

Endocrinology

DIABETES

• Definition, Classification and Pathophysiology of Diabetes

	Fasting glucose (mmol/L)	2 hour post GTT glucose (mmol/L)
Normal	≤ 6.0 and	≤ 7.7
IFT	6.1-6.9 and/or	≤ 7.8
IGT	≤ 7.0 and/or	7.8-11.0
Diabetes	≥ 7.0 and/or	≥ 11.1

Symptomatic patients – one diagnostic blood sugar test

Asymptomatic patients – two diagnostic blood sugar tests

Classification of diabetes:

1. Type 1 – immune-mediated β cell destruction
2. Type 2 – insulin resistance (often associated with obesity)
3. Others:
 - a. Genetic – autosomal, mitochondrial
 - i. β cell dysfunction – HNF-1 α (MODY 3), glucokinase (MODY 2), HNF-4 α (MODY 1), IPF-1 (MODY 4), HNF-1 β (MODY 5), mitochondrial DNA
 - ii. Defects in insulin action – several rare syndromes
 - b. Pancreatic disease – pancreatitis, pancreatectomy, CF, haemochromatosis
 - c. Endocrinopathies – Cushing's, acromegaly, pheochromocytoma, glucagonoma
 - d. Drug/chemical induced – glucocorticoids, thiazides, GH, tacrolimus
 - e. Infections – congenital rubella, cytomegalovirus
 - f. Rare forms of immune-mediated diabetes

Note that gestational diabetes is a term used for diabetes of onset or first recognition in pregnancy, including women with diabetes unrecognised before diabetes (usually type 2). Re-classification after pregnancy is important – note that GTT criteria are different due to differences in glucose tolerance.

Treatment is not dependent on type, as all types of diabetes have various stages through which patients progress – the treatment depends on the stage rather than aetiology.

Type 1 diabetes (previously insulin dependent diabetes, juvenile onset diabetes) is characterised by permanent insulinopenia and propensity for ketoacidosis without evidence of autoimmunity. Patients are often of African or Asian origin with family history and acute onset of symptoms.

1. Epidemiology:
 - a. Highest prevalence in developed nations, though varies (e.g. in Europe childhood rate varies from 3 per 10⁵ per year in Macedonia to 5 per 10⁵ per year in Finland)
 - i. In New Zealand the rate in <20 year olds is 19 per 10⁵ per year
 - ii. In most developed nations incidence is rising (particularly in young children)
 - b. Peak incidence in childhood and adolescence, but can occur at any age – more than 50% of type 1 diabetes cases start after the age of 20
2. Aetiology is unclear, but risk factors include:
 - a. Genetic factors:
 - i. Family history increases lifetime risk from 1% to 3-5%
 - ii. Moderately high concordance in identical twins (~50%)
 - b. Environmental factors:
 - i. Varying incidence in different countries
 - ii. Seasonal variation in presentation
 - iii. Dietary factors (not proven) include nitrosamines, cow's milk proteins
 - iv. Possible viral triggers
 - c. Associated autoimmune diseases – autoimmune thyroid disease (hypothyroidism, postpartum thyroiditis, Grave's disease), premature ovarian failure, pernicious anaemia, Addison's disease, coeliac disease, vitiligo
3. Pathogenesis
 - a. Results from cell-mediated autoimmune destruction of the β cells
 - i. Markers (90% sensitive) – isle cell Ab, insulin Ab, anti-GAD, anti-IA2
 - ii. Rate of destruction of β cells is variable – tends to be faster in younger subject, slower with associated autoimmune disease
 - iii. Strong HLA associations with the DQA and DQB genes and influenced by DRB genes (may be predisposing or protective)

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- b. Ketoacidosis may be the first manifestation, but others may only develop severe hyperglycaemia and/or ketoacidosis in the presence of infection or other stress
 - i. Some may retain sufficient β cell function (latent autoimmune diabetes in adults - LADA)
- c. In later stages there is little or no insulin secretion and insulin is required for survival

Type 2 diabetes is characterised by insulin resistance with relative insulin deficiency.

1. Epidemiology:
 - a. Prevalence increases with age and obesity – worldwide incidence is rising, mirroring the rise in obesity and urbanisation creating an obesogenic environment:
 - i. Increased availability and marketing of foods
 - ii. Reduction in home prepared meals
 - iii. Increases in TV watching and computer use
 - iv. Greater reliance on motorised transport
 - v. Reductions in physical education at schools
 - vi. Decrease in physical labour
 - b. Age of onset is also falling – it is not uncommon for patients in their teens and early twenties to develop type 2 diabetes.
2. Risk factors:
 - a. Central obesity – weight gain \rightarrow higher insulin resistance, weight loss \rightarrow reversal
 - b. Genetic factors:
 - i. Strong family history
 - ii. Concordance in identical twins is high (~100%)
 - c. Prenatal factors:
 - i. Small babies prone to metabolic syndrome in later life (Barker hypothesis)
 1. Poor maternal nutrition, placental insufficiency, fetal metabolic defects \rightarrow fetal malnutrition
 2. Modified metabolic pathways ('imprinting') \rightarrow metabolic syndrome
 - ii. Maternal type 2 diabetes in pregnancy may predispose to early onset type 2 diabetes in the child
3. Pathogenesis:
 - a. Insulin resistance occurs at all levels (liver, fat, muscle) – post-receptor defects:
 - i. IRS proteins \rightarrow glucose transport, glycogen synthesis, antilipolysis (acute)
 - ii. SHc \rightarrow MAPK \rightarrow growth and proliferation (chronic)
 - b. Strongly related to truncal obesity and other components of the metabolic syndrome
 - i. Excess energy intake + low activity \rightarrow truncal obesity, insulin resistance
 - ii. Metabolic syndrome – glucose intolerance, hypertension, dyslipidaemia, endothelial dysfunction (inflammatory markers, procoagulant state)
 - c. Insidious onset and progressive as insulin secretion falls, dietary and drug therapy fails and patients require insulin (6-7% per annum)

• Presentation and Clinical Phenotype of Diabetes

	Type 1	Type 2
Age (years)	Young and <40	Older >50, occasionally <20
BMI (kg/m ²)	<26	>30 (<25 in Asians)
Family history	Negative	Positive
Ethnicity	European	Maori, Pacific Island
DKA	Positive (not always)	Negative (except 10%)
Prominent symptoms	Yes (rarely absent)	Yes (rarely severe)
Retinopathy at diagnosis	No (except LADA)	Maybe
Glucose values	Vary variable	Often quite stable
Withdraw insulin	Abrupt \uparrow glucose	Gradual \uparrow glucose
Anti-GAD antibodies	90% positive	Negative
C-peptide	Low	Normal

Useful notes:

1. Waist circumference is a surrogate marker of visceral fat:
 - a. Women >88cm = increased risk (80 for Asians)
 - b. Men >102cm = increased risk (90 for Asians)

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2. Family history:
 - a. 1st degree relative – 90% negative type 1, mostly positive type 2
 - b. Identical twin – 50% risk type 1, near 100% risk type 2
 - c. Dominant inheritance – no type 1, yes type 2 (MODY)
3. Stiff-man syndrome – CSF IgG antibodies target GABA nerves, associated with autoimmune disease (anti-GAD (glutamic acid decarboxylase) antibodies also recognise pancreatic islets). The titre is 500x higher in stiff-man than those with type 1 diabetes and difference epitope
 - a. Anti-GAD – 70% positive in type 1
 - b. ICA – 80-90% positive in type 1
 - c. IA2 – 60% positive in type 1
 - d. Other glands – 1-10% positive in type 1
 - e. All of the above <10% in type 2
4. Bottom line:
 - a. Young, thin, European, no family history, lots of symptoms = type 1
 - b. 55 year old, obese, Maori, brother diabetic, asymptomatic = type 2

• Microvascular Complications of Diabetes

Microvascular complications of diabetes are major causes of morbidity and mortality and are amongst the leading causes of end-stage renal failure, blindness and amputation. Note that the main risk for development is the duration of disease (particularly for type 2 – latent asymptomatic period)

1. Glycosylation of structural proteins in capillaries of the retina, glomeruli and vasa nervorum
2. Development of complications is related to glycaemic control as well as duration of disease
3. Complications tend to develop in parallel

Retinopathy:

1. Natural history – takes a minimum of five years of diabetes to develop
 - a. Early – micro-aneurysms (dots), circular haemorrhages (blots) and/or hard exudates classified as background retinopathy (not sight threatening)
 - b. Deteriorating – preproliferative retinopathy characterised by flame-shaped haemorrhages, venous tortuosity and cotton-wool spots
 - c. Advanced – retinal angiogenesis (→ haemorrhage, detachment), proliferative retinopathy (sight threatening)
2. Detection
 - a. 2-yearly visual acuity and retinal examination ± fluorescein angiography
 - b. Ophthalmology surveillance if more than mild background change
3. Treatment:
 - a. Good glycaemic control delays onset and slows progression of early disease
 - b. Laser therapy for preproliferative and proliferative retinopathy prevents blindness
 - i. Complications include loss of peripheral and night vision
 - c. Others – vitrectomy, blood pressure reduction, smoking cessation

Nephropathy:

1. Natural history – note that only half of diabetic patients are susceptible (? reason)
 - a. Early – microalbuminuria, increased GFR, mildly elevated BP
 - b. Deteriorating – further increases in albumin excretion (macroalbuminuria) and blood pressure, declining GFR
 - c. End-stage – heavy proteinuria (nephrotic), severe hypertension, end-stage failure

	Normal	Hyperfiltration	Incipient	Established	End-stage
GFR	N	↑	N	↓↓~1mL/min per month	<15mL/min
BP	N	N	N, ↑ (nocturnal)	↑ progressively increasing	↑↑
Albumin	N	N	Microalbuminuria	>300mg/day, progressive ↑	Nephrotic

2. Detection
 - a. Asymptomatic in early stages so all diabetic patients should be screened for nephropathy by regular BP checks and 1-2 yearly estimates of albumin excretion

	mg/day	µg/min	Albumin : Creatinine ratio
Normal	<30	<20	<3
Microalbuminuria	30-300	20-200	3-30
Macroalbuminuria	300-3000	200-2000	30-3000
Nephrotic	>3000	>2000	>300

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- b. Type 2 diabetes – hypertension and proteinuria is very common and not always due to nephropathy, but a strong risk factor for macrovascular complications
3. Treatment:
 - a. Good glycaemic control prevents development of early nephropathy
 - b. Progression can be slowed by aggressive hypotensive therapy (BP <130/80mmHg)
 - i. As GFR falls, BP becomes more difficult to control
 - ii. ACE inhibitors or AT₂-blockers offer advantages (nephroprotective)
 - iii. Multidrug treatment is often necessary
 - c. End stage – dialysis and/or transplantation (poor prognosis)

Neuropathy:

1. Natural history – mediated by involvement of vasa nervorum, mainly longer nerves
 - a. Peripheral neuropathy – predominantly sensory, affecting feet and legs
 - i. Early – asymptomatic or symptomatic (dysaesthesia, paraesthesia)
 - ii. Late – anaesthetic feet prone to ulceration or pressure areas
 - iii. Advanced – neuropathic (Charcot) joints, recurrent ulceration, upper limb
 - b. Autonomic neuropathy:
 - i. Most commonly impotence in men
 - ii. Advanced disease (pupillary abnormalities, gustatory sweating, resting tachycardia, postural hypotension, gastroparesis, diabetic diarrhoea, neurogenic bladder) rare but disabling
2. Detection:
 - a. Peripheral neuropathy detected by sensory testing (vibration/pressure best, but note age-related changes) e.g. monofilament testing, nerve conduction studies
 - b. Ankle reflexes usually absent
3. Treatment
 - a. Good glycaemic control delays onset and slows progression
 - b. Podiatry, education and footwear for patients with at-risk feet
 - c. Treatment of co-existing peripheral vascular disease (ABI >50% for healing)
 - d. Acute management – non-weight bearing, antibiotics, removal of necrotic tissue

Diabetes Control and Complications Trial – external insulin pump or >2sc insulin injections for tight control with monitoring, mean follow-up 6.5yrs, goal HBA_{1c} <8%

1. Overall, impressive decreases in organ pathology – 39-76% reduction (primary and secondary) in retinopathy, neuropathy and nephropathy
2. However, 3-fold increase in incidence of severe hypoglycaemic episodes, though external pumps had much lower incidence than injection
3. Intensive insulin therapy helps sustain endogenous insulin secretion, which helps prevent hypoglycaemia and complications, and retards progression
4. In the long term, intensive insulin therapy may have less advantage over regular therapy (same mortality) but still reduces retinopathy/nephropathy

• Macrovascular Complications

Epidemiology:

1. The absolute risk for cardiovascular disease (IHD, CVA, PVD) is 2-4x greater than age-matched non-diabetic control populations – e.g. for MI risk:
 - a. Non-diabetic previous MI – 19% no MI – 4%
 - b. Diabetic previous MI – 45% no MI – 20%
2. The excess of risk is present in both types of diabetes and affects women more than men
 - a. At the time of diagnosis of type 2 diabetes, more than 50% of patients have CVD
 - b. CVD is responsible for 75-80% of hospital admissions and deaths of diabetic patients
 - c. Risk especially high with diabetic nephropathy
3. Lipids, smoking and hypertension do not account for the excess risk seen

Ticking clock hypothesis – microvascular complications begin at the onset of hyperglycaemia, while macrovascular complications begin before the diagnosis of hyperglycaemia.

Clinical presentation:

1. Ischaemic heart disease – prevalence increased 2-4x in diabetes
 - a. Poorer prognosis following MI

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- b. More extensive and more distal coronary artery disease present
2. Heart failure – increased prevalence due to incidence of hypertension and IHD
 - a. Diabetic cardiomyopathy – heart failure in the absence of other identifiable risk factors, diastolic dysfunction usually present
3. Stroke – prevalence increased 2x in diabetes, survival poorer
4. Peripheral vascular disease – prevalence increased 4x in diabetes
 - a. Propensity to develop distal atherosclerosis (distal to trifurcation of popliteal artery)
 - b. Proximal disease also increased in prevalence

Clinical manifestations:

1. Present the same way as non-diabetic subjects, though silent IHD is more common
2. Signs include carotid/femoral bruits, loss of foot pulses
3. Acute management – use GIK infusion in post-MI period (even if no diabetes and blood glucose >11.0mmol/L) and maintain glucose in the normal range

Risk factor modification:

1. Glycaemic control:
 - a. In non-diabetic populations, high blood glucose → increased cardiovascular risk
 - i. Unclear if this is due to the glucose, associated metabolic syndrome risk factors, or genetic or behavioural characteristics
 - b. In patients with type 2 diabetes there is a definite association between increasing hyperglycaemia and macrovascular disease
 - i. For every 1% increase in HbA1c there is an 11% increase in CVD prevalence
 - ii. For every 1% decrease there is a 12-16% decrease in MI, stroke and CHF
 - iii. For every 1% decrease there is a 37% decrease in microvascular endpoints
2. Blood pressure control (target <130/80mmHg)
 - a. Hypertension is >2x more prevalent in diabetic populations, increasing CV risk ~3x
 - b. Every 10mmHg lowering of systolic pressure → 12-19% reduction in both micro-and macrovascular disease
 - i. No threshold below which risk reduction does not occur
 - ii. Another study – CV risk halved when diastolic BP reduced 90 → 80mmHg
 - c. Drug treatment needs to be individualised but in the absence of contraindications ACE inhibitors are the initial drug of choice
3. Lipid control (targets HDL >1mmol/L, TG <2mmol/L, total cholesterol <5mmol/L)
 - a. For a given total cholesterol CV risk is 4x higher in diabetic patients
 - i. Type 1 diabetes – lipids related to glycaemic control
 - ii. Type 2 diabetes – high triglycerides and low HDL-cholesterol
 1. Increased FFA and glucose, less breakdown of triglycerides
 2. → Small, dense LDL more prone to oxidation (atherogenic)
 - iii. Centrally obese patients ± IGT have a similar lipid profile to type 2 diabetes
 - b. No evidence for lipid lowering prior to symptomatic disease, but it's logical
 - i. High TG, low HDL (e.g. syndrome X) – consider a fibrate
 - ii. High LDL – consider a statin (high dose will also reduce TG levels)
4. Other interventions:
 - a. ACE inhibitors – lower vascular risk independent of BP (? better endothelial function)
 - b. Aspirin – 1° cardiovascular prophylaxis in diabetics >30yrs (Reye's syndrome <21)
 - c. Smoking – particularly important to quit if diabetes present

• Treatment of Diabetes

Glycaemic targets:

1. HbA_{1c} 6.5-7.5%, but take into account adherence, hypoglycaemic awareness, life expectancy, co-morbidities, patient's wishes and understanding
2. An improvement to below 10% can be very significant for an individual
3. Setting unrealistic targets guarantees 'failure'

Dietary therapy:

1. For all – reduced simple carbohydrates, reduced fat
2. For the overweight (including most type 2 diabetics) – hypocaloric diet
3. Read food labels, aim for <10% saturated fat

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Drug therapy is indicated by inadequate glycaemic control despite diet:

1. **Biguanides** – metformin 500-800mg after meals od
 - a. Decrease hepatic glucose production and increases insulin mediated uptake of glucose in muscle – doesn't cause hypoglycaemia, encourages weight loss
 - b. Adverse effects – nausea, abdominal pain, diarrhoea
 - c. Contraindications (lactic acidosis) – CRF (creatinine >150µmol/L), liver disease, CHF
2. **Sulphonylureas** – gliclazide 40-320mg, glipizide 2.5-20mg, glibenclamide 2.5-20mg per day
 - a. Increase insulin release by direct effect on β cells but can cause hypoglycaemia, tend to encourage weight gain and has flat dose-response curve at the upper end
 - b. Adverse effects – hypoglycaemia (worst with elderly, malnourished patients with renal impairment particularly with glibenclamide – long acting), photosensitivity
3. **Acarbose** – 100-200mg tid, starting 50mg daily with first mouthful → increase weekly
 - a. Inhibits alpha glucosidase in the intestine, delaying the breakdown of complex carbohydrates to simple carbohydrates, reducing post-prandial hyperglycaemia
 - b. Adverse effects – GI side effects very common
4. **Thiazolidinedione** (glitazones) – rosiglitazone, pioglitazone
 - a. Activate the PPARγ nuclear receptor, reduce HbA_{1c} by 1-2% (hypoglycaemia rare)
 - i. Production of proteins involved in insulin response is enhanced e.g. GLUT-4
 - ii. Decreased hyperinsulinaemia and FFA
 - iii. Decreased triglycerides and LDL cholesterol
 - b. Note the role of free fatty acids in pathogenesis of type 2 diabetes:
 - i. Muscle – substrate competition → lower insulin mediated glucose uptake
 - ii. Pancreas – lipotoxicity → inhibits β cell function
 - iii. Liver – increased hepatic glucose output
 - c. Adverse effects – high food intake, body weight, peripheral oedema, anaemia, LFTs

Insulin therapy is indicated by symptoms of insufficiency (lassitude, hyperglycaemia, weight loss, ketosis), failure of oral hypoglycaemics (check diet, natural history), pregnancy in type 2 diabetes (and gestational diabetes) and surgery or intercurrent illness.

1. **Inpatient regimens:**
 - a. Not seriously ill, good glycaemic control – continue usual regimen
 - b. Elective surgery, good glycaemic control – GIK regimen
 - c. Unstable diabetes – variable rate insulin infusion (not “subcutaneous sliding scale”)
2. **Outpatient regimens:**
 - a. Nocturnal long-acting and daytime oral hypoglycaemics
 - b. Once daily long-acting (day or night)
 - c. Twice daily (usually mixed short/long acting)
 - d. Three times daily (mixed at breakfast, short acting at lunch, long acting at bed)
 - e. Four times daily (short acting pre-meals and long acting at bed)
 - f. Five times daily (long acting before twice-daily and ultra-short acting pre-meals)
 - g. Continuous subcutaneous insulin (variable basal rate, variable meal bolus)
3. **Adjusting insulin:**
 - a. Look for reproducible patterns and adjust appropriately
 - b. Change 10-15%, not more frequently than every 3 days
 - c. Reasons for chaotic patterns – poor injection technique, fat hypertrophy at injection site, hypoglycaemia avoidance, too frequent dose adjustment, no monitoring, missing injections, eating pattern

		Novo Nordisk	Eli Lilly
Ultra short acting	1-2h	Aspart	Humalog
Short acting	2-6h	Actrapid	Humulin R
Intermediate acting	4-16h	Protophane	Humulin N
		Monotard	Humulin L
Long acting	6-22h	Ultratard	Humulin U
Mixtures	Syringe	Mixtard 30/70	Humulin 30/70
	Pen device	Penmix 30/70	Humulin 30/70

Self-monitoring provides patients with information about day-to-day glycaemic control (including hypoglycaemia), allowing adjustments to diet/medication in relation to illness/activity/driving. It also provides the medical professional with information to allow appropriate treatment advice.

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1. Not insulin treated – before breakfast and 2 hours after main meal, one or two days a week
2. On insulin:
 - a. Before meals and at bed time, one or two days a week
 - b. Once a day testing, varying times through the week
 - c. Occasional tests 2-3am may be useful
 - d. Post-prandial testing in pregnancy

Hypoglycaemia is a life-threatening effect of glycaemic control – the lower the HbA_{1c}, the higher the risk of hypoglycaemia. This may be mild (self-correctable) or severe (involving another person).

1. Symptoms – autonomic (sweating, shaking, shivering), confusion, coma, fitting
 - a. In type 1 diabetes, hyperglycaemic awareness (autonomic) may be lost after several years (frequent attacks → higher threshold) – improved by meticulous avoidance
2. Causes include insulin error, unusual exercise, alcohol, missed meals, adrenal/pituitary insufficiency, weight loss, 'honeymoon period' (initial high sensitivity to insulin)
3. Treatment:
 - a. Glucose sweets or fruit juice by mouth (eat after capillary glucose >4mmol/L)
 - b. IV glucose – 50-100mL of 10% dextrose
 - c. Glucagon injection – 1mg IM (should be carried at all times – educate family)

• Obesity, Weight Gain and Type 2 Diabetes

Epidemiology – current WHO statistics show 250 million people worldwide are obese, with strong associations with being overweight, obesity and type 2 diabetes.

1. US Nurses Study – when BMI increases about 30, risk of diabetes increases ~18x
 - a. Risk is even greater in men – by BMI 35, risk of diabetes is 60x normal (BMI <25)
2. For every kg weight gain the risk of diabetes increases by up to 9% (double risk every 10kg)
3. Abdominal obesity further increases risk – waist circumference >102cm men, >88cm women
4. Prevalence of diabetes in the US rose 4.9 to 6.5% 1990-1998; obesity rose 12 to 18%

Mechanism – recently discovered adipose proteins (adipokines) may provide the link with diabetes:

1. Resistin
 - a. Circulating levels higher in the obese patient (more adipose tissue)
 - b. High levels are associated with hyperglycaemia and insulin resistance in humans
 - c. Animal models:
 - i. Resistin injection worsens glucose tolerance and reduces insulin action
 - ii. Induction of insulin resistance increases circulating resistin
2. Adiponectin
 - a. Circulating levels are lower in the obese patient (? antagonist TNF- α)
 - b. Low circulating levels are associated with hyperglycaemia and insulin resistance
 - c. Animal models show injection of adiponectin can:
 - i. Increase fat oxidation and hence enhance weight loss
 - ii. Decrease hyperglycaemia
 - iii. Reverse insulin resistance and hence improve diabetes risk

Weight loss – note that the WHO has calculated that >60% and >70% of diabetes in men and women respectively would be prevented if there were no BMIs above 25

1. Surgical treatment – 163 obese diabetics given gastric bypass, 141 → normal glucose
2. Drug treatment – 175 obese diabetics randomised to placebo or sibutramine, active patients lost 4.3kg (5% weight loss) and plasma glucose fell by 1.4mmol/L

Improvement in fasting glucose may be due to increase in tissue glucose uptake, where it is oxidized or recycled mainly as lactate, or from decreased hepatic glucose output (normally from glycogen breakdown and gluconeogenesis precursors lactate, alanine, glycerol).

Dietary recommendations:

1. 30% fat – <10% SFA, <10% PUFA, <300mg/day cholesterol
2. 10-20% protein
3. 50-60% carbohydrate
4. 20-35g fibre (soluble and insoluble)

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• Childhood and Adolescent Diabetes

Aetiology:

1. Type 1 diabetes – common, usually no family history
 - a. Presents with polyuria, polydipsia, weight loss, ketonuria (DKA is unusual)
 - b. Investigations – ICAs, anti-GAD, anti-IA2, anti-insulin antibodies, insulin level
2. Type 2 diabetes – increasingly common in puberty, often a family history
 - a. No polyuria, polydipsia or ketonuria; candidiasis, acanthosis nigricans may present
 - b. Associated with obesity and ethnic minorities
3. MODY (Maturity Onset Diabetes of Youth) – rare, autosomal dominant
 - a. Variable presentation depending on the protein involved (types 1-6)
 - b. Management varies from diet alone to insulin
4. Mitochondrial diabetes – rare, maternal vertical transmission (highly variable penetrance)
 - a. Associated with other systems (development delay, cardiovascular, marrow defects)

Management strategy varies with the child's age, and must consider social situation (dysfunctional family), support networks, ability to utilise available therapies and cultural issues. Individualised management plans have a realistic specific goal, variable frequency clinic visits, phone contacts and family-based interventions (don't just treat the child).

1. Toddlers are characterised by a short waking day, poor communication, food refusal/grazing, unpredictable activity, temper tantrums and aversion to needles
 - a. Insulin – twice daily split dose (0.7-1.0 units/kg/day) of rapid acting (dilute in infants)
 - b. Relatively protected from hyperglycaemia, but note recurrent hypoglycaemia → ↓IQ
 - c. Expect rollercoaster profile – glucose 5-15mmol/L (80%), HbA_{1c} 7.0-9.0%
2. Children are characterised by development of independence, regular food/exercise patterns, self testing (5-7yrs) and administration (7-8yrs), need for supervision (factitious records)
 - a. Insulin – twice daily split dose (0.7-1.0 units/kg/day), 20-25% benefit from split evening dose, basal bolus regimens (4x injections daily) usually fail
 - b. Meters with a memory useful – glucose 4-13mmol/L (80%), HbA_{1c} 7.0-8.0%
 - c. After five years of type 1 → annual urine microalbumin and 2-3 yearly eye review
3. Adolescents are characterised by denial, feelings of invulnerability (living the 'here and now'), experimentation/risk-taking, social and emotional lability, fear of obesity (particularly girls)
 - a. Insulin – split daytime short and long at night (1.0-1.5 units/kg/day – puberty → insulin resistance), 10-20% benefit from basal bolus regimen, rapid if good compliance
 - b. Type 2 DM – lifestyle, metformin (1.0-3.0 g/day up to bd), sulphonylureas 2nd line
 - c. Individualised goals – glucose 4-13mmol/L, HbA_{1c} 7.0-8.0%
 - d. Lifestyle advice, annual urine microalbumin and fasting lipids, two-yearly eye review
 - e. Psychiatric support – higher risk of RTC, suicide, eating disorders

THYROID DISORDERS

• Hypothyroidism and Nodules

Thyroid physiology:

1. The thyroid gland produces both T₄ and T₃, both highly protein bound (T₄ 99.95%, T₃ 99.7%)
 - a. More T₄ produced → peripherally converted to T₃ (more potent)
 - b. TSH (pituitary derived) stimulates production – may be normal in pituitary abnormality
 - c. TRH (hypothalamus derived) stimulates TSH secretion
2. Factors that affect T₃ and T₄ levels:
 - a. Age
 - b. Thyroid function
 - c. Protein binding: TBG>TBPA>albumin (familial dysalbuminaemic hyperthyroxinaemia)
 - d. Peripheral T₄ → T₃ conversion (non-thyroidal illness)

Primary hypothyroidism is one of the commonest conditions affecting thyroid function. Its symptoms are protean and mostly non-specific:

1. Aetiology:
 - a. Congenital:
 - i. Structural – thyroid aplasia
 - ii. Metabolic – defects in iodine transport, organic binding, iodotyrosine coupling/dehalogenase, secretion
 - b. Acquired:
 - i. Inflammatory – autoimmune (e.g. Hashimoto's thyroiditis)

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- ii. Metabolic – iodine deficiency, iodine excess
 - iii. Iatrogenic - post ¹³¹I, post-surgery, anti-thyroid drugs (lithium)
 - iv. Idiopathic – peripheral resistance to thyroid hormones
 - c. 2° – Sheehan's syndrome (post-partum pituitary infarct), pituitary, hypothalamus
2. Manifestations are numerous:
- a. Skin – hyaluronic acid → oedema (eyes, dorsum of hands), cool, dry, eyebrow loss
 - b. Cardiorespiratory – ↓CO, ↑PVR, pericardial/pleural effusion, bradycardia, OSA
 - c. GI – weight increase, appetite loss, constipation, achlorhydria (50% of autoimmune)
 - d. Neurological – lethargy, dementia, depression, myxoedema coma, cerebellar ataxia
 - e. Musculoskeletal – growth retardation (prepubertal), carpal tunnel syndrome
 - f. Others – hyponatraemia, anaemia, menorrhagia

Clinical features:

1. Clinical syndromes:
 - a. Mild hypothyroidism may be asymptomatic or cause fatigue, weight gain, constipation, heavy periods, dry skin, mental slowness, cold sensitivity or hair loss
 - b. Severe hypothyroidism may present with dementia, cerebellar syndromes, myopathy, and eventually coma and death
 - c. Infants (cretinism) – feeding problem, failure to thrive, somnolence, retardation of physical and mental development, growth retardation,
 - i. Signs – dry skin, broad flat nose, widely set eyes, periorbital puffiness, large tongue, sparse hair, rough skin, short neck, protruding abdomen
2. Examination – cool skin, slow pulse, periorbital puffiness, goitre, slow relaxing tendon reflexes
3. Investigations:
 - a. Measure T₄ (free or adjusted) and TSH
 - i. Initially TSH rises, then T₄ drops before T₃ (TSH → thyroid tends to make T₃)
 - b. Thyroid antibodies positive in 80% of these with idiopathic primary hypothyroidism
 - c. Severe hypothyroidism may → hyponatraemia, elevated CK and serum cholesterol
4. Management:
 - a. Thyroxine (T₄) aiming to normalise T₄ and TSH levels
 - b. Average dose 100-150µg/day (increase gradually in patients with IHD and the elderly)
 - c. Half-life of T₄ is about a week, so follow up with TFTs in 4-6 weeks
 - d. Remember the possibility of Addison's disease

Thyroid nodules (5th year) – is this diffuse (unlikely to be malignant/significant, just test TSH) or focal (needs ultrasound to determine single or multinodular) enlargement? Note that for a single lump or prominent lump in multinodular enlargement – 90% benign, 10% neoplasia → biopsy.

• Thyrotoxicosis

Thyrotoxicosis (hyperthyroidism) is a condition caused by increased circulating thyroid hormones

1. Aetiology:
 - a. Diffuse toxic goitre (Grave's disease – 85%)
 - i. Prevalence 1%, 8:1 female to male ratio
 - ii. Autoimmune – IgG antibody stimulates TSH receptor (intrauterine can rarely cause intrauterine and neonatal thyrotoxicosis)
 - iii. Distinctive triad – thyrotoxicosis, diffuse goitre with bruit, exophthalmos
 - iv. Grave's dermopathy – hyaluronic acid → pretibial "pigskin" appearance, usually associated with dysthyroid eye disease (myositis of lid muscle)
 - b. Toxic nodular goitre (Plummer's disease)
 - i. May be a complication of long-standing euthyroid nodular goitre
 - ii. Diffuse/simple colloid goitre → multinodular → toxic (polyclonal mutations)
 - c. Toxic adenoma ('hot nodule') – benign neoplasm
 - i. T₃ hyperthyroidism in 5%
 - ii. Suppressed TSH – normal tissue inactive, active after ¹³¹I or surgery
 - d. Subacute thyroiditis (de Quervain's thyroiditis ? viral)
 - i. Tender thyroid with pain radiating to the ears
 - ii. Acute phase proteins/ESR raised, anaemia of chronic disease, LFTs odd
 - iii. Biochemical hyperthyroidism → hypothyroid phase → recovery in 3-5 months
 - iv. Glucocorticoids relieve symptoms dramatically (rarely recur)
 - e. Amiodarone – don't even try to work this out.

Endocrinology

- i. Goitre, hypothyroidism, hyperthyroidism
 - ii. FT₄ normal or high, FT₃ normal or low, TSH normal or slightly high (600mg/d)
2. Symptoms – weight loss, increased appetite, heat intolerance, tremors, palpitations, nervousness, fatigue, muscle weakness, frequent bowel motions
3. Signs – goitre, tachycardia, AF, wasting, thyroid bruit (Grave's disease only), tremor, myopathy, heart failure, proptosis, onycholysis (Plummer's nails – typically ring finger)

Investigations:

1. Suppressed TSH is the best screening test (99% sensitive, not specific)
 - a. Normal – 0.4-4.0 mU/L (excludes hyperthyroidism in 99% of cases)
 - b. Reduced – 0.004-0.4 mU/L (goitre, sickness, some drugs)
 - c. Suppressed – <0.004 mU/L
2. Raised serum thyroid hormones:
 - a. Serum free T₄ (normal 10-25 pmol/L) – 95% sensitive but not specific (raised by sickness, drugs and protein binding anomalies)
 - i. T₄ hyperthyroidism (normal T₃, suppressed TSH) in 5%
 - b. Serum free T₃ (normal 2.5-5.5 pmol/L) – 99% specific but not sensitive (reduced by sickness and drugs e.g. amiodarone)
 - i. T₃ hyperthyroidism (normal T₄, suppressed TSH) in 5%
3. Other investigations:
 - a. Autoimmune markers – anti-thyroglobulin (Tg Ab), anti-thyroid peroxidase (TPO Ab)
 - i. Titre reflects lymphocyte infiltration (not causal of autoimmune dysfunction)
 - ii. Thyroid microsomal antibody titre – positive in Grave's disease (80%)
 - iii. TSH receptor stimulating Ab → adult, intrauterine, neonatal hyperthyroidism
 - b. Thyroid scintigraphy (thyroid gland trapping rate)
 - i. Per technetate anion competes with iodide → trapping related to T4 output
 1. Increased in Graves or toxic nodular goitre
 2. Absent in subacute thyroiditis and iodine contamination
 - ii. Guide to thyroid size/shape, pattern/function and radioiodine therapy (also useful for detecting ¹³¹I uptake in metastases of thyroid cancer)
 - iii. Inferior to ultrasound for structure

TSH (mU/L)	4.0-40+	1° hypothyroidism		TSH secreting pituitary tumour
	0.4-4.0	2° hypothyroidism	NORMAL RANGE	Euthyroid hyperthyroxinaemia (non-thyroidal illness, drug effect)
	0.04-0.4	Sick euthyroid syndrome	Thyroid autonomy e.g. goitre	
	<0.04			Thyrotoxicosis
		<10	10-25	>25
		T4 (pmol/L)		

Management:

1. Radioiodine therapy – definitive therapy of choice in use since 1950 (proven safety record)
 - a. Single dose oral outpatient therapy delivering 3-10,000 rads to thyroid
 - b. Effective as single dose in 70%, usually within 6-12 weeks
 - c. Used in adults >20yrs, though pregnancy should be avoided for 3 months
 - d. 50-70% develop hypothyroidism within a year, lifetime risk of hypothyroidism
2. Thionamide drugs – carbimazole (15mg bd → od) or propylthiouracil (150mg bd → od)
 - a. Deplete T₄ and T₃ stores in 2-6 weeks by blocking iodide organification and coupling
 - b. Used 6-12 weeks before ¹³¹I or surgery, or a one-year course (30-50% → remission)
 - c. Adverse effects – rash (3%), agranulocytosis 0.3%, carbimazole teratogenic
3. Other therapies:
 - a. Beta blockers (atenolol 50mg od) – relieves palpitations, anxiety, insomnia
 - b. Iodides (Lugol's iodine 1mL bd) – used after antithyroid drugs have blocked the gland
 - c. Glucocorticoids – thyroid crisis, subacute thyroiditis, eyes
 - d. Lithium – occasionally used to block proteolysis
 - e. Potassium perchlorate – useful for some amiodarone hyperthyroidism
4. Subtotal thyroidectomy
 - a. Indications limited to patient preference, some amiodarone hyperthyroidism

Endocrinology

- b. Side effects – recurrent thyrotoxicosis, hypothyroidism, recurrent laryngeal nerve palsy, hypoparathyroidism, keloid scar formation

Pregnancy – special issues:

1. Measure TSH-R antibodies in the 2nd trimester
2. Remission common during pregnancy, but relapse post-partum
3. Foetal brain <20 months needs maternal T₄ (maternal FT₄ should be >10nmol/L)
4. Hypothyroid women need 1/3 extra T₄

Summary of standard treatment:

1. Atenolol 50mg nocte
2. Early radioiodine treatment – when hypothyroid
3. Carbimazole 15mg bd
4. Replace thyroxine to a normal TSH
5. Other drugs as indicated:
 - a. Diltiazem effective for rate control in AF
 - b. Warfarin if AF chronic, abnormal 2DE or >65
 - c. Amiodarone hyperthyroidism – carbimazole 30mg bd