Complications of diabetes mellitus

- **Vascular**
  - Large arteries (macroangiopathy): atherosclerosis and related complications
  - Arterioles: hyaline arteriolosclerosis
  - Microangiopathy/microvascular: capillary basement membrane thickening
- **Renal**
  - Diabetic nephropathy
  - Infection -> acute and chronic pyelonephritis
  - Atherosclerosis related including infarction and renal artery stenosis
- **Ocular**
  - Cataracts
  - Glaucoma
  - Diabetic retinopathy
    - Non-proliferative
    - Proliferative
    - Macular oedema
- **Neuropathy**
  - Peripheral nerves
  - Autonomic nerves
  - Mononeuropathy
  - Diabetic polyradiculopathy
- **Skin**
  - Ulcers: multifactorial
    - Impaired sensation due to neuropathy
    - Predisposition to infection
    - Impaired blood supply due to atherosclerosis and microangiopathy impair healing
  - Necrobiosis lipoidica diabetica (rare)
  - Infection
    - Predisposition to infection (e.g. pulmonary, urinary tract, skin) related to hyperglycaemia and impaired function of phagocytes and other inflammatory cells
  - Liver: non-alcoholic steatosis, steatohepatitis and cirrhosis
  - Acute metabolic complications
    - Diabetic ketoacidosis (primarily in type 1)
    - Non-ketotic hyperosmolar coma (type 2)
    - Hypoglycaemia from too much insulin or hypoglycaemics

**Nephropathy, atherosclerosis, neuropathy, ocular complications**

- Are late complications
- Risk increases in relation to duration of hyperglycaemia
- Usually become apparent in 2nd decade of hyperglycaemia, may be present at time of diagnosis of type 2 which often has a long asymptomatic period
- Better blood glucose control reduces risk
- Other undefined factors modulate the risk e.g. genetic
- Nephropathy, neuropathy, retinopathy are largely related to microangiopathy

**Basement membranes (BM)**

- All epithelial, endothelial and mesothelial cells sit on a BM
- Similar material surrounds Schwann cells and various other connective tissue cells (e.g. adipocytes, smooth muscle cells) – termed basal lamina
• Composition
  • Specialised extracellular matrix
  • Central electron dense layer (lamina densa) with less distinct electron lucent layers (lamina rara) on either side (all 3 together sometimes termed basal lamina)
  • Delicate network of type IV collagen in a matrix of glycoproteins (e.g. laminin) and other extracellular components (e.g. heparan sulphate proteoglycan) largely produced by the overlying cells
  • +/- reticular layer: collagen type III originating from underlying extracellular matrix cells
  • Often too thin to be seen distinctly on H&E with light microscopy except in areas where it is thicker (e.g. trachea) but can be seen with special stains on light microscopy

• Function
  • Bonds cells to underlying connective tissue
  • Provides framework for cell development and regeneration
  • Freely permeable to small molecules but impedes passage of macromolecules

Arteries
Layers (general):
  • Intima: endothelium (simple squamous), basement membrane, (+ small amount of connective tissue/elastin in some), internal elastic lamina (except in smallest arterioles)
  • Media: variable amounts of smooth muscle and extracellular matrix, predominantly elastin; in some vessels an external elastic lamina is also present
  • Adventitia: extracellular matrix including abundant elastin, vasa vasorum in larger vessels

Media
  • Large arteries (aorta and its main branches): abundant elastic tissue
  • Medium (distributing arteries) and small (<2mm) arteries: predominantly smooth muscle
  • Arterioles (diam 100um or less): several layers of smooth muscle cells only

Smooth muscle cells produce the extracellular matrix including elastin

In diabetes there is generalised thickening of vascular and non-vascular basement membranes. Proposed general mechanisms underlying basement membrane thickening:
• Complex and not fully understood, different pathways that interact
• Hyperglycaemia ->
  • Formation of advanced glycation end products (AGE) – glucose binds to irreversibly to protein amino groups. AGE may also form on lipids, nucleic acids.
    • AGE modified extracellular matrix components
      • Lead to protein cross-linking
      • Are resistant to proteolytic digestion
      • Trap other proteins (e.g. plasma proteins)
      • May promote cell damage
      • Non-enzymatic glycation of haemoglobin: HbA1c – serves as marker of glycemic control
      • May alter intracellular signalling, gene expression and oxygen derived free radicals
  • Increase in aldose reductase pathway
    • In cells not requiring insulin for glucose uptake e.g. Schwann cells, retinal pericytes, lens of eye
    • Metabolism of excess intracellular glucose -> excessive glucose metabolites (e.g. sorbitol) with reduced synthesis of an important antioxidant -> osmotic cell injury and increased susceptibility to oxidative injury
  • Production of reactive oxygen species ->
    • Upregulation of growth factor expression e.g. VEGF
    • Alteration of proteins and lipoproteins
    • Cell damage
  • Increased activation of protein kinase C (PKC) signal transduction pathway
    • May be related to AGE formation
    • Activation of signal transduction pathways for extracellular matrix protein production
  • Overactive renin-angiotensin system
    • Angiotensin II stimulates production of important growth factors e.g. TGF-beta that plays a role in extracellular matrix formation in the renal mesangium and VEGF is important in proliferative retinopathy
    • Important in nephropathy and retinopathy
• Genetic factors in the patient are an important influence

Understanding pathogenesis helps in the development of potential treatments e.g. use of inhibitors of AGE formation, antioxidants, angiotensin II inhibitors

The simplified version
Increased amounts of extracellular matrix with altered function due to:
• Upregulation (various mechanisms) of production of various growth factors and cytokines -> increased extracellular matrix production
• AGE modified extracellular matrix proteins -> cross-linking, plasma protein trapping, reduced proteolytic digestion
Cell damage e.g. via aldose reductase pathway and osmotic injury, activation of reactive oxygen species

The microangiopathy (capillary basement membrane thickening), hyaline arteriolar changes and mesangial thickening in diabetes are caused by the above processes. Hypertension may play a role in the development of hyaline arteriolosclerosis.
Normal renal glomerular structure

- Filtration barrier
  - Endothelial cells, epithelial cells and basement membrane
  - Endothelium
    - Fenestrated with large pores that only prevent blood cells and platelets from passing through
    - The diaphragm that typically spans fenestrations between endothelial cells in certain other vascular beds is absent
  - Epithelial cells (podocytes)
    - Extensive array of processes that interdigitate on outside of capillary with slit like spaces (filtration slits) between
    - Each filtration slit is spanned by a thin filtration slit diaphragm or membrane
  - Glomerular capillary basement membrane (BM) of central importance
    - Made by epithelial and endothelial cells
    - Composed of collagen type IV, glycoproteins and proteoglycans
    - No reticular component
    - Size barrier: molecules larger than about 69,000 daltons unable to cross
    - Charge barrier: proteoglycan component is anionic (negatively charged), therefore repels negatively charged molecules
    - Albumin has a molecular weight of 69,000 daltons and is negatively charged

- Mesangium
  - Mesangial cells and extracellular matrix (various collagens and ground substance)
  - Function
    - Supports capillary loops
    - Cells have phagocytic function and clean the basement membrane
    - May regulate blood flow in capillaries

Diabetic nephropathy

- Approximately 25-35% of patients with longstanding diabetes (types 1 and 2) develop diabetic nephropathy and renal failure.
- Time to development of overt proteinuria is 10-15 years or more after diabetes onset. Once significant proteinuria develops, end stage renal disease develops in about 5-10 years. However, there is considerable variability between patients.
- Diabetic retinopathy often also present
- Morphology: changes include:
  - Early in the course of disease, glomeruli may appear slightly enlarged
  - Diffuse and nodular diabetic glomerulosclerosis
    - Diffuse
      - Diffuse thickening of glomerular capillary BMs (not seen on light microscopy until very thickened)
      - Diffuse increase in mesangial matrix +/- mild proliferation of mesangial cells
      - Which develops first
    - Nodular (Kimmelstiel-Wilson lesion)
      - Localised nodular areas of increased mesangial matrix with few cells
      - Less common than diffuse and generally superimposed on diffuse lesion
  - Insudative glomerular lesions: Eosinophilic nodular accumulations of plasma constituents in capillary loops or in Bowman's capsule
  - Hyaline arteriolosclerosis in both afferent and efferent arterioles
  - Tubular basement membrane thickening
  - Most of the changes are not specific for diabetes
- Immunofluorescence: non-specific (not immunologic) trapping of plasma albumin and IgG in tubular and capillary basement membranes
- Hyaline arteriolosclerosis (afferent arteriole only) also develops with age and in hypertension.
- Macroscopically the kidneys may be slightly enlarged with a granular surface, or small due to co-existent changes related to hypertension or chronic pyelonephritis.
- Progression
  - Initial glomerular hyperfiltration associated with enlarged glomeruli (cause uncertain) commencing within first few years of onset
  - Microalbuminuria
  - Diffuse glomerular mesangial and capillary BM thickening (which develops first), onset of overt proteinuria +/- nephrotic syndrome +/- hypertension. Glomerular changes -> narrowing of capillary lumina and glomerular ischaemia, hyaline arteriolosclerosis contributes to glomerular ischaemia. Hypertension can contribute to glomerular injury.
  - Falling GFR: damaged glomeruli -> impaired renal function. Progressive irreversible glomerulosclerosis, related tubules atrophy and interstitial tissue undergoes fibrosis -> further impairment of renal function
  - End stage renal disease
- Pathogenesis of diabetic glomerulosclerosis: complex, at least partly related to microangiopathy (pathogenesis outlined above)

Various pathways implicated, pathways interact

- Haemodynamic factors
  - Hyperglycaemia -> glomerular hyperfiltration and microalbuminuria, altered tubuloglomerular feedback
  - Vasoconstrictor effect of angiotensin II more potent on efferent arteriole -> increased glomerular capillary pressure
Hypertension may contribute via glomerular hyperfiltration and endothelial and mesangial damage due to haemodynamic stress.

Metabolic factors e.g. AGE mechanism, activation of protein kinase C

Hormonal factors: overactive renin angiotensin system (RAS), also contributes to development of hypertension. Angiotensin II
  - Can downregulate nephrin, an important protein of the slit diaphragm, leading to proteinuria
  - Can activate other cytokine pathways such as transforming growth factor-beta (TGF-beta) and vascular endothelial growth factor (VEGF) systems. TGF-beta-1 stimulates an increase in mesangial matrix deposition and glomerular basement membrane (GBM) thickening
  - Impairs nitric oxide function which has vasodilatory and protective role

Genetic influences

Clinical Progression slowed by good blood glucose control, strict blood pressure control, administration of ACE inhibitors or angiotensin receptor blockers (ARBs) and treatment of dyslipidemia.

Proteinuria and nephrotic syndrome
  - From diabetic glomerulosclerosis
  - Alterations in capillary BM impair normal function
  - Albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 diabetes

Hypertension in diabetics
  - From diabetic glomerulosclerosis
  - From chronic renal failure
  - Other risk factors e.g. obesity, familial
  - Renal artery stenosis (less common)

Chronic renal failure (CRF)
  - Diabetic glomerulosclerosis and hyaline arteriolar sclerosis -> chronic glomerular ischaemia -> glomerular obsolescence/sclerosis and also chronic renal ischaemia with tubular atrophy and interstitial scarring -> poorly functioning kidneys
  - Approx. 30% of patients develop chronic renal failure

Chronic pyelonephritis and hypertension may also cause/contribute to CRF

Remember also that diabetics can get other renal diseases.

Ocular complications
  - Cataracts: from lens swelling and opacity
  - Glaucoma: formation of fibrovascular membranes on iris related to ischaemia (from microangiopathy) -> blockage of outflow channels of aqueous humour
  - Diabetic retinopathy
    - Develops in about 75% within 15 years of disease onset
    - More prevalent among patients with type 1 diabetes than type 2
    - Often coexists with diabetic nephropathy, but they can also occur independently of each other
    - Non-proliferative: microvascular changes with pericyte and also ultimately endothelial cell loss, leads to increases in vascular permeability, vascular weakening and alterations in retinal blood flow, including blockage of capillaries -> exudates, haemorrhages, microaneurysms, microinfarcts
    - Macula oedema
    - Proliferative: ischaemia from microvascular changes -> proliferation of small vessels, initially on surface of retina and later into the vitreous -> haemorrhages, fibrosis and retinal detachment.
    - Increased VEGF expression, contributed to by hypoxia and oxidative stress is important in pathogenesis of proliferative retinopathy
    - VEGF is an angiogenic growth factor and increases vascular permeability

Neuropathy
  - Distal symmetric sensory or sensorimotor neuropathy
    - Symmetric, motor and sensory
    - ?from Schwann cell injury -> demyelination
    - ?from axonal injury
    - ?from microangiopathy impairing blood flow and nutrition of nerve
  - Autonomic neuropathy
    - -> impotence, bowel and bladder dysfunction etc
    - ?similar pathogenesis
  - Diabetic polyradiculopathy
    - Severe disabling pain in the distribution of one or more nerve roots
    - May be accompanied by motor weakness
  - Focal or multifocal asymmetric neuropathy/mononeuropathy
    - Affects larger nerves
    - ?from microangiopathy impairing blood flow and nutrition of nerve
Atherosclerosis

- Slow build up over years of lipids and fibrous material in the intima of large and medium sized arteries
- In diabetics may extend more distally than usual
- Pathogenesis in diabetes
  - Vascular basement membrane and endothelial changes -> increased permeability, trapping of lipids in intima
  - Dyslipidaemia
  - Hypertension
- Effects
  - Chronic narrowing of the vessel lumen -> acute or chronic ischaemia
  - Acute plaque event (ulceration, fissuring, haemorrhage into plaque) -> formation of overlying occlusive or non-occlusive thrombus
  - Occlusive thrombus may -> infarction
  - Atrophy of media may -> aneurysm formation ->
    - Rupture
    - Thrombus formation -> embolism
  - Embolism: thrombus or plaque itself may embolise (thrombo-embolus, athero-embolus) -> ischaemia or infarction downstream
- Important sites
  - Coronary arteries -> angina, myocardial infarction, sudden cardiac death, cardiac failure
  - Abdominal aorta -> aneurysms, emboli to legs, kidneys
  - Renal arteries -> renal artery stenosis -> chronic renal ischaemia and hypertension
  - Carotid arteries -> cerebral infarction, transient ischaemic attacks
  - Femoral arteries -> claudication, skin ulcers, gangrene
  - Mesenteric arteries -> acute or chronic ischaemia, infarction of bowel

Sources


