Diabetes mellitus

THE ENDOCRINE PANCREAS

- The endocrine pancreas consists of about 1 million clusters of cells, the islets of Langerhans, which contain four major and two minor cell types.
- The four main types are β, α, δ, and PP (pancreatic polypeptide) cells.
- They can be differentiated by the ultrastructural characteristics of their granules, and by their hormone content.

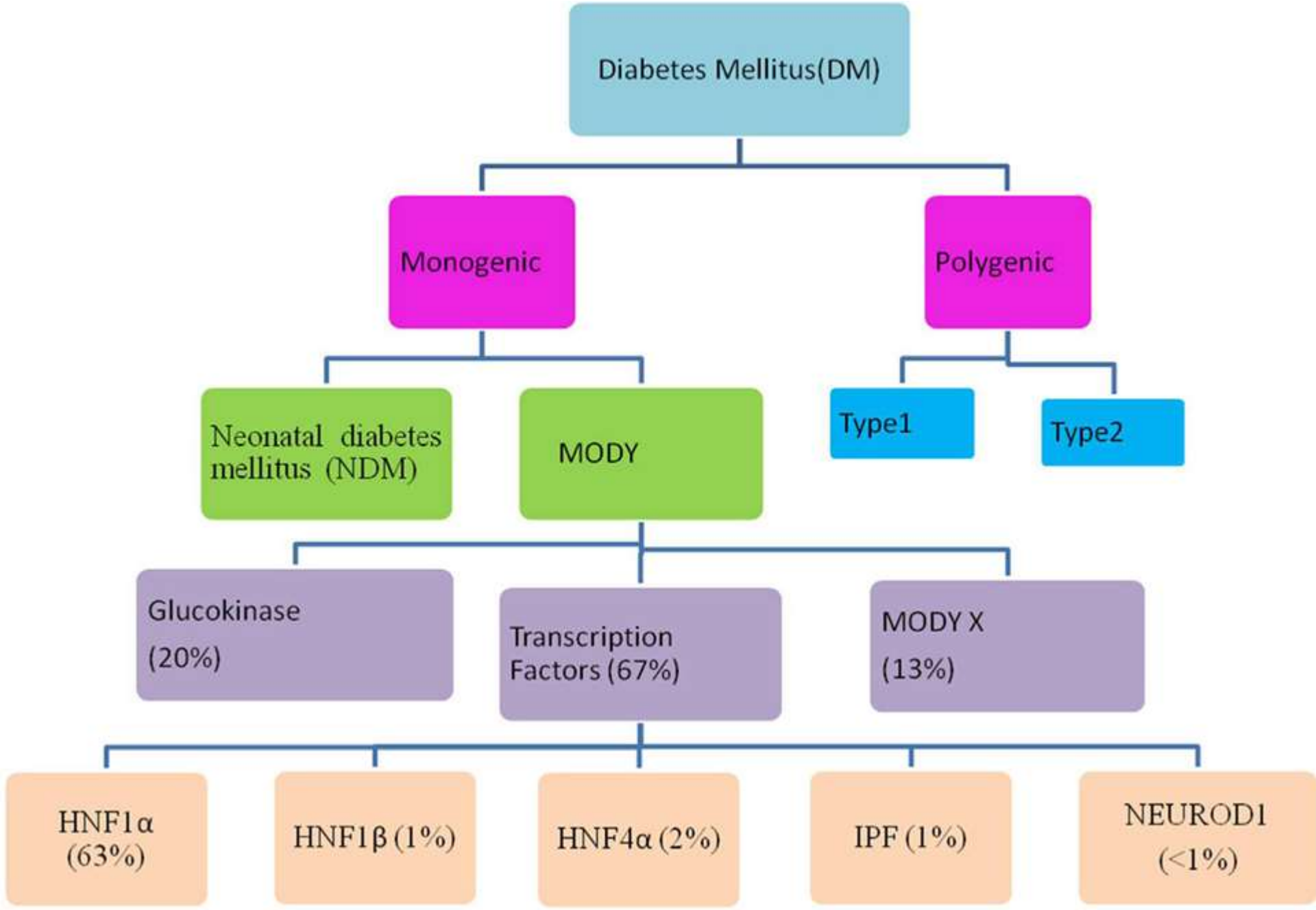
Types of cells

- The β cell produces insulin.
- The α cell secretes glucagon, inducing hyperglycemia by its glycogenolytic activity in the liver.
- δ cells contain somatostatin, which suppresses both insulin and glucagon release.
- PP cells contain a unique pancreatic polypeptide that stimulates secretion of gastric and intestinal enzymes and inhibits intestinal motility.

DIABETES MELLITUS

- Diabetes mellitus is not a single disease entity but rather a group of metabolic disorders underlined by hyperglycemia.
- Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both.

CLASSIFICATION


Diabetes Mellitus(DM)
Monogenic
Polygenic
Neonatal diabetes mellitus (NDM)
MODY
Type1
Type2
Glucokinase (20%)
Transcription Factors (67%)
MODY X (13%)
HNF1α (63%)
HNF1β (1%)
HNF4α (2%)
IPF (1%)
NEUROD1 (<1%)

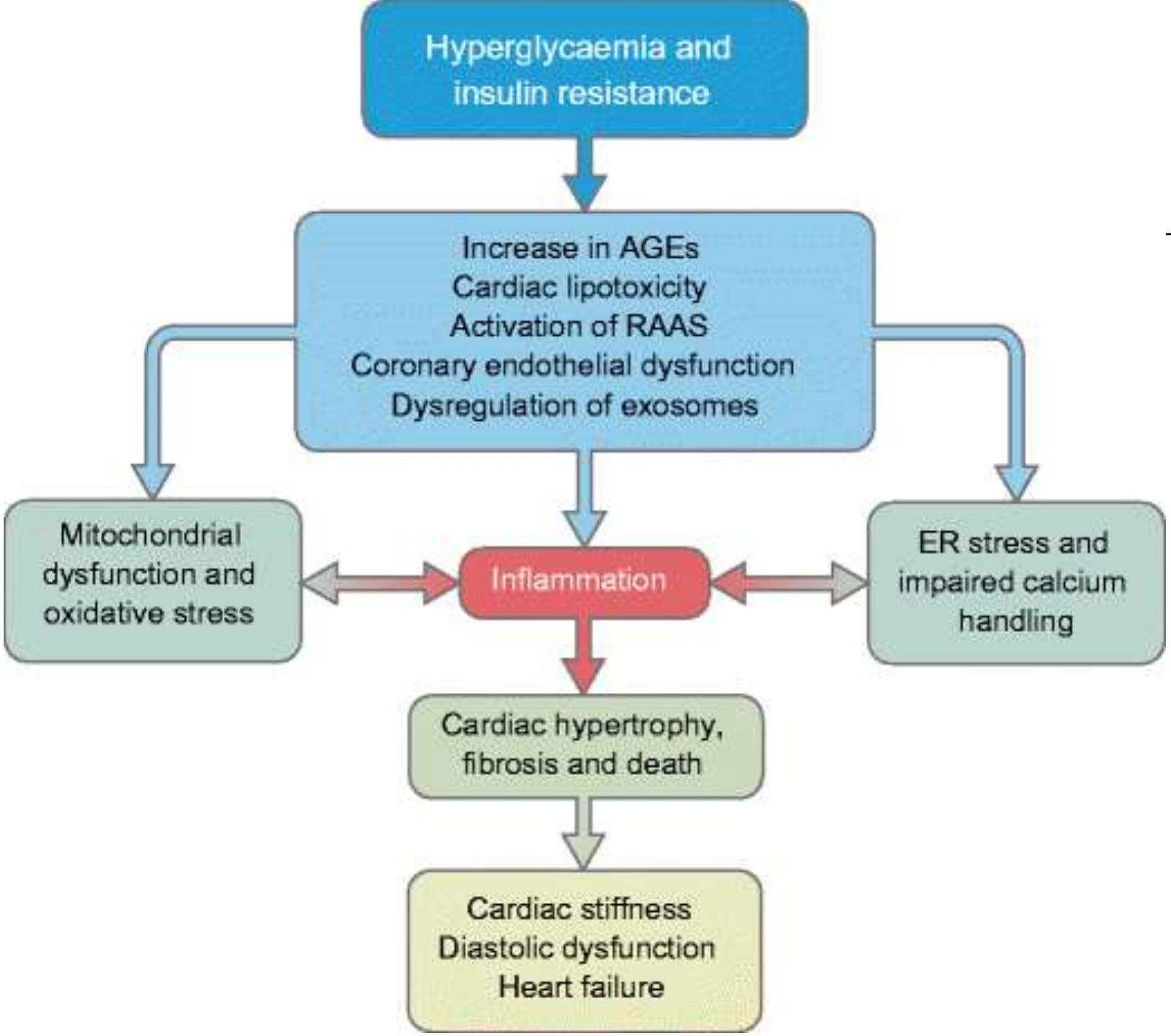
PATHOGENESIS

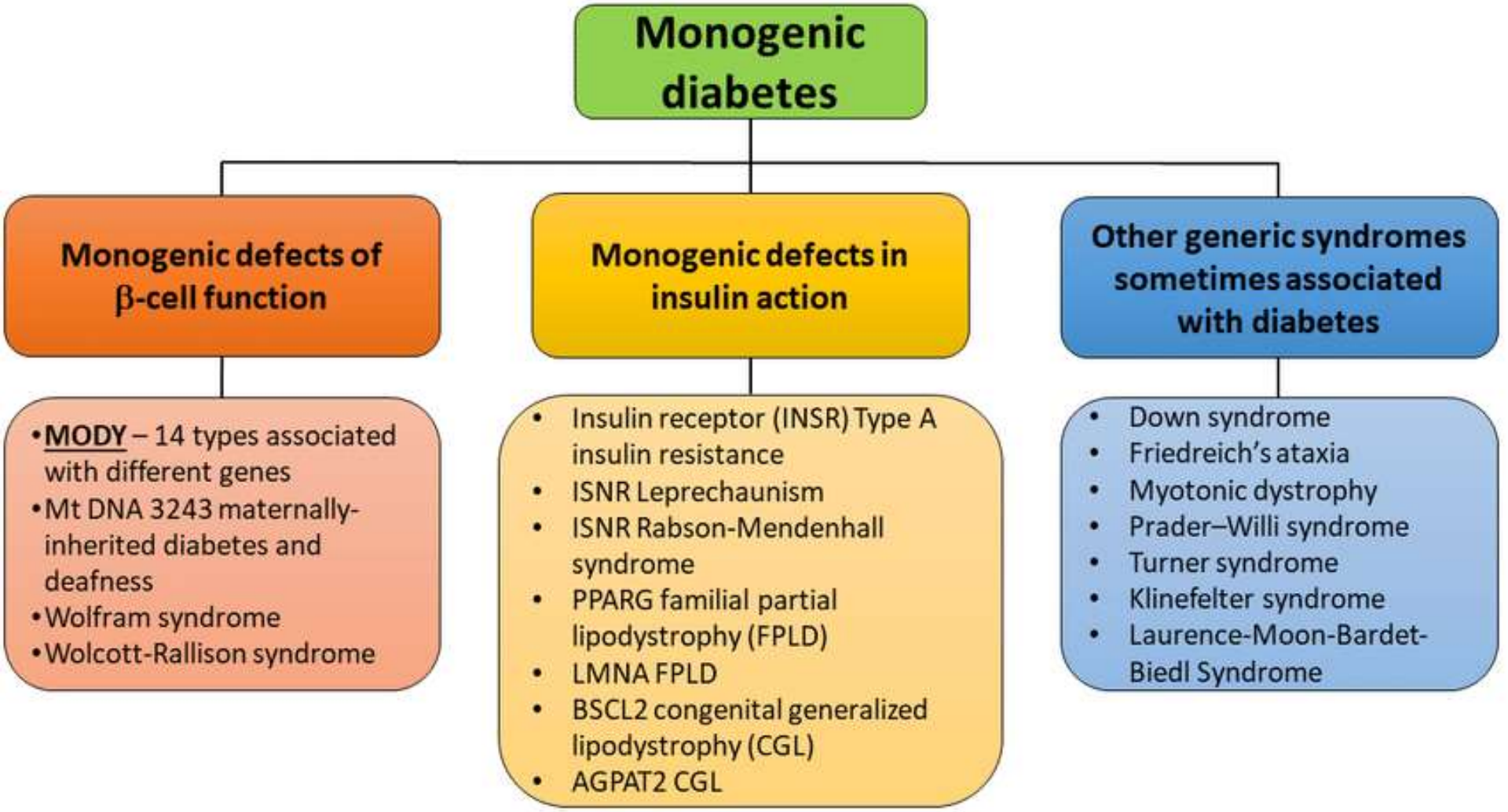
PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

- Type 1 diabetes most commonly develops in childhood, becomes manifest at puberty, and progresses with age.
- Used to be called “juvenile diabetes”
- As with most autoimmune diseases, the pathogenesis of type 1 diabetes represents interplay of genetic susceptibility and environmental factors

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

- Type 2 diabetes most commonly develops in adulthood or elderly.
- Used to be called “senile diabetes”
- Obesity is a key factor


Hyperglycaemia and insulin resistance
Increase in AGEs
Cardiac lipotoxicity
Activation of RAAS
Coronary endothelial dysfunction
Dysregulation of exosomes
Mitochondrial dysfunction and oxidative stress
Inflammation
ER stress and impaired calcium handling
Cardiac hypertrophy, fibrosis and death
Cardiac stiffness
Diastolic dysfunction
Heart failure


Monogenic diabetes
Monogenic defects of β-cell function
•MODY – 14 types associated with different genes
•Mt DNA 3243 maternally-inherited diabetes and deafness
•Wolfram syndrome
•Wolcott-Rallison syndrome
Monogenic defects in insulin action
• Insulin receptor (INSR) Type A insulin resistance
• ISNR Leprechaunism
• ISNR Rabson-Mendenhall syndrome
• PPARG familial partial lipodystrophy (FPLD)
• LMNA FPLD
• BSCL2 congenital generalized lipodystrophy (CGL)
• AGPAT2 CGL
Other generic syndromes sometimes associated with diabetes
• Down syndrome
• Friedreich's ataxia
• Myotonic dystrophy
• Prader–Willi syndrome
• Turner syndrome
• Klinefelter syndrome
• Laurence-Moon-Bardet-Biedl Syndrome

Clinics

Clinics

- 3 poly: - Polyuria
  - Polydipsia
  - Polyphagia

Pathogenesis of acute metabolic complications

Hyperosmolarity

- Diabetic hyperglycemic hyperosmolar syndrome (HHS) is a complication of type 2 diabetes.
- It involves extremely high blood sugar (glucose) level without the presence of ketones.
- Symptoms include signs of dehydration, weakness, leg cramps, vision problems, and an altered level of consciousness.
- Onset is typically over days to weeks.
- Complications may include seizures, disseminated intravascular coagulopathy, mesenteric artery occlusion

Diabetic ketoacidosis (DKA)

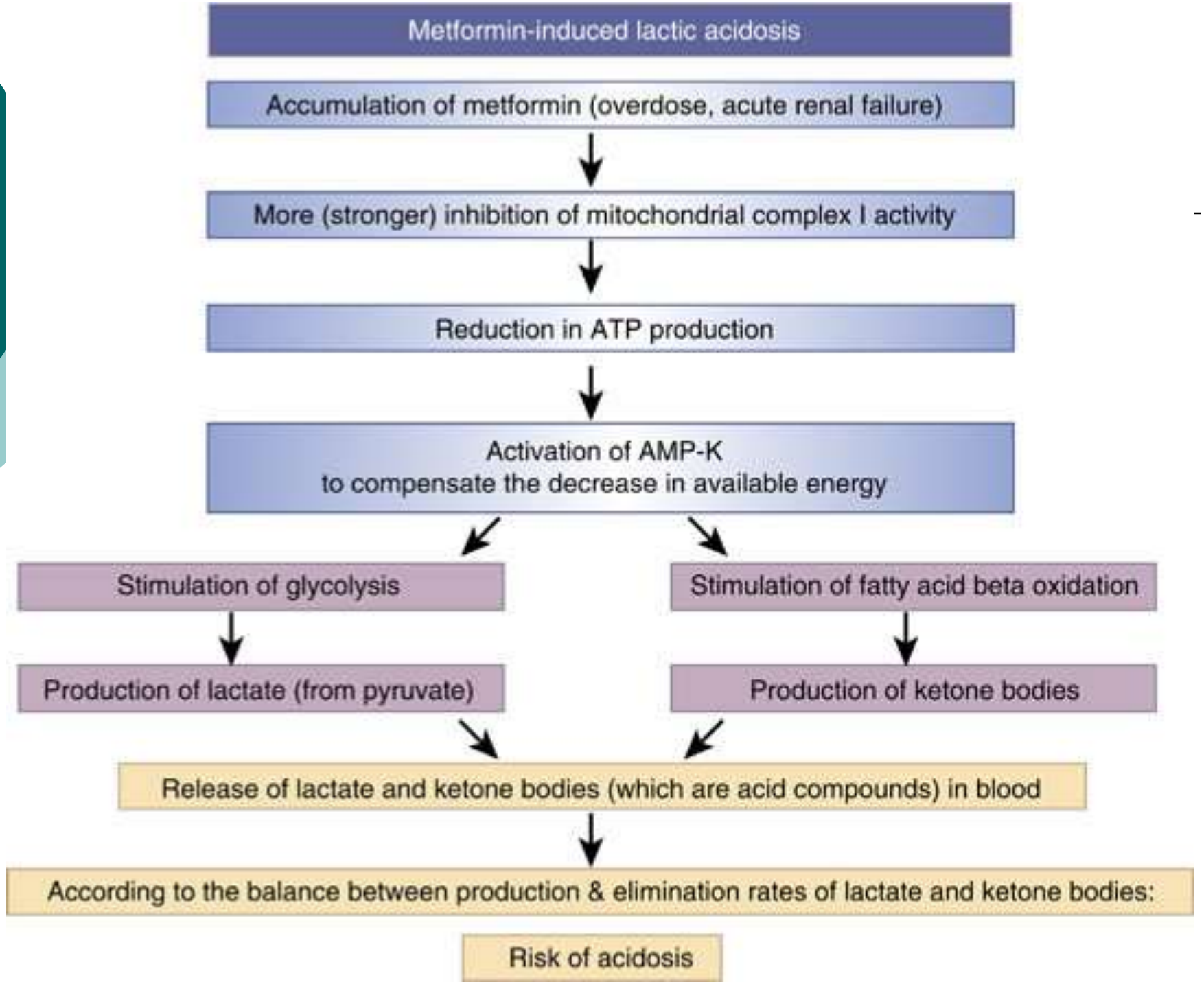
- is a potentially life-threatening complication in people with diabetes mellitus.
- It happens predominantly in those with type 1 diabetes, but it can occur in those with type 2 diabetes under certain circumstances.

Diabetic ketoacidosis

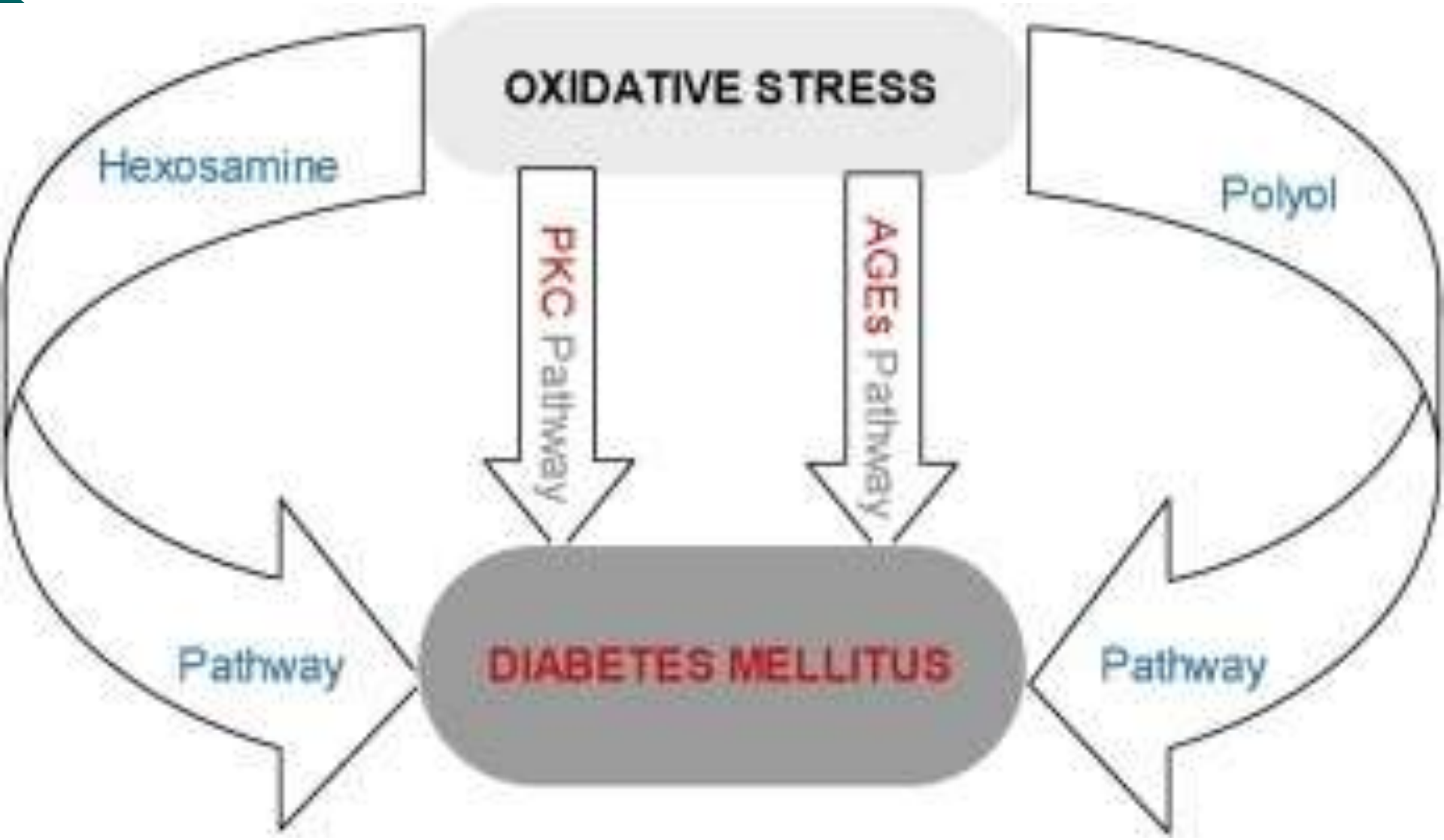
- Marked insulin deficiency, and the release of epinephrine blocks any residual insulin action and stimulates the secretion of glucagon. It excess decreases peripheral utilization of glucose and increase gluconeogenesis.
- Hyperglycemia causes an osmotic diuresis and dehydration characteristic of the ketoacidotic state.
- Insulin deficiency stimulates lipoprotein lipase,and increases levels of free fatty acids, which are esterified to fatty acyl coenzyme A in liver. Oxidation of fatty acyl coenzyme A molecules within the hepatic mitochondria produces **ketone bodies**.
- The rate at which ketone bodies are formed may exceed the rate at which acetoacetic acid and β-hydroxybutyric acid can be utilized by peripheral tissues, leading to **ketonemia and ketonuria**.
- If the urinary excretion of ketones is compromised by dehydration, **systemic metabolic ketoacidosis results**.

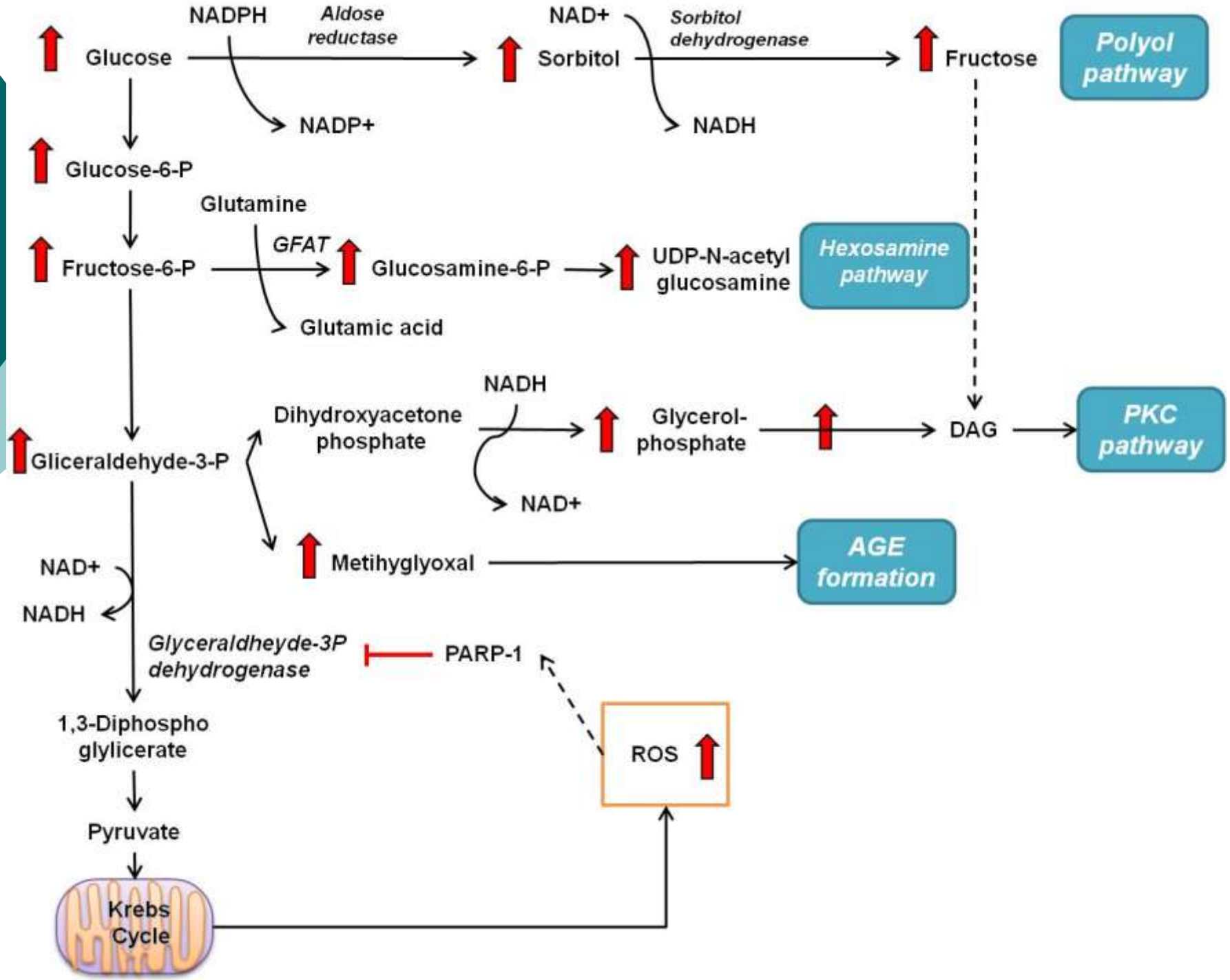
Lactic acidosis

- Lactic acidosis occurs whenever lactate production exceeds its utilization. This can occur with tissue hypoxia or in nonhypoxemic conditions when cellular metabolism is impaired.
- Lactic acidosis presents with non-specific symptoms such as lethargy, nausea, vomiting, altered level of consciousness and abdominal pain.
- Biochemical features of lactic acidosis are those of an elevated anion gap metabolic acidosis with high blood lactate concentrations.
- There appears to be no direct correlation between blood concentrations of metformin


Metformin-induced lactic acidosis
Accumulation of metformin (overdose, acute renal failure)
More (stronger) inhibition of mitochondrial complex I activity
Reduction in ATP production
Activation of AMP-K
to compensate the decrease in available energy
Stimulation of glycolysis
Stimulation of fatty acid beta oxidation
Production of lactate (from pyruvate)
Production of ketone bodies
Release of lactate and ketone bodies (which are acid compounds) in blood
According to the balance between production & elimination rates of lactate and ketone bodies:
Risk of acidosis

Pathways of complications


OXIDATIVE STRESS
Hexosamine
PKC Pathway
AGEs Pathway
Polyol
Pathway
DIABETES MELLITUS
Pathway


NADPH
Aldose reductase
NAD+
Sorbitol dehydrogenase
Glucose
Sorbitol
Fructose
Polyol pathway
NADP+
NADH
Glucose-6-P
Glutamine
GFAT
Fructose-6-P
Glucosamine-6-P
UDP-N-acetyl glucosamine
Hexosamine pathway
Glutamic acid
NADH
Dihydroxyacetone phosphate
Glycerol-phosphate
DAG
PKC pathway
Gliceraldehyde-3-P
NAD+
Metihyglyoxal
AGE formation
NAD+
NADH
Glyceraldheyde-3P dehydrogenase
PARP-1
1,3-Diphospho glylicerate
ROS
Pyruvate
Krebs Cycle

MORPHOLOGY OF DIABETES AND ITS LATE COMPLICATIONS

- Pathologic findings in the pancreas are variable and not necessarily dramatic.
- The important morphologic changes are related to the many late systemic complications of diabetes.
- In individuals with tight control of diabetes, the onset might be delayed.

Diabetes morphology

- macrovascular disease (macroangiopathy)
- microangiopathy
- nephropathy
- retinopathy
- neuropathy
- and other

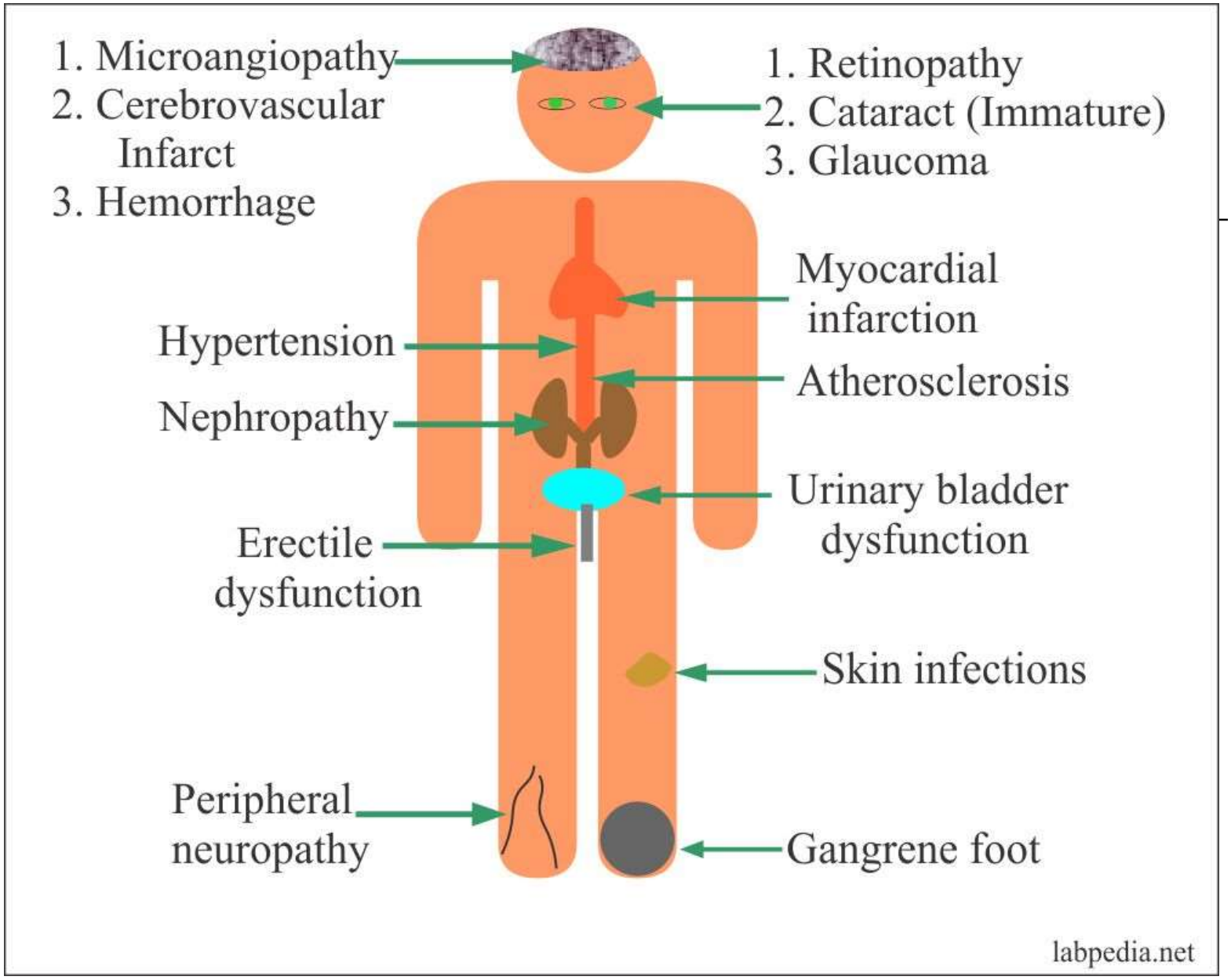
- These changes are seen in both type 1 and type 2 diabetes.

MORPHOLOGY PANCREAS.

- **One or more of the following alterations may be present:**
- Reduction in the number and size of islets.
- Leukocytic infiltrates in the islets (insulitis).
- In type 2 diabetes there may be a subtle reduction in islet cell mass.
- Amyloid deposition within islets in type 2 diabetes begins in and around capillaries and between cells.
- An increase in the number and size of islets is especially characteristic of nondiabetic newborns of diabetic mothers. Presumably, fetal islets undergo hyperplasia in response to the maternal hyperglycemia.

DIABETIC MACROVASCULAR DISEASE.

- Endothelial dysfunction.
- Accelerated atherosclerosis involving the aorta and large- and medium-sized arteries – hallmark of diabetes.
- Significantly, myocardial infarction is almost as common in diabetic women as in diabetic men.
- Gangrene of the lower extremities.
- The larger renal arteries are also subject to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation.


1. Microangiopathy
2. Cerebrovascular Infarct
3. Hemorrhage
1. Retinopathy
2. Cataract (Immature)
3. Glaucoma
Myocardial infarction
Hypertension
Atherosclerosis
Nephropathy
Urinary bladder dysfunction
Erectile dysfunction
Skin infections
Peripheral neuropathy
Gangrene foot
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DIABETIC MICROVASCULAR DISEASE.

- **Hyaline arteriolosclerosis**, the vascular lesion associated with hypertension, is both more prevalent and more severe in diabetics than in nondiabetics, but it is not specific for diabetes and may be seen in elderly nondiabetics without hypertension.

DIABETIC MICROVASCULAR DISEASE.

- diffuse thickening of basement membranes.
- most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla.
- It should be noted that despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins.

Diabetic Nephropathy

- Kidney is a target organ.
- **Three lesions are:**
- glomerular lesions
- renal vascular lesions (principally arteriolosclerosis)
- pyelonephritis, including necrotizing papillitis.

Diabetic Nephropathy

- The most important glomerular lesions are capillary basement membrane thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis.

Nodular Glomerulosclerosis.

- Kimmelstiel-Wilson disease
- The glomerular lesions take the form of ovoid or spherical, often laminated, nodules of matrix situated in the periphery of the glomerulus.
- Approximately 15% to 30% of individuals with long-term diabetes develop nodular glomerulosclerosis.

Pyelonephritis

- One special pattern of acute pyelonephritis, necrotizing papillitis (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics.

Diabetic Ocular Complications.

- The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma.

Gestational diabetes

Gestational diabetes

- in the second or third trimester of pregnancy,
- resolves after the birth of the baby.
- increasing levels of placental hormones, HPL and increasing maternal insulin resistance, especially after 20 weeks

Gestational diabetes is usually asymptomatic

- **risk factors**
  increasing maternal age
- family history of type 2 diabetes or GDM
- previous unexplained stillbirth
- previous macrosomiaobesity (three-fold risk of GDM)
- smoking
- change in weight between pregnancies: an inter-pregnancy gain of more than three BMI points doubles the risk of GDM

Risks of diabetes in pregnancy

fetal macrosomia
birth trauma (to mother and baby)
induction of labour or caesarean section

- miscarriage
- congenital malformation
- stillbirth
- transient neonatal morbidity
- neonatal death
- obesity and/or diabetes
- developing later in the baby's
- life.

Causes of mortality

Causes of mortality

- Macrovascular complications such as myocardial infarction, renal vascular insufficiency, and cerebrovascular accidents are the most common causes of mortality in long-standing diabetes.

Causes of mortality

Diabetes favor the development of adverse cardiovascular events.

- Insulin resistance is believed to contribute to "diabetic dyslipidemia" by favoring the hepatic production of atherogenic lipoproteins and by suppressing the uptake of circulating lipids in peripheral tissues.
- So **induce the formation of atherosclerotic plaques.**

- Diabetics are plagued by enhanced susceptibility to infections, which can lead to **sepsis**.