TGF-β)

↳ production of extracellular Matrix And B.M

→ Phenotype Activation, Diabetic

→ Atherosclerotic plaque.

3) Disturbance in Metabolic Pathway

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Formation of fructose from glucose

Some tissue do not require insulin for glucose transport:

⇒ Persistent hyperglycemia $\uparrow$ → As excess intracellular glucose is metabolized by the enzyme Aldose Reductase to Sorbitol → fructose

→ Reduction of NADPH

→ Oxidative stress.