PHAR3818 Notes – Endocrine, Diabetes and Reproduction

Diabetes mellitus

Epidemiology

- 7% Australian adults, 23% elderly (>75yo), additional 16% have glucose intolerance
- Mortality of T2D is 2-3 times that of rest of population – mainly due to CVD
- Diabetes mellitus – chronic hyperglycaemia due to deficient action of insulin on target tissues
    - Excess calorie intake, high visceral fat, insufficient insulin, insulin resistance

	Incidence	**Age of onset**	**Ketosis**	**Onset**	**Weight**	**Family history**
T1D	10-15% cases	Young adult	Prone	Rapid	Lean, wasted	Less common
T2D	85% cases	Middle aged	Not prone	Gradual (insidious)	Obese (80%)	Common

Metabolic syndrome

- Cluster of risk factors for CVD and T2D
- Includes: abdominal obesity, hyperinsulinaemia, hyperlipidaemia, low HDL-c, hypercoagulability, hypertension, high fasting plasma glucose, impaired glucose tolerance

Type 1 diabetes

- *Absolute* insulin deficiency
    - Insulin replacement *required* for survival, to prevent ketoacidosis, coma and death
- Auto-immune pancreatic β-cell destruction – idiopathic
    - Markers of immune destruction are present in 85-90% patients
    - E.g. islet cell antibodies, antibodies to insulin, anti-glutamic acid decarboxylase (GAD)
- Symptoms – polyuria, thirst, hunger, blurred vision, weight loss (fatty acid breakdown)
    - Hyperglycaemia, glycosuria, ketonuria, ketoacidosis, sweet breath, coma

Type 2 diabetes

- *Relative* insulin deficiency + insulin resistance
- Insulin resistance + some beta cell failure + genetics and environmental (overeating) input = T2D
    - Increased hepatic glucose production and glucagon secretion – ↑BGL
    - Increased gastric emptying rate and hunger, and decreased amylin secretion
    - Impaired incretin effect – reduced GLP-1/GIP and thus insulin secretion
- Symptoms – often absent (gradual onset)
    - Polyuria, thirst, lethargy, blurred vision, numb feet/legs, recurrent infections (UTI, skin)
- Natural progression of T2D: pre-diabetes (impaired fasting glucose and glucose tolerance) → insulin resistance → impaired insulin production

Risk factors for T2D

- Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)
- >55yo, or >35yo if Indigenous Australian, Pacific Islander, Indian, Chinese
- Mothers with – previous gestational diabetes, baby birth weight >4.5kg, poor obstetric history
- All people with clinical CVD
- Taking antipsychotic medication, mental health issues, corticosteroids
- People aged >45yo with: obesity, T2D family history, hypertension, polycystic ovarian syndrome

Long-term complications	**Consequences**
Peripheral vascular disease	Diminished circulation – slow healing, gangrene
Macrovascular	Atherosclerosis, hypertension, angina, heart attack

Microvascular	Thickening of capillary walls that perfuse eyes, kidneys and nerves
	- Nephropathy, retinopathy
	- Neuropathy – peripheral (limbs), motor sensory, autonomic
	  - Loss of sensation, numbness, tingling, burning
	  - Monofilament neurologic examination

Progression to:	Blindness, renal failure, CHD, amputation, disability, death

Biochemical influences

- Hyperglycaemia in small vessels → mitochondrial over-production of reactive oxygen species (ROS)
- ROS drive four major biochemical pathways that cause *microvascular* disease:
    - Polyol, hexosamine flux, advanced glycation end-products (AGEs), protein kinase C
    - AGEs = non-enzymatic glycation of proteins

Pathway	**Complications**
Polyol	Peripheral neuropathy, nephropathy, retinopathy, keratopathy, cataract
Hexosamine flux	Diabetic nephropathy
AGEs	Neuropathy, nephropathy, retinopathy, Alzheimer's, pulmonary fibrosis
Protein kinase C	Diabetic macular oedema, proliferative retinopathy, diabetic kidney disease

Therapeutic goals and guidelines

- Eliminate symptoms of hyperglycaemia and avoid hypoglycaemia
- Reduce long-term complications
    - Control BP – prevents microvascular complications, ACEI/ARA are nephroprotective
    - Reduce lipid levels – decrease macrovascular complications
- Normal lifestyle with diabetic control – trial 6 months weight loss and diet first

Factor	**Target**	**Purpose**
Blood glucose	6.1 – 8.0mM (fasting); 6.0 – 10.0mM (2h postprandial)	
HbA1c	<7% (53mmol/mol)	- Target depends on age, stage of diabetes
Blood pressure	<130/80mmHg <125/75mmHg with proteinuria	- Prevent microvascular complications - Prevent stroke and nephropathy
TC/TG/HDL	<4.0mM/<2.0mM/>1.0mM	- Reduce macrovascular, MI, CVD

Lifestyle modifications

- Calories for normal growth (T1D – early onset) vs. weight loss if overweight (T2D)
    - 5-10% weight loss improves insulin sensitivity – orlistat, phentermine, liraglutide
- Balance food intake with insulin/anti-diabetic medication – alter insulin dose if required
- Complex carbohydrates (50-60%) – low glycaemic index, slower absorption
    - Avoid simple sugars e.g. mono/di-saccharides which induce hyperglycaemia
    - Sucrose does *not* impair BG control
- Fibre can modify rates of digestion and absorption of carbohydrates
- Limit saturated and trans fats and cholesterol (<300mg/day)
- Healthy eating – smaller plate and portions, minimise eating out, avoid distractions while eating
- Smoking cessation, reduce alcohol intake, maintain physical activity

Effects of insulin

- Acts on liver, muscle and adipose tissue
- Anabolic effects – building energy stores, requires high insulin (e.g. post-prandial)
    - ↑ Glucose uptake (via GLUT-4), glycolysis, glycogen synthesis and storage
    - ↑ Amino acid uptake and protein synthesis
    - ↑ Lipoprotein lipase activity → TG breakdown → FFA and glycerol uptake
- Anti-catabolic effects – requires low-insulin (e.g. fasting)
    - Liver/muscle – inhibits gluconeogenesis and glycogen breakdown
    - Liver/adipose – promotes TG synthesis, inhibits TG breakdown
- Insulin deficiency – ↑hepatic glucose production, ↑hyperglycaemia, ↑FFA (ketosis)

Classification	**Insulin examples**	**Onset (h)**	**Peak (h)**	**Duration (h)**
Rapid-acting	Insulin lispro, aspart, glulisine	5 – 15 min	0.5 – 1	3 – 5
Short-acting	Neutral (regular, soluble)	0.5 – 1	2 – 3	5 – 8
Intermediate (basal)	NPH/lente	2 – 4	4 – 10	10 – 18
Long-acting (basal)	Glargine/determir/ultralente	1 – 4	Nil/nil/18	18 – 30
Pre-mixed (T2D only)	Biphasic – short-long-acting mix	0.5	4 – 12	16 – 24