PHAR3818 Endocrine, Diabetes and Reproductive

Diabetes Mellitus

- Diabetes mellitus is a syndrome with many causes characterised by chronic hyperglycaemia, due to the deficient action of insulin on target tissues. This may be due to inadequate insulin secretion, insulin resistance or both.
- Classification of diabetes:
    - Type 1 diabetes: absolute lack of insulin, unopposed actions of glucagon (hormone that promotes the breakdown of glycogen into glucose –released when energy needed). This occurs due to autoimmune b-cell destruction.
    - Type 2 diabetes: body does not respond properly to the insulin –problem with insulin signalling. Occurs due to progressive loss of beta cell. Insulin secretion occurs frequently in the background of insulin resistance.
    - Gestational diabetes mellitus (GDM): diabetes diagnosed in the 2nd or 3rd trimester of pregnancy that was not clearly overt diabetes prior to gestation –increased risk of subsequent diabetes
    - Specific types of diabetes due to their causes:
        - Monogenic diabetes syndromes: neonatal diabetes and maturity onset diabetes of the young
        - Diseases of the exocrine pancreas: cystic fibrosis
        - Iatrogenic diabetes: with glucocorticoid use, HIV/AIDS treatment, after organ transplantation
- Type 2 diabetes is a major problem, with prevalence rising greatly in correlation with rise in obesity levels
    - Prevalence of CVD is 2 times higher in people with diabetes

Type 1 diabetes (T1D)

- Beta cell destruction ultimately leads to diabetes mellitus, with absolute insulin deficiency. Insulin is required for survival and to prevent the development of ketoacidosis, coma and death.
- Can be due to:
    - An autoimmune process –markers of immune destruction, present in 85-90% of people e.g. islet cell antibodies, antibodies to insulin or anti-glutamic acid decarboxylase
    - Beta cell destruction, where neither the aetiology nor the pathogenesis is known (idiopathic)
- Onset of symptoms from lack of insulin occur very dramatically –high levels of glucose, exceed the renal threshold and overflow out into the urine. The body also switches to anaerobic metabolism (starvation mode) → breakdown of FFA into metabolites → formation of ketone bodies (acetone)
- 10-15% of diabetes cases are T1D –usually in adolescents/young adults. It has a rapid onset and is associated with weight loss (due to starvation).
- Family history is less common (genetic predisposition not strong).
- Prone to ketosis: switch to anaerobic metabolism and development of ketone bodies
- Signs/symptoms: polydipsia, polyuria, polyphagia, weight loss, blurred vision, hyperglycaemia, glycosuria, ketonuria, ketoacidosis, sweet smelling breath and coma

Type 2 diabetes (T2D)

- Characterised by insulin resistance (hence the link between obesity and increasing prevalence) and eventually the beta cell dysfunction –reduced ability of the beta cells to secrete insulin in response to hyperglycaemia
- In the early stages of T2D, hyperinsulinemia (high levels of insulin) can occur
- Insulin resistance: reduced response to circulating insulin in all tissue where insulin exerts its action. Hence there is reduction of glucose uptake in each of the target organs.
- Other aspects of T2D pathophysiology:
    - Increased hepatic glucose production
    - Increased glucagon secretion
    - Increased gastric emptying rate
    - Impaired incretin effect
        - ↓ secretion of GLP-1 (hormone that usually enhances pancreas response to glucose load)
        - Impaired response
    - Decreased amylin secretion
- Metabolic syndrome: a cluster of risk factors for CVD and T2D mellitus
    + Abdominal obesity and hyperinsulinemia
    + High fasting plasma glucose and impaired glucose tolerance
    + Hypertriglyceridemia and low HDL-C
    + Hypertension

- Insulin resistance is linked to a range of CV risk factors: hyperglycaemia, dyslipidaemia, hypertension, damage to blood vessels, clotting abnormalities and inflammation.
- 85% of diabetes cases are T2D –normally middle age (>35 years) and usually obese (80%). Family history is common. Not prone to ketosis. Malaise over a long time.
- In diabetes, over time, the pancreas begins to fail – normal decline in the function of pancreas activity is accelerated in people with diabetes.
- High risk groups for undiagnosed T2D include:
    - People with impaired glucose tolerance
    - People aged 55 and over
    - People aged > 35 from high-risk ethnic groups e.g. Australian aborigines, Pacific Islanders, Indian subcontinent and Chinese origin
    - Mothers of babies with birth weight more than 4.5kg, with a poor obstetric history or previous gestational diabetes
    - All people with clinical CVD
    - People aged 45 and over with one or more of the following:
        - Obesity (BMI >30)
        - First degree relative with T2D
        - Hypertension
        - Women with polycystic ovary syndrome who are obese
- Signs/symptoms: gradual in onset (insidious) and can be easily missed or mistaken as part of the normal aging process. Symptoms are often absent.
    - Thirst perception decreased in the elderly –dehydration can develop rapidly with hyperglycaemia
    - Blurred vision, tiredness, urinary frequency, constant thirst, numbness and tingling in the feet or legs and recurrent infections e.g. urinary tract or skin

Long term effects

- Macrovascular (atherosclerosis): effect on large blood vessels → hypertension, angina and heart attack (MI)
- Peripheral vascular disease: diminished circulation (slow healing and gangrene)
- Microvascular: effect on small blood vessels → thickening of the walls of capillaries which deliver nutrients to eyes, kidneys and nerves → nephropathy, retinopathy and neuropathy (atrophy of the peripheral nerves, motor sensory autonomic) → loss of feeling and bladder function → impotence
- In small vessels: hyperglycaemia causes mitochondrial over-production of reactive oxygen species - ROS (inhibit GADPH). This combines with lipids and proteins to form complexes that deposit in blood vessels in the different organs. Drives four major biochemical pathways that cause microvascular disease:
    - Polyol pathway: conversion of glucose to sorbitol (hence accumulation of sorbitol in the blood vessels) – contributes to diabetic peripheral neuropathy, nephropathy, retinopathy, keratopathy and cataract; accumulation of sorbitol leads to swelling and damage of the vessels.
    - Hexosamine Flux: acts on the fructose-6-phosphate part of the glucose metabolism pathway – contributes to diabetic nephropathy
    - Advanced Glycation End-products (AGE): non-enzymatic glycation of proteins results in advanced glycation end-products that deposit in the blood vessels, particularly in the basement membranes of the kidneys (kidneys become leaky → nephropathy → microalbuminuria) – contributes to retinopathy, nephropathy, neuropathy, Alzheimer's, ED and pulmonary fibrosis
    - Protein kinase C – contributes to macular oedema, proliferative retinopathy and kidney disease

Management

- Diabetes control & complications trial (T1D) – controlling blood glucose prevents microvascular complications
- UK diabetes Prospective study (T2D) – controlling blood glucose and BP prevents diabetes complications
- Other studies – reduction in lipid levels are associated with a decrease in macrovascular complications
- Aims of diabetes management:
    + Eliminate the symptoms of hyperglycaemia (while avoiding hypoglycaemia)
    + Reduce long term complications
    + Achieve growth and development in T1D
    + Normal lifestyle with diabetic control
    + Establish concordance with patient regarding management
- Therapy involves diet, exercise and medication
- Treatment targets: achieve glycaemic control (target depends on age and stage of diabetes) and to bring glycosylated Hb within 1% of the upper limit of normal (ULN)
- Dietary principles:
    - Calories for normal growth and ideal body weight

    - Maintain near normal blood glucose levels by balancing food intake with insulin or anti-diabetic medication and physical activity
    - Carbohydrate (CHO) intake should be spread through-out the day and not overloaded at any point (esp. with insulin therapy, where carbohydrate levels and insulin intake need to be balanced)
    - Attain individualised glycaemic, BP and lipid goals
    - Prevent/delay treatment of nutrition related risk factors and complications
    - Address individual nutrition needs based on personal/cultural preferences, health literacy/numeracy, access to healthy foods, willingness/ability to make behavioural changes and barriers to change
    - Complex CHOs (50-60%); preference for foods with low glycaemic index (<55)
    - Simple sugars (monosaccharides induce hypoglycaemia when consumed alone), fibre can modify rates of digestion and absorption of CHO, intake of sucrose as part of CHO allowance does not impair BG control
    - General misconception that CHOs should be avoided – no absolute prohibition (must be balanced)
    - Protein needed for growth 12-20%
    - Limit saturated and trans fats
- Small amount of weight loss in obese T2D patients significantly increases insulin sensitivity. This includes a balanced low-calorie diet and regular physical activity. Modest weight loss is shown to improve glycaemic control and reduce the need for glucose-lowering medications.

Insulin therapy

- Rapid acting insulins (insulin lispro, insulin aspart, insulin glulisine): newest development in insulin therapy – onset is 5-15 mins and works for 3-5 hours. Act rapidly and action declines very quickly meaning they can be given with a meal. Insulin dependent diabetics can vary the time of meals and not be restricted by certain time frames (improves QOL).
- Short acting/neutral insulins (regular, soluble) – onset is 0.5-1 hour and work for 5-8 hours.
- Basal insulins: given to mimic the effect needed to stop the catabolic/anti-anabolic effects
    - Intermediate (NPH/lente): onset is 2-4 hours and work for 10-18 hours
    - Long acting (glargine, detemir, ultralente, degludec): onset: 0.5-6 hours, duration: 18 - 24 hours
- Pre-mixed (biphasic) insulin: rapid acting + basal insulin – onset is 30 mins and work for 16-24 hours
    - Using 2 of the mixed dose insulin is better than a basal bolus regimen as there will be 2 injections that cover the 24-hour period (short/rapid acting and intermediate acting) – basal bolus involves 4 injections
    - This regimen requires patient to have snacks throughout the day to prevent hypoglycaemia
    - Control is not as good with this regimen compared to basal bolus but more convenient
- Single daily dose of intermediate insulin is used in T2D (that progresses to insulin dependent)
- Other regimens:
    - Two (morning/night) mixed short and intermediate injections (fixed ratio or self-mixed)
    - Basal bolus: 3 short-short acting with meals and intermediate at bed time
- Issues in insulin therapy:
    - Antigenicity: previously animal insulin was used and human body reacted to the presence of a foreign substance. Human (recombinant) insulin is now more commonly used.
    - Purity
    - Dosage: 0.3 to 1.0 unit per kg/day
    - Storage: can be stored at room temp. for up to 1 month
    - Methods of injection: rotation of injection sites, mixing of insulins and pens
- Insulin pump: a small electronic device that delivers insulin via an infusion set which is inserted under the skin (subcutaneously). The device delivers insulin in two ways:
    1. Basal – small amounts of insulin continuously in order to maintain cell function
    2. Bolus – delivering to account for the carbohydrates in meals or to correct high BGLs
- Hypoglycaemia: blood sugar becoming too low; caused by omitting a meal, increased activity without additional CHO or overdose of insulin
    - Common symptoms (related to SNS and nueroglycemia): weakness/trembling/shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness, irritability, hunger and numbness around lips and fingers
    - If not treated, may progress to loss of coordination, slurred speech, confusion and loss of consciousness
    - Treatment: 5-7 jelly beans or ½ can of soft drink, glucagon (if loss of consciousness) + follow up replenishment of CHO stores
        - Glucagon kit is used for severe hypoglycaemia where other methods of glucose replenishment are not possible, it gives an emergency dose of glucagon
    - Problems due to injection: lipoatrophy (allergy in lipid tissue), lipohypertrophy (overgrowth of fat) or a local allergy (rash, etc.). May also develop insulin resistance.

Anti-diabetic drugs

- Best to advise on lifestyle modifications (e.g. weight loss) before initiation of treatment. If blood glucose levels do not respond adequately or there is extreme hyperglycaemia, pharmacotherapy is required immediately.
- Anti-diabetic drugs can be divided in terms of their mechanisms and sites of action:
    - Liver:
        - Metformin and thiazolidinediones –enhance glucose sensitivity, decrease the level of hepatic glucose output, enhance sensitivity of target receptors to insulin
        - Incretins and amylin –decrease glucagon secretion
    - GI: incretins, α-glucosidase inhibitors, amylin and bile acid sequestrants –interfere with glucose absorption in the gut
    - Pancreas: sulfonylureas, meglitinides and incretins –increase/enhance insulin secretion (more likely to cause hypoglycaemia)
    - Kidney: SGLT-2 inhibitors –decrease glucose reabsorption
    - Blood vessels: thiazolidinediones and metformin –increase glucose uptake and utilization
    - Lipid: thiazolidinediones and salicylates
    - Appetite control: incretins and amylin –reduce appetite
- Metformin: used as a first line treatment (drug of choice in obese patients). It is a **biguanide** that suppresses hepatic gluconeogenesis by activation of AMP-activated protein kinase (AMPK), decreases hepatic glucose production and increases glucose utilisation.
    - Can be combined with sulfonylureas or insulin
    - Main ADRs: diarrhoea and lactic acidosis (only in significant renal impairment or CVD)
- Sulfonylureas: stimulate the release of insulin from the pancreas, used for T2D
    - Include glipizide, gliclazide, glibenclamide and glimepiride, which all differ in their MOA
    - Usually started with immediate release formulation, after stabilisation extended release is used
    - Main ADRs: weight gain, symptomatic hypoglycaemia and skin rashes
- DDP-4 inhibitors: prolong GLP-1 life by inhibiting the dipeptidyl-peptidase 4 responsible for its degradation
    - Include: sitagliptin, vildagliptin, saxagliptin and linagliptin
    - Main ADRs: URTI, stuffy or runny nose, sore throat and headache
    - Incretin hormones GLP-1 and GIP are released by the intestine throughout the day and their levels increase in response to a meal
- Thiazolidinediones: target insulin resistance by sensitising insulin receptors in adipose tissue, skeletal muscle and liver, so body can respond to its own insulin more effectively. Also improve function of beta cells, reduce insulin levels in the blood and redistribute fat from visceral adipose tissue to subcutaneous adipose tissue.
    - Include: rosiglitazone and pioglitazone, used alone or in combination with metformin/sulphonylureas
    - Can be taken as a single daily dose or in divided doses twice daily, with or without food
    - Main ADRs: increase in peripheral fractures (women), fluid retention (CI in heart failure) and possible increased risk of heart attack/CVD (with rosiglitazone)
- SGLT-2 inhibitors: work in the kidney to decrease the reabsorption of glucose –total glucose/day not reabsorbed = 5-80 grams. These include dapagliflozin, canagliflozin and empagliflozin.
    - 2 sodium-glucose transporters have been identified that cause glucose to be reabsorbed into the kidney: SLGT-1 found in gut/other tissues, and SLGT-2 found only in proximal tubule of kidney and accounts for most of the glucose reabsorption)
    - Metabolic effects of SGLT-2 inhibitors:
        - Fasting plasma glucose reduced 15-20 mg/dl
        - A1C reduced 0.5-0.7%
        - Body weight reduced 2-3kg in 12 weeks
        - Systolic BP reduced by 3-5 mmHg
    - ADRs: constipation and diahoerra, nausea (more common in patients taking combination with metformin) some reports of hypoglycaemia, some women develop vaginal infections (due to glucose in urine), ↑ serum Mg, PO_3 and haematocrit (possibly due to diuresis) and ↓ uric acid
- α-glucosidase inhibitors: delay carbohydrate digestion, used as a monotherapy or combined with sulfonylureas/metformin –not very effective treatment, useful in post-prandial hyperglycaemia
    - Main ADRs: (not well tolerated) flatulence and diahoerra. Do not cause hypoglycaemia.
- Meglitinides: short-acting (t ½ = 1hr), can be taken just after a meal
    - Repaglinide: increases release of insulin from pancreas, highly protein bound, undergoes rapid hepatic metabolism to inactive metabolites
    - ADRs: GI disturbances (take 15 mins before meal), URTIs, arthralgia, headache