DIABETES MELLITUS & DISORDERS OF GLUCOSE HOMEOSTASIS

Diabetes is the most common endocrine disease & comprises a heterogenous group of hyperglycaemic disorders characterised by high serum glucose & disturbances of carbohydrate & lipid metabolism.

Long term complications include disorders of blood vessels (especially microvascular). The cardiovascular system, eyes, kidneys & nerves are of particular susceptibility.

Normal Physiology.

- CNS cannot synthesize glucose & only stores a few minutes supply.
- Normal serum glucose is tightly controlled between 5-8mmol/L.
- Glucose is derived from three sources:
    - *intestinal absorption* (dietary)
    - *glycogenolysis* (breakdown of glycogen stores)
    - *gluconeogenesis* (formation of glucose from precursors including lactate, pyruvate, amino acids & glycerol).

Insulin.

- Beta-cells of the pancreas sense elevations in blood glucose & trigger insulin release.
- Under normal circumstances, insulin is rapidly degraded through liver & kidneys.
    - Half life is 3-10mins.
- Only liver & kidney contain *glucose-6-phosphatase* (the enzyme necessary for release of glucose into circulation).
- Insulin inhibits both gluconeogenesis & glycogenolysis.
- Insulin is required to transport glucose across fat-cell membranes.

Glucose-regulatory mechanisms.

- Regulation of glucose involves hormonal, neurohumoral & autoregulatory factors.
- Glucoregulatory hormones include:
    - Insulin, glucagon, adrenaline, cortisol & growth-hormone.
- *Insulin:*
    - Suppresses endogenous glucose production.
    - Stimulates glucose uptake, storage & utilisation.
- *Glucagon:*
    - Released by alpha-islet cells of pancreas.
    - Increases both glycogenolysis & gluconeogenesis.
    - Results in increased ketone production by liver.
- *Adrenaline:*
    - Stimulates both hepatic glucose production & limits glucose use.
    - Increases both hepatic glycogenolysis & gluconeogenesis.

Types of Diabetes.

Type I.

- Characterised by abrupt failure of insulin production (w/ tendency towards ketosis)
- Parenteral insulin is required to sustain life.
- Results from auto-antibody formation in 85-90% of cases.
- *Pathophysiology:*
    - Chronic autoimmune process (existing in a preclinical state for years)
    - Hyperglycaemia and ketosis is the classical manifestation.
    - Near-total lack of insulin-secreting beta-cells of pancreas, with preservation of the remaining pancreatic cells left intact.
    - Strong HLA- associations exist.

Type II.

- High incidence of obesity.
- Patients remain asymptomatic for long periods & show low, normal or elevated levels of insulin due to tissue-resistance.
- Ketosis is rare.
- A subgroup of patients (< 25 years of age) have a glucokinase gene mutation.

Gestational Diabetes.

- Characterised by abnormal oral glucose tolerance test (occurring in pregnancy) which may or may not revert to normal post-partum.
- Presentation is that of non-ketotic hyperglycaemia in pregnancy.

Impaired glucose tolerance.

- ie. impaired glucose tolerance testing or an impaired fasting glucose.
- Plasma glucose levels are between normal & diabetic levels.
- Pathogenesis is related to tissue insulin resistance.

Clinical Features.

Type I.

- Patient is usually leaner, younger (< 40 years) & ketosis prone.
- Plasma insulin levels are absent or low. (Glucagon levels high).
- Onset of symptoms are abrupt
- Polyuria, polydipsia, polyphagia & weight loss.
- DKA.
- Cardiovascular & circulatory abnormalities, retinopathy, nephropathy, neuropathy, foot ulcers, severe infections & skin lesions.

Type II.

- Typically middle-aged or older, overweight with normal to high insulin levels.
- Symptom onset is gradual (even, asymptomatic).
- Decompensation leads to hyperosmolar nonketotic coma rather than ketosis.

Diagnostic Strategies.

Serum Glucose.
- Random plasma glucose > 11.1mmol/L
- Fasting glucose > 7mmol/L
- Abnormal oral glucose tolerance test.

Glycosylated Haemoglobin.
- An important way of testing the level of glucose control.
- Provides insight into the quality of glycaemic control over time (over preceding 6-8 weeks).
- Normal value is 4-6%.

Urine Glucose.
- Typically reagent tests (copper-reduction tests) or dipsticks.
- Both tests are imperfect and have multiple substances that can react with the test to create false readings.

Urine Ketones.
- A good test for *acetoacetate* (but not for beta-hydroxybutyrate).

Dipstick Blood Glucose.
- An accurate and easy way to monitor blood glucose.
- Haematocrits <30% or >50% will yield inaccurate readings.

Late Complications of Diabetes.

These result in significant morbidity and mortality & generally develop 15-20 years after the onset of overt hyperglycaemia.

Vascular Complications.
- Increased risk of atherosclerosis & thromboembolic complications.
    - A major cause of morbidity and premature death.
- Atherosclerotic lesions are widespread resulting in multi-organ pathology.
    - Coronary artery disease & stroke are common.
    - Increased incidence of *'silent'* MIs & CCF.
- Peripheral vascular disease: claudication, non-healing ulcers, gangrene & impotence

Diabetic Nephropathy.
- Approximately 1/2 of all ESRF in USA is a result of diabetic nephropathy.
- Involves two pathological patterns: *diffuse & nodular.*
- Disease usually progresses:
    - Enlarged kidneys w/ ↑ GFR
    - Microalbuminuria.
    - Macroproteinuria w/ HTN.
    - Reduced GFR.
    - Renal failure.
- Progression of renal failure is accelerated by HTN (which should be aggressively managed)
- ACE inhibitors are effective in managing HTN and lowering microalbuminuria.

The appearance of microalbuminuria correlates w/ presence of CAD & retinopathy.

Retinopathy.

- Diabetes is the leading cause of blindness in the USA.
- Background (simple) retinopathy is found in most diabetics who have prolonged disease.
    - Microaneurysms, small vessel obstruction, cotton-wool spots or soft-exudates, hard-exudates & macular ischaemia.
- Complications include: vitreal haemorrhage, cataracts & retinal detachment.
- Treatment = photocoagulation.
- Maculopathy involves central vision & requires urgent laser therapy.

Neuropathy.

- DM can result in both autonomic & peripheral neuropathies.
- May result from diabetic effects on the *vasa nervorum.*
    - Segmental demyelination.
- Symptoms include; anaesthesia, hyperaesthesia or pain.
    - Pain typically worse at night and is difficult to control.
- *Mononeuropathy (mononeuropathy multiplex)*
    - affects both motor & sensory nerves (of one nerve at a time).
    - Rapid onset with wasting & tenderness of involved muscles.
        - eg. sudden wrist-drop, foot-drop or cranial nerve palsy.
- *Autonomic neuropathy* occurs in many forms.
    - Poor swallowing, delayed gastric emptying, constipation, nocturnal diarrhoea.
    - Impotence, bladder dysfunction.
    - Orthostatic hypotension, syncope or cardiac arrest.
- **The Diabetic Foot.**
    - Sensory neuropathy, ischaemia & infections.
    - Loss of sensation leads to pressure necrosis (in poorly fitting footwear).
        - Small wounds go unnoticed.
    - All diabetic foot ulcers should be debrided of devitalised tissue.
    - Examination should focus on foreign bodies, soft-tissue gas, bony abnormalities etc.
    - Deep life-threatening infections are suggested by:
        - Full thickness ulcers.
        - Cellulitis greater than 2cm diameter (w/ or w/out lymphangitis)
        - Bone or joint involvement
        - Systemic toxicity.
        - **Typically *poly-microbial* (incl. gram-neg bacilli & anaerobes).**
            - **Require empiric broad-spectrum ABx coverage.**
            - **Often require amputation.**

Infections.

- DM patients are most susceptible to complications of infections due to their inability to limit microbial invasion.
    - Ineffective PMN leukocytes & lymphocytes.
- Increased incidence of extremity infections & pyelonephritis.
- Increased susceptibility to TB, candidiasis, mucormycosis, soft tissue infections, gangrene, osteomyelitis & malignant pseudomonas otitis externa.

Cutaneous Manifestations.

- Dermal sensitivity is manifested by *pruritic, erythematous indurations* that occur over insulin injection sites.
- Insulin *lipoatrophy*: raised areas of subcutaneous fat deposits at insulin injection sites
    - Can be avoided by rotation of injection sites to various locations.
- Diabetic oral hypoglycaemic agents can induce various rashes.
- Other skin conditions include:
    - Fungal infections
    - Acanthosis nigricans
        - Velvety brown-black thickening of keratin layer (usu. flexor surfaces)
    - plus others....
- Three forms of *diabetic thick skin:*
    - Scleroderma-like changes to fingers & dorsum of hand.
        - Stiff joints / poor mobility.
    - Measurably thick skin.
    - 'Scleroderma-adultorum'
        - Increased dermal thickness over back and upper neck.
- **Insulin Allergy:**
    - Mediated by IgE.
    - Local itching and pain, urticaria or anaphylaxis.
    - Requires hospital admission for desensitisation.

<u>Diabetes in Pregnancy.</u>

Prior to the discovery of insulin, the foetal death rate w/ diabetes in pregnancy was 60-70%, with a maternal morbidity of ~30%.

Pregnant women have a special predisposition to both glucose intolerance and excess ketone production. Pregnancy is also associated with a progression of retinopathy.

- Although nephrotic syndrome occurs in up to 71% of pregnancies, BP and proteinuria eventually return to 1st-trimester values.
- Nephropathy is assoc. w/ increased preterm labour, still-birth, neonatal death, foetal distress and intrauterine growth retardation.

Hypoglycaemia is also common in pregnancy, due to intensive insulin treatment required to maintain euglycaemia.

Ketoacidosis is associated with 50-90% foetal mortality !!

Oral Hypoglycaemic Agents.

Sulfonylureas.

- Mainstay of DM therapy.
- Increase insulin secretion by bind to specific beta-cell receptors.
- Works best in early T2DM.
- Renal failure/impairment predisposes to hypoglycaemia.

Metformin.

- Biguanide.
- Decreases hepatic glucose output & increases peripheral uptake of glucose.
- Decreases insulin resistance.
- *DOES NOT CAUSE HYPOGLYCAEMIA*
- Renal insufficiency can lead to *lactic acidosis.*
    - Should be withheld for 48 hours before or after iodinated contrast media.

Thiazolidinediones.

- Reduce insulin resistance.
- Include *rosiglitazone.*

Alpha-glucosidase inhibitors.

- Delay intestinal monosaccharide absorption & prevent complex carbohydrate breakdown.
- Associated w/ GI side effects.