DIABETES MELLITUS

Definition Diabetes Mellitus is a group of disorderes sharing the common feature of hyperglycemia.

Diagnosis - American Diabetes Association, -

	Diabetes	Prediabetes/impaired glucose tolerance
• Fasting Plasma glucose	≥126mg/dl	100-125mg/dl
• Random plasma glucose (in pt c hyperglycemic signs)	≥200mg/dl	-
• 2h plasma glucose during OGTT c 75g	≥ 200mg/dl	140-199 mg/dl
• HbA_{1c} level	≥6.5%	5.7-6.4%

CLASSIFICATION

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Type 1 Diabetes	Type 2 Diabetes
Clinical	
Onset: usually childhood and adolescence	Onset: usually adult; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies (anti-insulin, anti-GAD, anti-ICA512)	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma more common
Genetics	
Major linkage to MHC class II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*, and insulin gene VNTRs	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes (e.g., *TCF7L2, PPARG, FTO*)
Pathogenesis	
Dysfunction in T-cell selection and regulation leading to breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by β cells
Pathology	
Insulitis (inflammatory infiltrate of T cells and macrophages) β-cell depletion, islet atrophy	No insulitis; amyloid deposition in islets Mild β-cell depletion

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- Genetic defects of β cell function-

* ① Maturity Onset Diabetes of the young- (MODY)
mutation

- MODY1 - Hepatocyte nuclear factor 4α (HNF4α).
- MODY2 - Glucokinase (GCK)
- MODY3 - Hepatocyte nuclear factor 1α (HNF1α)
- MODY4 - Pancreatic & duodenal homeobox1 (PDX1).
- MODY5 - Hepatocyte nuclear factor 1β (HNF1β)
- MODY6 - Neurogenic differentiation factor 1 (NDOF1)

② Neonatal Diabetes · mut^{n} KCNJ11 & ABCC8
↓ Kir6.2 ↓ SUR1

* ③ Maternally inherited Diabetes & Deafness
mitochondrial DNA mutation

④ Defects in proinsulin conversion

⑤ Insulin gene mutations.

* Insulin actions genetic defects- ① Type A Insulin resistance
② Lipoatrophic diabetes.

Exocrine pancreatic defects-

Infections- CMV, CoxsackieB. congenital Rubella.

Endocrinopathies Acromegaly · glucagonoma · cushing

Drugs -

Genetic syndromes ⓐ diabetes- Turner
Downs
Kleinfelter
Prader-Willi

* Gestational diabetes mellitus

GLUCOSE HOMEOSTASIS

tightly regulated by 3 inter-related process -

1> glucose production in livere
2> peripheral uptake & utilisation
3> hormonal regulation.

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INSULIN RELEASE

Oral glucose intake
↓
blood sugar ↑
↓
opening of ↑K_m GLUT2 receptors on β cells Islets.
↓
ATP production from glucose
↓
inhibition of ATP sensitive K^+ channel
↓
no K^+ efflux
↓
depolarisation
↓
activation of Ca^{2+} channels
↓
Ca^{2+}
↓
stimulus

Proinsulin
↓ golgi bodi
Insulin + C peptide → surrogate of β-cell function
In secretory granules
↓
Secretion

Oral glucose

K cell of Proximal small bowel
↳ Glucose dependent insulinotropic polypeptide (GIP).

L cell of ileum & colon
↓
Glucagon like Peptide 1 (GLP-1)

Incretins

DPP4

↑ Insulin
↓ glucagon
delay gastric emptying → satiety

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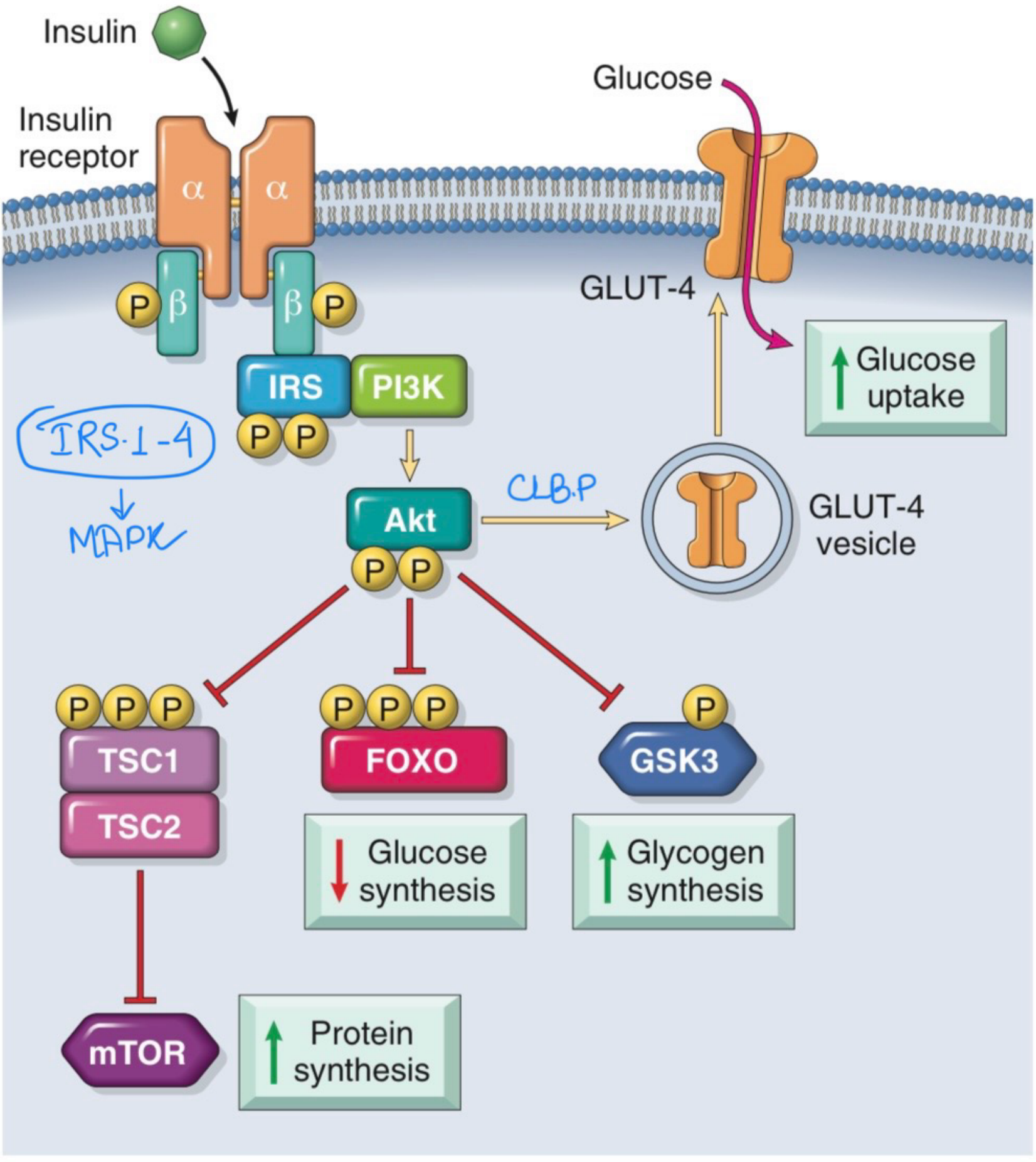

Figure 24.30 Insulin action on a target cell. Insulin binding to the tetrameric receptor initiates a cascade of phosphorylation events that result in activation of PI-3-kinase/Akt signaling. Akt is a serine threonine kinase that mediates its effector functions via phosphorylation-dependent events. For example, Akt phosphorylates and inhibits the function of the tuberous sclerosis complex *(TSC)* proteins, leading to activation of the downstream mammalian TOR *(mTOR)* complex, which enhances protein synthesis. Akt also inhibits the function of Forkhead box O *(FOXO)* protein, which, in turn, reduces glucose synthesis, while inhibition of glycogen synthase kinase 3 *(GSK3)* enhances glycogen production. Finally, Akt enhances intracellular glucose uptake by translocation of GLUT-4 vesicles to the cell membrane. *IRS,* Insulin receptor substrate; *PI3K,* phosphoinositide 3-kinase. (Modified from Brendan Manning, Harvard T.H.

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Pathogenesis

DM type I

Genetic succeptibility
HLAD3, HLAD4
Polymorphism CTLA4, PTPN22.
AIRE

Infect^{n} - molecular mimicry

↓

breakdown of tolerance
defective clonal deletion
dysregulat^{n} of regulatory T cells

↓

TH1 cells, TNF, INFγ
autoimmune attacks against
Islets autoantigens
Glutamic acid decarboxylase (GAD)

DM type II

Genetic succeptibility - >30 loci
Polymorphism in genes a/w
insulin secretion
(PPARG, FTO, TCF7L2)

Metabolic deficits - Insulin Resistance

Obesity (central >> peripherical)
more lipolytic.

① ↑FFA → overwhelm intracellular FA oxidation
↓
accumulation of cytoplasmic
intermediate
like DAG

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↑ gluconeogenesis ← attenuate signalling through insulin

② competetion ↓ glucose for substreate oxidat^{n}.
↓
feedback inhibition of glycolysis

③ ↑ fat → ↓ adiponectin
↓
↓ insulin sensitivity

④ ↑ FFA & glucose in mϕ & β cells
↓
inflammosome format^{n}
↓
IL-1 & tissue destruct^{n}

B cell dysfunction-
- ↑ FFA ⇒ attenuate insulin release
- ↓ GIP, GLP-1.
- amyloid deposition.

Type A Insulin resistance-

Insulin receptore mut^{n}
↓
Problem in (Rc) synthesis
binding
TrK activity

- ↑ Insulin resistance - hyperglycemia
- a/w Acanthosis nigricans - velvety hyperpigmentation of skin.
- a/w PCOD(♀)

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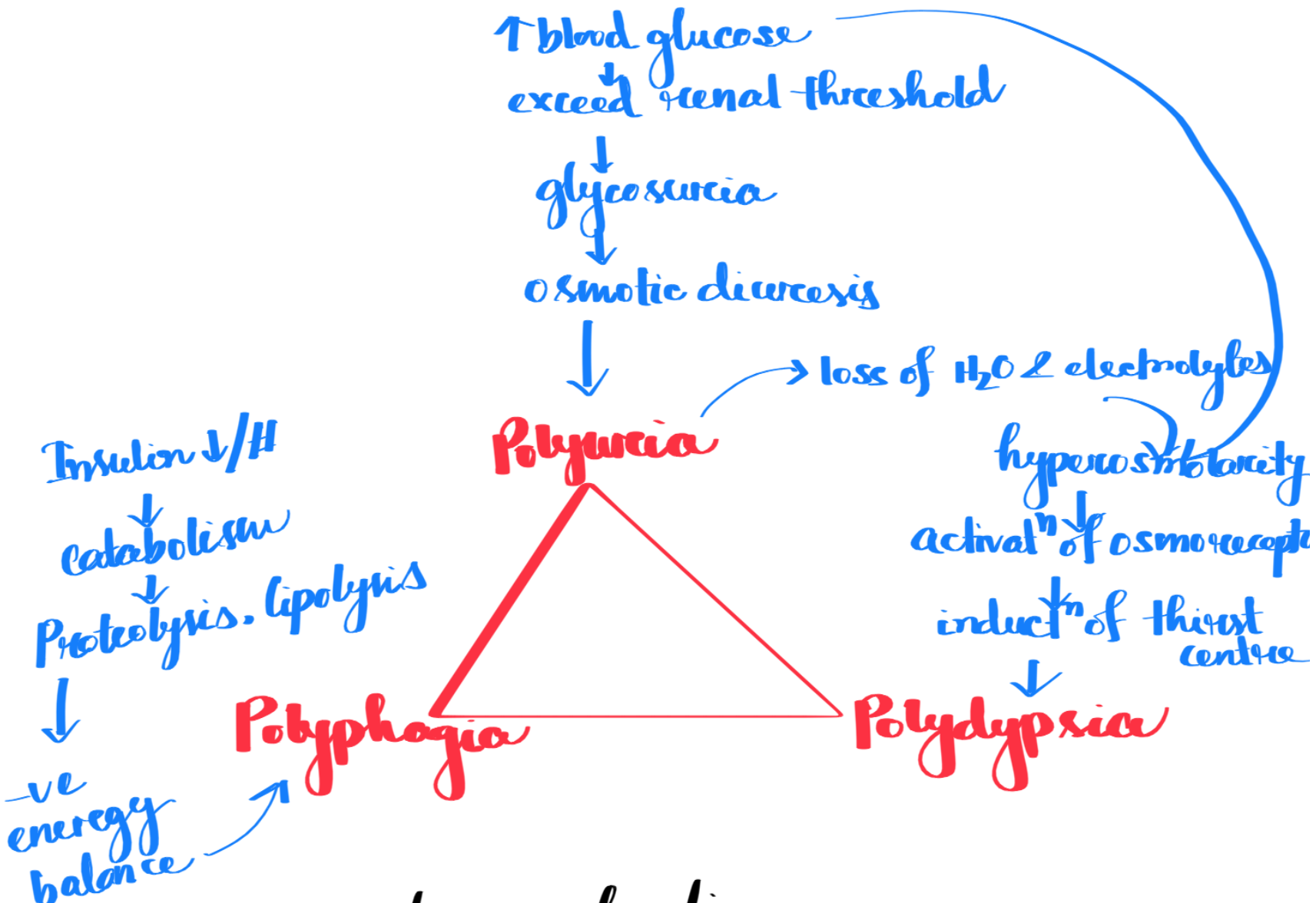
Lipoatrophic diabetes - Insulin resistance
- hyperglycemia
- hypertriglyceridemia
- acanthosis nigricans
- hepatic steatosis
- loss of adipose tissue in subcutaneous fat

Gestational diabetes - hormonal milieu in pregnancy (diabetic / euglycemic ♂ ♀ predisposing factors) favor insulin resistance

- still birth
- macrosomia (overweight delivery)

Clinical Features of Diabetes Mellitus



acute complication

Diabetic ketoacidosis (a/w type I)

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↳ infect^{n}, trauma

↳ ↑ N-adrenaline

↓

block residual insulin act^{n} ↑ glucoga

↓

Gluconeogenesis

↓

severe hyperglycemia (250–600 mg/dl)

↓

osmotic diuresis & dehydration

↓

ketoacidosis

↳ Ketonemia & ketonuria

dizziness
nausea, vomiting
abdominal pain
Kussumaul's breathing
coma

(2) stimulate lipoprotein lipase ← (1)

↓

↑FFA

↓

oxidation

↓

ketone bodies

Ketogenic AA
catabolism

Insulin treatment

Hyperosmolar coma – (a/w type II)

no ketoacidosis due to ↑Insulin in portal vein

↓

check FFA & Ketogenesis

Chronic diuresis → hyperosmolarity

↓

severe dehydration & mental status alteration

no other clinical symptoms.

↓

no medical help

↓

severe hyperglycemia (600–1200 mg/dl

- hypoglycemia.

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Chronic Complications

Mechanisms - 4 ....

non enzymatic reactions b/w intracellular glucose derived dicarbonyl precursors (eg. glyoxal) & intracellular & extracellular proteins

↓

format^{n} of Advanced Glycation End products

↓

AGE - RAGE signalling (Receptor AGE + int on mφ, T cells) → ↑ procoagulant activity

↓

cytokine & growth factors

TGFβ → deposit^{n} of basement membrane

VEGF, PAI

↓

Generation of ROS

↓

Proliferation of vascular smooth muscles & ECM synthesis

↑ glucose

↓

↑ DAG synthesis

↓

Ca^{2+} independent DAG signalling

↓

PKC

RAGE independent

↓

cross-linking of ECM proteins

- collagen I - ↓ elasticity ↑ sheer stress - endothelial injury.
- collagen IV - ↓ endothelial cell adhesion - extravasation of fluid.
- also trap non-glycated protein, LDL

↓

↑ atherogenesis

abnormal expression of

↑ glucose influx through hexosamine pathways

↓

↑ fructose-6-phosphate (substrate for glycosylation of proteins)

↑ proteoglycan

↑ glucose

↓

↑ polyol pathway

(glucose → sorbitol → fructose)

→ aldol reductase uses NADPH

↓

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↓ NADPH
↓
↓ GSH regeneration
↓
↑ succeptibility to oxidative stress.

Morphology & Complications

Pancreas – Type I - ↓ islet cells & size
leucocytic infiltrations.

Type II - amyloid deposition around capillaries and b/w islets.
↑ islet hyperplasia & hypertrophy in non-diabetic newborn of diabetic mother due to maternal hyperglycemia.

Diabetic macrovascular disease – • endothelial dysfunctn
• accelerated atherosclerosis (hallmark)

Coronary artery – MI

renal artery
↓
HTN → hyaline arteriosclerosis

Diabetic neuropathy – >50% affected.
↓ axon numbers
axonal damage
degenerating myelin sheaths
regenerating axonal clusters.
hyalinization.
endoneurial arteriolar thick
duplication of basement membra

Paraesthesia
numbness
loss of pain sensation

ANS – HTN
urine retention
↳ recurrent infectn
sexual dysfunctn

glove & stocking
• distal symmetric diabetic polyneuropathy

Older individuals ē long history of diabetes

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↳ assymetric presentation
- mononeuropathy - footdrop, wristdrop
- cranial neuropathy
- radiculoplexus neuropathy

Diabetic nephropathy -

1) Glomerular lesion
2) Renal vascular lesions – arteriosclerosis
3) Pyelonephritis – necrotizing papillitis

- capillary - basement membrane thickening.
- tubular - " " "
- diffuse mesangial sclerosis – PAS (+ve).
- nodular glomerulosclerosis → intercapillary sclerosis - Kimmelsteil-Wilson disease.
- fibrin caps, hyalinosis.

microalbuminuria 30-300mg/day
macroalbuminuria - > 300mg/day

Diabetic microangiopathy -

thickening of capillary basement membrane - skin, retina, muscle, renal.
↓
leaky capillary, to plasma protein

Retinopathy, nephropathy, neuropathy

Diabetic retinopathy.

cataract
glaucoma
↳ optic nereve damage

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Non-proliferative

- retinal blood vessel basement membrane thickening
- ↓ pericytes to endothelial cells
- micro aneurysms
- ↑ VEGF — breakdown of blood retinal barrier
- macular edema
- exudate in outer plexiform layer
- micro-occlusion

Proliferative

- new vessel sprouting on optic nerve - neovascularization of disc
- on retinal surface - neovascularization elsewhere
- breach internal limiting membrane of retina
- web formed - neovascular membrane
- posterior vitreous detatchment - massive hemorrehage
- wrinkling of retina
- scarring - photoreceptor orientation disruption
- Traction retinal detatchment

contract^{n} of neovascular membrane - adhesion b/w iris & trabecular meshwork - neovascular glaucoma

enhanced susceptibility of infect^{n} to skin.
Pneumonia
TB

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