Lecture 19 Summary – Gestational Diabetes and Complications of Diabetes

Gestational diabetes;

- Type of diabetes that only develops during pregnancy
  - Usually diagnosed in late pregnancy
  - Causes high blood sugar → can affect pregnancy and health of baby
  - Blood sugar usually returns to normal after delivery
    - Baby is at greater risk of developing T2D
- Causes;
  - Pregnancy hormones disrupt signalling b/w insulin receptors and GLUT4 activation
    - Leads to rise in mother's blood glucose
  - As baby grows, placenta makes more and more insulin blocking hormones.
    - All pregnant women have some insulin resistance during late pregnancy.
  - Placental hormones provoke rise in the blood sugar to a level that can affect the growth of the baby.
- Risk factors;
  - Age >25
  - Family/personal health history;
    - Pre-diabetes
    - Family history of T2D
    - Had gestational diabetes in previous pregnancy
    - Delivered a baby that weighed >9 lbs.
    - Unexplained stillbirth
  - Excess weight: BMI 30 or higher
  - Race: black, Hispanic, American Indian, Asian more susceptible.
- Risks

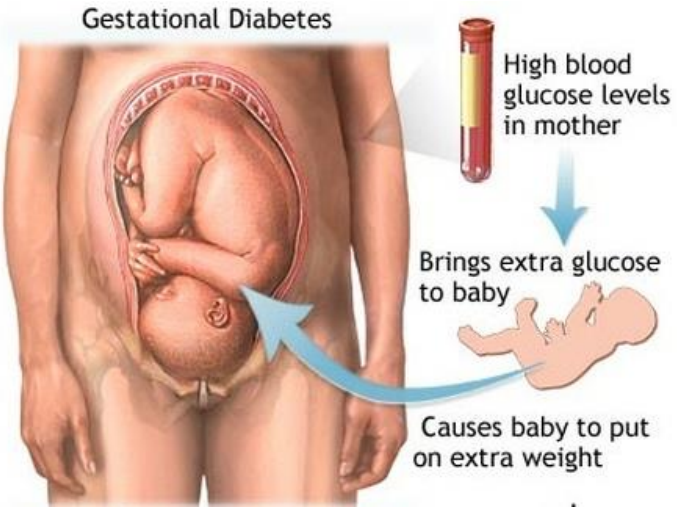


TABLE 2

Adverse maternal and fetal outcomes associated with gestational hyperglycemia

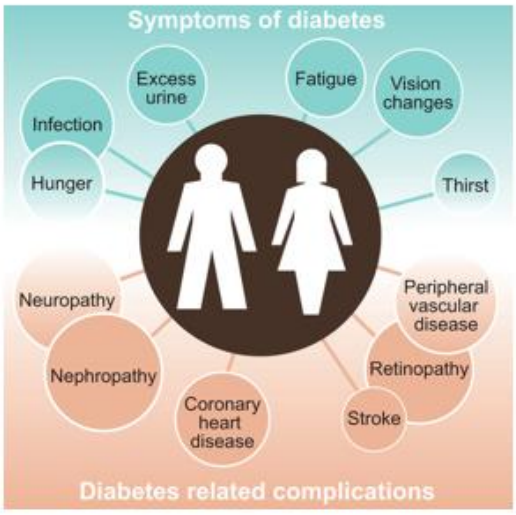
Fetal	Maternal
• large for gestational age/macrosomia • respiratory distress syndrome • neonatal jaundice • neonatal hypoglycemia • polycythemia • hypocalcemia • hypomagnesemia • shoulder dystocia (fracture, brachial plexus injury)	• preclampsia/gestational hypertension • birth trauma • increased risk of developing T2DM

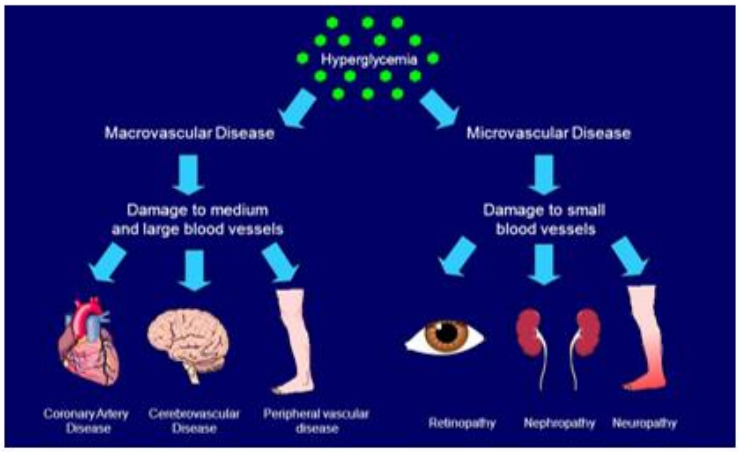
Recall:

Type 1	Type 2	Gestational
Usually young	Usually older	First detected in pregnancy
Short history- acute onset	Insidious onset	Routine testing
Not overweight	Often overweight	Often overweight
Insulin deficiency	Insulin resistance	Usually insulin resistance - placental hormones
Rare	Common	Becoming more common
Requires insulin from diagnosis	Diet and lifestyle change can reverse it Then add oral medications May require insulin	Diet and lifestyle plus medications to limit effects on the growing baby
Often random	Strong family history	Family history of T2DM

- Type I → complete lack of insulin production due to β-cell destruction
- Type II → insulin resistance leading to lack of insulin via β-cell degradation
    - Both lead to hyperglycaemia if left untreated

<u>Major complications of diabetes;</u>

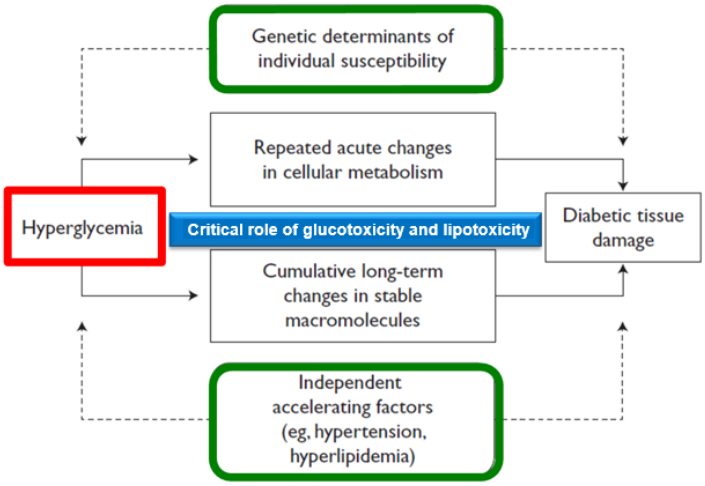




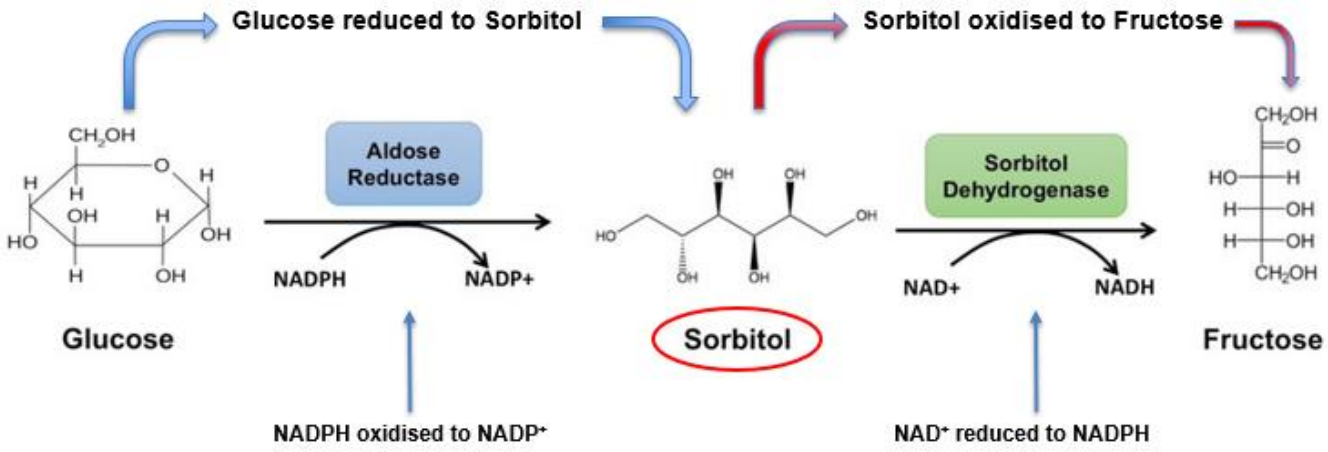
<u>Common features leading to vascular complications</u>

Complications of chronic hyperglycaemia;

- Glucose shunting into polyol pathway
    - Polyol pathway used for tissues that don't rely on insulin for glucose transport eg; sorbitol aldose reductase pathway.
        - Tissues such as; kidneys, nerves, RBCs, blood vessels, eyes.

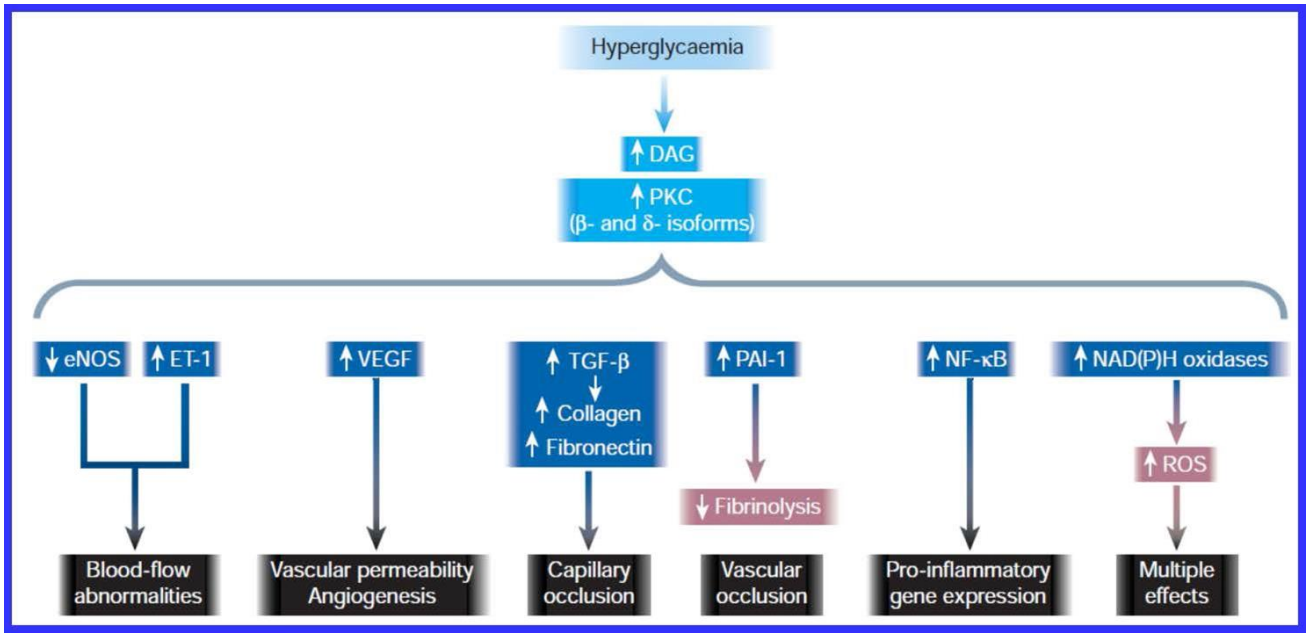


- Glucose is normally phosphorylated by hexokinase but when there is excess glucose, hexokinase become saturated
    - Any excess glucose is shunted into the polyol pathway where aldose reductase reduces glucose to sorbitol → sorbitol is slowly converted to fructose by sorbitol dehydrogenase.

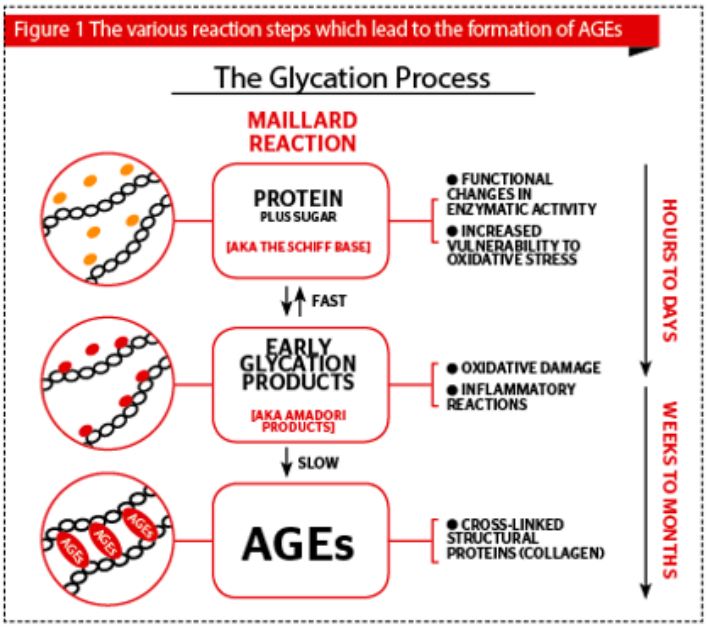


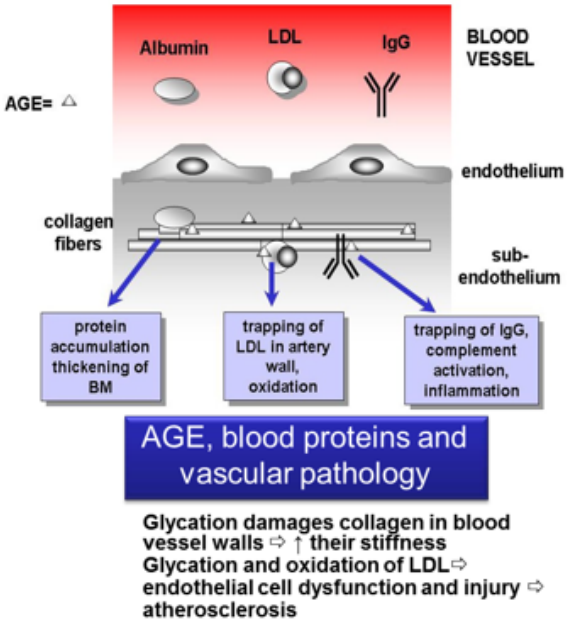
    - Sorbitol concentration in the eyes kidneys and nerves is usually minimal or absent.
- Sorbitol can't pass through cell membranes → therefore, it builds up inside cells. This increases cellular osmotic pressure and water moves into the cell.
    - Can cause direct cell injury
- Polyol pathway lowers the concentration of NADPH and NAD+ → these are required for redox reactions eg; reducing glutathione.
    - Leads to oxidative stress and reduced NO production (decreased vasodilation)
- High sorbitol concentration can induce glycation of proteins → increased formation of AGEs (non-enzymatic modification of proteins)

- Activation of protein kinase C
    - PKC needed for intracellular signalling
    - Regulates vascular functions eg; permeability vasodilation, endothelial activation and growth factor signalling
    - Elevated PKC levels in diabetics
        - From increased diacylglycerol production (from glucose)
        - Occurs in cells that don't rely on insulin for glucose absorption
        - Contributes to vascular damage in the retina, kidney and nerves.

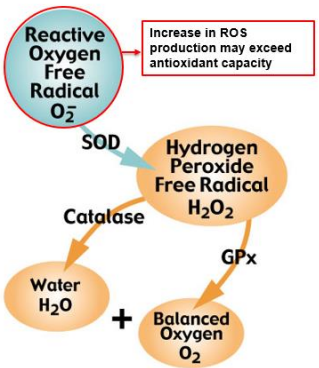


- Production of advanced glycation end products (AGEs)
  - Non-enzymatic attachment of glucose to proteins, lipids and NAs
  - Dietary AGEs are ingested from browned foods (cooked foods)
  - Endogenous AGE production is normal but increases from persistent hyperglycaemia → evident in non-insulin dependent tissues.
  - Leads to cross-linking and trapping of proteins eg; albumin, LDL, immunoglobulins, complement proteins (alters structure and function of proteins)
  - Increases lipid oxidation and oxidative stress.
  - Bind to cellular receptors and induce release of pro-inflammatory cytokines and growth factors
    - Stimulates cell prolif. eg; smooth muscle in blood vessels and collagen synthesis.
  - Causes structural changed to vascular basement membrane
    - Increased vascular stiffness
    - Increased permeability
  - Reduces NO → decreased vasodilation
  - Contributes to vascular and eye dysfunction
  - RAGE – receptor for AGEs
    - Found on many cells eg; endothelial, smooth muscle, immune cells.

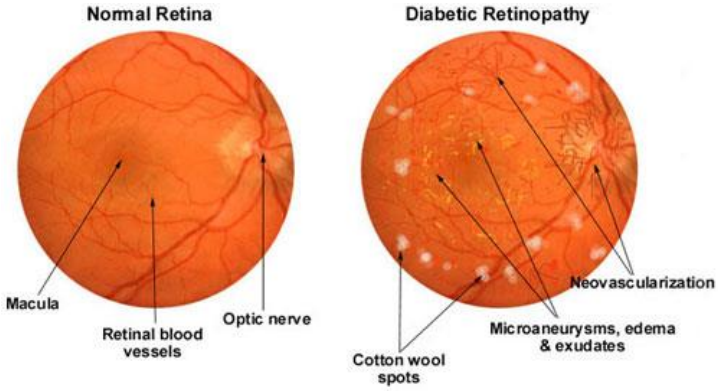




- Increased production of ROS and oxidative stress
  - Glucose & FA metabolites undergo oxidative phosphorylation in mitochondria to produce ATP
  - ROS form as natural by-product of the normal metabolism of oxygen
    - Initially as a superoxide
    - Endogenous defence → antioxidants eg; superoxide dismutase, catalase and glutathione.
  - Excess glucose and FFA → increases oxidative phosphorylation
    - Elevated ROS → exceeds the anti-oxidant capacity.
  - Major contributor to tissue damage in diabetic patients;
    - Oxidative stress
    - DNA damage
    - Pro-inflammatory response
    - Mitochondrial impairment and dysfunction
    - Apoptosis
    - Cancer

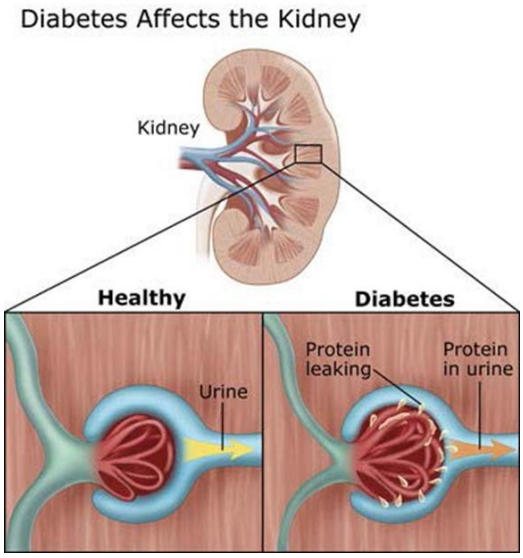


Microvascular complications;



Hyperglycaemia and retinopathy;

- Stage I (non-proliferative);
  - Increased retinal capillary permeability and dilation
  - Formation of micro-aneurysms
  - Haemorrhage
- Stage II (pre-proliferative);
  - Ischaemia and reduced perfusion
  - Localised infarctions
- Stage II (proliferative);
  - Neovascularisation and formation of fibrotic tissue
  - Retinal detachment and haemorrhage into the vitreous humour
  - Macular oedema

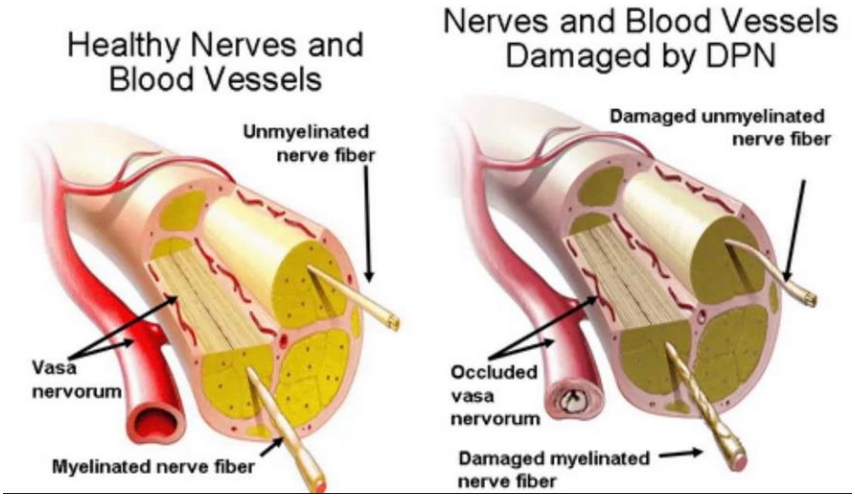


Hyperglycaemia and nephropathy;

- Most common cause of end-stage renal failure
- Glomerular capillaries are damaged
- Intra-glomerular hypertension
  - Hyperfiltration → leakage of stuff into the filtrate
  - Glomerular enlargement
  - Basement membrane thickening
  - Glomerulosclerosis
  - Albuminuria
  - Loss of GFR → loss of kidney function → affects the buffer system, RBC count, etc.

Hyperglycaemia and neuropathy;

- Most common complication of diabetes
  - From AGE accumulation and polyols damaging blood vessels → causing ischaemia
  - Degradation of Schwann cell → demyelination and conduction abnormalities.
- Weakness and/or numbness and pain due to nerve damage
  - Focal or diffuse in nature
  - Somatic and autonomic
  - Sensory nerve affected more than motor nerves.



Hyperglycaemia and diabetic foot;

- Due to macro and micro vascular disease
  - Peripheral neuropathy → nerve damage – loss of sensation
  - Damage to blood vessels → poor circulation and poor wound healing
  - Impaired immune system → increased risk of infection

Macrovascular Complications;

Hyperglycaemia and CVD;

- Polyol pathway activation
  - Increased oxidative stress
  - Reduced NO production
  - Increased formation of AGEs
- Elevated PKC
  - Increased permeability
  - Decreased vasodilation
  - Endothelial activation and cell proliferation
- Increased generation of AGEs
  - Protein cross-linking → lack of function
  - Elevation lipid oxidation
  - Loss of vasodilation ability → increased vascular stiffness
  - Increased permeability
  - Release of pro-inflammatory cytokines
- Generation of ROS
  - DNA damage
  - Increase in pro-inflammatory cytokines → direct damage
  - Mitochondrial impairment and dysfunction
  - Apoptosis

Hyperglycaemia and cerebrovascular disease

- Cerebral arteriosclerosis
- Thrombosis/embolism
- Aneurysm
- Haemorrhage
- Cerebral ischemia and infarction
- Cerebrovascular deaths = 16% men, 33% women due to diabetes