ENDOCRINOLOGY H+E (OBESITY)

OBESITY [eating habits + psychology + underlying co-morbidity]

1. HPS

GENERAL: fatigue ➔ fever/swelling/rash ➔ sleep (OSA – insomnia)/weight gain/loss

Eating Disorder

- **EATING HABITS:** Over-nutrition (too many meals) + **Previous diets + regularity of eating + food groups**
  - *Do you worry about your weight?*
  - *How do you feel about your weight?*
  - *Do you **diet**? or What other things have you tried to control your weight?*
  - *Have you made yourself sick after meals? Skip meals? Where do you go after meals – toilet?*
- **Weight Hx**
- **Mood** (risk of self-harm)
- **Feeling about food** (reasons for avoiding food)
- **Physical signs of anorexia nervosa**
  - Cold dizzy, weak, thin hair
  - Reduced libido
  - Menstrual changes (amenorrhoea – central / functional cause)
  - **Postural drop, bradycardia**
  - **Hypothermia**
  - **Electrolyte abnormalities**
  - **QTc > 450ms**

Medical Cause of weight gain

- **Endocrine = PCOS, Cushing's, Hypothyroidism**
- **CV** = HTN HF, IHD, PE and CAD
- **MSK** = OA, immobility, Turner's, achondroplasia
- **Resp** = OSA

	Definition	DSM-V Criteria	Complications
Anorexia nervosa	excessive dieting followed by vomiting or purging	1. **Restriction of energy intake** 2. **Intense fear of gaining weight**; 3. **Disturbance in body image** (cannot recognise seriousness of the current low body weight)	• **OP (dexa scan)** • **Sinus bradycardia** • **Hypothermia** • **HypoTN** • **Low electrolytes – arrythmia** • **Depression**
Bulimia nervosa	Frequent binge eating followed by vomiting or purging [compensatory]	1. **Recurrent episodes of binge eating** (excess food consumed AND a sense of lack of control) 2. **Recurrent inappropriate compensatory behaviours** (e.g. vomiting, fasting excessive exercise) **3. Frequency of at > 1x /every 3/12** 4. Self-evaluation unduly influenced by body shape and weight 5. Absence of anorexia nervosa	• **Mallory-weiss tear** • **Oesophagitis** • **Depression** • **Altered electrolytes**

2. PMHx

Conditions

- **MetSyn: HT, hypercholesteroleamia, diabetes (hyperinsulinemia),**
- **GORD, PCOS**

Previous surgeries

- ***Previous bariatric surgery → risk of:***
  - Vitamin def. – oral B12, folate
  - Anaemia – oral Fe
  - OP
  - Regain weight (bad habits)
  - Marjolin ulcers → PPI

Medications	Gain weight = COCP, anti-depressants, anti-psychotics, corticosteroids
Tests (exploratory	**Fasting BGL (HbA1C), blood tests, Ultrasound (PCOS)**
Allergies & Vaccinations	*strep. Pneumoniae*, *FluVax*

3. SHx

- **Background:** Thalassaemia (Mediterranean/South Asian), sickle cell disease (Africans)
- **Occupation:** sedentary
- **Lifestyle:** diet restrictions/regularity + physical activity
- **Smoking/Alcohol/Drugs**
- **Overseas travel** (*malarial infection or intestinal parasitic*)

4. FHx

- 1st degree relatives with CV risk factors (i.e. obesity, stroke, HF)
- PCOS (strongly inherited)

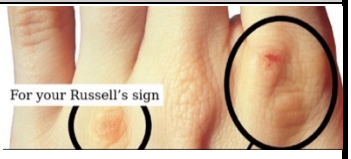
5. SR

- **CNS, MSK:** joint pain/aches, muscle pains/aches, muscle tremor, muscle wasting, LOC
- **CVS** – [chest pain] CAD SPIFE, **RESP** – [shortness of breath] SCSC FAWIF
- **GU** – dysuria? Vaginal discharge? | menstrual cycle for 20-50s (menorrhagia – bleeding) | menopause > 50

Examination Procedure

Peripheral signs

- **General**: baggy clothing, peripheral cyanosis
- **Hands ➔ dry skin, brittle nails + skin turgor (dehydration), dorsal finger callous (Russell's sign), lanugo (hair growth)**
- **Mouth ➔** fruity breath (ketosis – starvation state = AN), dental enamel erosion (purging), gingivitis,
- **Head & neck ➔** parotidomegaly, xerosis (dry mouth, eyes and skin)
- **Legs** – Swelling (oedema), capillary refill time (<3s)



Examination

- **Measurements: Height, weight, BMI**
- **CV**: Bradycardia, Hypotension (+postural), Hypothermia
  - **Long QT syndrome (hypokalaemia)**
  - **Reduced cardiac contractility** (hypoPO4)
- **MSK**: squat test (muscle power) – Gower's sign

Classification	BMI (kg · m⁻²)
Underweight	<18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Obesity	
Class I	30.0-34.9
Class II	35.0-39.9
Class III (extreme obesity)	≥40.0

Waist-to-Hip Ratio (WHR) Norms

Gender	Excellent	Good	Average	At Risk
Males	<0.85	0.85–0.89	0.90–0.95	≥0.95
Females	<0.75	0.75–0.79	0.80–0.86	≥0.86

GENERAL ENDOCRINE + DIABETES H+E

1. History of presenting complaint [Think Systems]

NEURO/CNS	• **Headaches [SOCRATES], vision issues (bitemporal hemianopia)** → [pituitary tumour] – foot drop, carpul tunnel	
CV [CADSPIF]	• **Chest pain [SOCRATES]** • **palpitations, diaphoresis, swelling in leg** [CLAUDICATION]	
RESP [SCSC]	• **SOB** (dyspnoea, PND, Orthopnoea), **OSA (snoring)** • **Cough** → sputum?	
GI [BLIND CRAP]	• **Nausea + Vomiting** (how much?) | **Bowel habits (constipation** | diarrhoea) • **Abdominal Pain [SOCRATES] + Abdominal bloating**	
Renal [FUNDWISE]	• **Polyuria/Nocturia, Polydipsia** → postural hypotension, electrolyte loss • **UTIs & Urethra discharge**	
Gynae	• ♀: **Irregular cycles** / **Period volume** **Menorrhagia** (pain/volume) / **Galactorrhoea** / infertility • ♂: **ED / gynaecomastia /** loss of libido / infertility	
Skin	• **Hyperpigmentation** OR Bruising • **Hair** (loss or excess growth)	• Rashes + Redness
MSK	• Muscle tremor • **Fractures/Bone pain**	• Muscle wasting • Joint pain
General	• **Fever** | **Unintentional Weight gain/loss** | **Appetite** | **Sleep** (insomnia, very sleepy)	

Excess GH	Excess TSH	Excess ACTH	Excess LH/FSH	Excess Prolactin
IGF-1	T3/T4	Aldosterone & cortisol & androgens (TT)	Estrogen & testosterone	**PrL levels**

• **Physically bigger** (cannot wear wedding ring)
• **Dysphagia (closure of oesophagus)**
• **Hoarseness** (compress vocal folds)
• **Arrythmias**
• **Snoring** (OSA)
• **Skin tags + acanthosis nig.**
• **Bone pain** (excess bone growth)
• **Sweaty warm palms**
	• **Neck lump**
	• **"Anyone comment about eyes"**
	• **Weight loss** (Increased metabolic rate)
	• **SOB** (↑RR)
	• **Diarrhoea** (↑ GI motility)
	• **Hypertension + tremor** (↑ contractility + HR)
	• **Hyperglycemia**
	• **Sweaty Warm skin** (Increased metabolic rate)
		Effects of aldosterone:
		• **Polyuria**
		• **Low renin-aldosterone ratio**
		• **Hypernatremia, hypokalemia** → arrhythmia
		• **Met. Alkalosis**
		• **Hypertension** → Na+ water retention
		
		Effects of cortisol:
		• **Circadian rhythm** → cognitive, mood, memory
		• **Stress:**
		  ○ **Liver: GGN, GNG** → hyperglycemia → weight loss
		  ○ **Muscle:** Proteolysis → cachexia
		  ○ **AT:** lipolysis → weight loss
		• **↑BP** = BV vasoconstriction
		• **↓ immune system** = **↓ inflammation** (↑ infection)
		• **↑ osteoclasts** = osteoporosis
		• **↓ GnRH** = **↓ androgens** = irregular menses and infertility + **↓ libido**
			Females:
			• **Increased muscle mass**
			• **Increased libido**
			• **Heavy menses**
			• **Hirsutism**
			• **Ovulation**
			• **Vaginal secretion** = *vaginal dryness*
			• **↓ osteoclast** = fracture
			
			Males:
			• ↑ spermatogenesis
			• **Increased libido (+ erection)**
				• **Galactorrhea** (↑ prolactin)
				• **Amenorrhea & irregular menses** (LH/FSH suppressed)
				• **Gynecomastia** (↑ prolactin)
				• **Loss of libido**
				• **ED**
				• **Infertility**
				
				Rx: cabergoline (dop. Agonist)

	Acute Hyperglycemic (>15mm)	Acute Hypoglycemic (<3.5mm)
Suspected T2DM	• **Polyuria** & Unintentional **Weight** • **Dehydrated** (Polydipsia) • Blurred **Vision** (Lens Shape Change) , • **Fatigue** • Recurrent **Infections** • **DKA Or HHS Admission (If Severe)**	• Sweating, • Fainting, • Paraesthesia, • Visual Disturbances, • Tremor, • **Decreased Awareness (If Severe, Need Paramedics)**
Diagnosed	**When? How? What Type?** Prediabetes = IGT/IFT + Diabetes → 25% of hospital admission doubles hospital stay time	
Management & Compliance	• **Recent Hba1c, BSL Trend (Vs Hx)** → Regular Checks? → Target ≤ 6.5% • **Test Method:** HBGM, CGMS (T1DM)? • **# Of Admissions (E.**G. DKA, Hypoglycemia) • **MDT (***Endocrinologist, Optometrist, GP, Carers*	• **Hypoawareness (**Asymptomatic) • **Specific Patterns** (Fasting Vs Post-Prandial) • ***Methods of administration****: flexipen, injection, insulin pump [convenience, cost, lifestyle, preference, tech advancement*
Microvascular [*Damage to smaller BVs*]	• **Neuropathy** (Feet Paraesthesia & Shooting Pain + **Ulcers + Recurrent Infection**) • **Retinopathy** (long-term → **Blurred Vision, Myopia Cataracts, Glaucoma** – Intraocular Pressure) • **Nephropathy (**Polyuria/Nocturia, Proteinuria, Glycosuria**) + Polydipsia (flow/colour/hesitancy)**	
Macrovascular *Damage to larger BVs*	• **CV – HTN** (Chest Pain On Rest/Exertion, Previous MI) → Previous Stents, ECGs • **TIA/Stroke** • **PVD** (Claudication + Repeated Distance → **Unilateral/Bilateral)**	
Other	• **Female**: Utis, Vaginal Thrush • **Autonomic**: **Gastroparesis, ED (issues with erection, atypical silent MI** (High Risk For Coronary Heart Disease Esp. >50) • **General**: Fever, Weight Gain/Loss, Appetite, Sleep	

2. Past MHx [CHOMV STAVE]

Conditions	• **Hypertension** (possible pheo, Cushing's or Conn's). • **Vascular Risk: BP, Lipids (HC)** → *Patients With* Metsyn = *2x Risk Of CVD And 5x Risk Of T2D* • **Metabolic Risk: PCOS/GDM, Gout, OSA, Thyroid Disease, Non-Alcoholic Hepatic Steatosis, NAFLD** • **Previous Hx**: endocrine condition , existing autoimmune (e.g. coeliac)
Medications	• **antithyroid drugs**, thyroid hormone or radioactive iodine • **HRTs (e.g** *glucocorticoids -prednisone for asthma*, *estrogen → menopause)* • **antiarrhythmic drug amiodarone** (contains iodine → commonly causes hypo- or hyperthyroidism)
Surgeries/ Treatments	• *partial thyroidectomy* → **leads to** hypothyroidism AND hypoparathyroidism (damage to PTH glands) • *Surgery on the adrenals or pituitary* → decreased adrenal or pituitary function • **IV contrast**

3. Social Hx

- **Occupation/study:** *stressful jobs*
  - **Moderate alcohol = hyperglycaemia**
  - **Binge drinking → hypoglycaemia**

4. FHx

1. **Autoimmune diseases** (E.g. Grave's, hashimoto, pernicious anaemia, coeliac → link with T1DM)
2. **1st deg. Relatives with CV-related death < 50.**
3. **FHx of diabetes, multiple-endocrine neoplasia (MEN)** + CV risk factors,

Thyroid Gland Examination

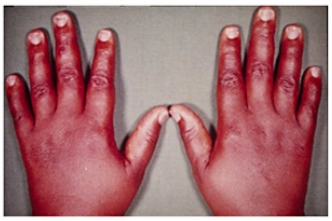
Summary:

- Today I conducted a thyroid examination on _____, a ____ year-old male.
- On general inspection, he had ____ (any tremors, redness, temperature, sweaty) with no other peripheral signs of thyroid disease
- There was NO? evidence of thyroid eye disease and no goitre
- To complete the examination, I would like to conduct some blood tests looking specifically at the TSH and T4 levels

Exposure	***This will involve me generally inspecting before me moving in closer to look and feel the thyroids in the neck.***	
Peripheral signs	**General**	• Weight | Anxiety | fidgety ➔ **hyperthyroidism** | mental/physical sluggishness ➔ **hypothyroidism**
	Hands/Wrist [*arms out*] [**paper + pulse**]	• **hypothyroidism** =**PUFFY WRISTS/Cool/ dry palms ➔ bradycardic ➔ palmor crease pallor** • **hyperthyroidism** [*SNS overactivity*] = **Sweaty/palmar erythema/ Peripheral tremor/tachycardic or AF**/ irregular pulse **onycholysis** ○ **Grave's disease = clubbing (thyroid acropachy)**
	Arms	• **ARM/LEG**: Biceps or knee reflex = **hyporeflexia** (**hypothyroidism**)
	Face	• **hypothyroidism** = **dry and cool skin** | **loss of outer 3rd eyebrow** or thinned eyebrows • **hyperthyroidism** = **excessive sweating**
	Eyes *Look from side/behind* [*H-TEST*]	• **Grave's disease**: bilateral **exophthalmos** (bulging eyes = **LOOK FROM SIDE**) ○ **NB: Upper eyelid retraction** (**SCLERA VISIBLE**) = **ANY form of thyrotoxicosis** • **H-TEST** = **diplopia/ ophthalmoplegia** (e.g. restricted eye movement) **& pain during eye movement** • **Move finger up/down** = **Upper lid lag** [von Graefe's sign]
Inspect Thyroid [*swallowing & tongue protrusion*]	• **Masses ➔ Pseudogoitre** (excess fat pad = obese) OR **Goitre** = outward bulge [*80% euthyroid, 10% hypo nd 10% hyper]* • **Scars**: thyroidectomy scar • **Erythema** (suppurative thyroiditis)	
	• **Prominent veins upper chest wall** ➔ thoracic inlet obstruction • **Pemberton's sign** ➔ SVC obstruction	
	• **Swallow Water**, and watch **neck swelling** during swallowing➔ **Mass rises?** = goitre, thyroglossal cyst, • **Stick tongue Out Mass rises? Yes** = thyroglossal cyst, **No** = thyroid gland mass, lymph node	
Palpate lobes and isthmus (from behind then front x2)	*For any nodule/swelling*: **Size | Shape (symmetry) | consistency | tender** (thyroiditis) | **mobility [repeat swallowing]** • **Soft** (but firmer than a fat pad) = NORMAL • **Firm** = **simple goitre** • **firm and tender gland** = **de Quervain's thyroiditis** • **rubbery hard** = **Hashimoto's thyroiditis** • **stony, hard node** = **carcinoma | calcification in a cyst |fibrosis** **Patient flex neck to relax SCM** • **Lymphadenopathy** (all lymph nodes) ➔ palpate using pads of 2nd, 3rd, 4th fingers • **Tracheal deviation** (large goitre)	
Percuss	Sternal notch ➔ change from resonant to dull ➔ **retrosternal goitre** (extends **inferiorly** BUT unreliable sign)	
Auscultate	• **Listen over each lobe for a bruit ➔ specific sign of increased blood supply for Grave's**) • **Retrosternal goitre/mass** compress lateral lobes ➔ **Stridor** ➔ thoracic inlet obstruction	
SPECIAL TESTS	• **ARM**: arms crossed + stand up ➔ **proximal myopathy**, (**multinodular goitre & Grave's**) • **LEGS**: Rolls pants up ➔ **pretibial myxoedema** (rare for **Grave's disease**) = bilateral firm, elevated dermal nodules and plaques [pink, brown or skin coloured] due to **mucopolysaccharide accumulation (glycosamioglycans)**	

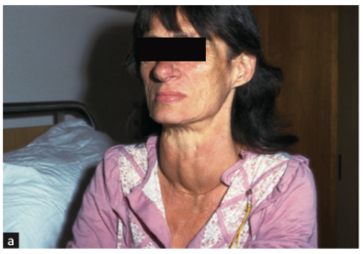
DIFFERENTIAL DIAGNOSIS OF THYROID NODULES

1. Carcinoma (5% of palpable nodules)—fixed to surrounding tissues, palpable lymph nodes, vocal cord paralysis, hard, especially if larger than 4 centimetres (most are, however, smaller than this)
2. Adenoma—mobile, no local associated features
3. Big nodule in a multinodular goitre—palpable multinodular goitre



Palpating the thyroid from behind while the patient swallows sips of water

Goitre.



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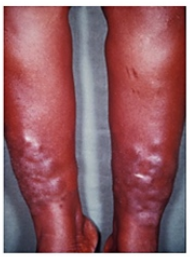
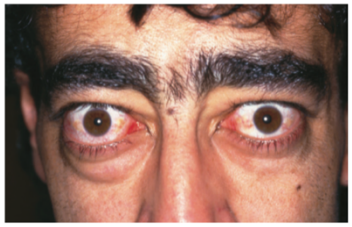
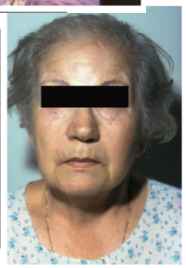




Thyrotoxicosis: thyroid stare and exophthalmos

Onycholysis (Plummer's nails)



Myxoedema

GOOD SIGNS GUIDE 28.2
Hypothyroidism

Sign	LR+	LR–
SKIN		
Coarse	2.6	0.71
Cool and dry	5.1	0.69
Cold palms	1.6	0.82
Dry palms	1.5	0.80
Periorbital puffiness	3.2	0.61
Puffiness of wrists	3.1	0.80
Loss of eyebrow hair	1.95	0.83
SPEECH		
Hypothyroid speech	2.3	0.83
THYROID GLAND		
Goitre	2.6	0.68
PULSE		
<70 beats per minute	3.9	0.64

The Diabetes Foot Examination

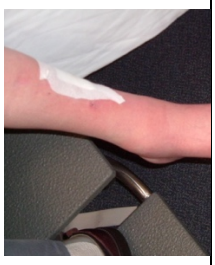
General Inspection (Standing)

- Responsive?
- **Obese ➔ Weight & height (BMI >30, WHR)**
- **Vitals ➔ Kussmaul's breathing (DKA → acetone breath), Tachycardia, Hypotension**
- **Dehydrated** (osmotic diuresis)
- ***Cachexia* = *quadriceps muscle wasting* ➔** femoral nerve mononeuropathy

High risk diabetic foot?

- **Charcot's foot clinical features**
  - Dusky hairless foot
  - Absent pulses + monofilament sensation (charcot neuropathy)
  - Dry callused skin
  - Charcot's arthropathy) ➔ no foot arch + clawed toes + Metatarsal head prominence
- **Ulcerations** (microvascular impairment) ➔ lead to signs of neuropathy
- **Osteomyelitis** (BOTH autonomic & peripheral neuropathy)
- **Positive Buerger's test (critical limb ischemia**) ➔Sign = elevation pallor/ischemia [*PAD mainly assoc. with smoking diabetics*]

(Diabetic foot examination



- Burning hot feet when hanging foot over bed (when restoring BV supply)

Inspect (foot)

1.	**Shape of foot**	[**T1D – arched), (T2D- Flat) + clawing/dystrophic nails** = onychogryphosis - intrinsic cachexia]
2.	**Colour**	• **Blue/Purple** = ischemia (Buerger's test) • **Red** = infection/acute **Charcot's joint (deformed)**
3.	**Hair loss**	Small-vessel vascular disease ➔ ischemia
4.	**Ulcers**	@ pressure points [ischeamia + peripheral neuropathy] • size, position, number, **infection risk** (cellulitis, discharge and heat) + sepsis (fever, malaise)
5.	**Amputation**	Amputated knee or amputated toes
6.	**Dry skin**	• **Dry, callus** (reduced innervation of sweat glands due to BOTH **autonomic/peripheral neuropathy**

Palpate

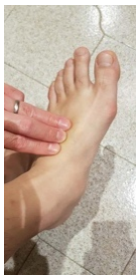
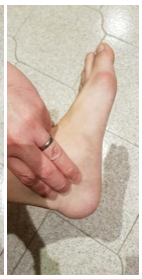
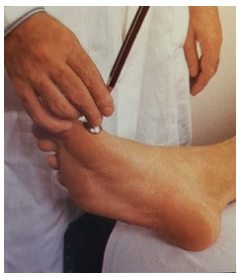
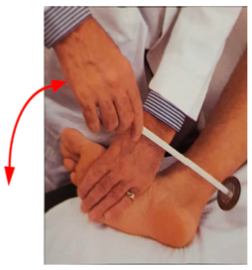
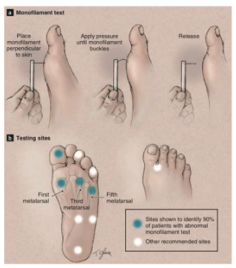
Vascular

- **Absent** Dorsalis pedis + posterior tibial peripheral pulse + **Buerger's test** (arterial insufficiency)
- **Delayed capillary refill time (> 3s) = *microvascular disease*,**
- **Cold feet,**
- **ABI < 0.9 ➔ PVD**

Move

Neurological exam

1. **Monofilament testing ➔ (***test: 1st, 3rd, 5th metacarpals + plantar surface of distal hallux)* **➔ most sensitive early sign of PN at feet+ sensation loss = increases risk of ulceration**
2. **Vibration sense (128Hz tuning fork)** = 1st metatarsal head
3. **Deep tendon reflex (ankle jerk)** = gentle flick of wrist to land on Achilles tendon

Monofilament testing for peripheral neuropathy in the feet

Upper limbs/ Axilla

- **Skin** **Skin tags, acanthosis nigricans**) [also check for acromegaly =GH = insulin resistance]
  - **Necrobiosis lipodica diabeticorum**
  - **Scleroderma diabeticorum ➔** thickened skin of upper back & shoulders [NOT sclerodermal]

Face (Eyes)

Eyes

- visual acuity ➔ lens shape change (due to hyperglycaemia and water retention)
  (*hyperglycemia ➔ glucose converted to sorbitol → accumulates in lens → when BGL falls → osmotic gradient pulls water into lens ➔ swelling of lens ➔ lens shape change*)
- cataracts ➔ sorbitol deposition in the lens
  retina ➔ **non-proliferative** (ischaemia of BV) & **proliferative** (angiogenesis → fragile vessels → rupture)

CV

- **carotid arteries** evidence of vascular disease
- **Oedema**
- $CHADS_2$ **Score** for Atrial Fibrillation Stroke Risk

Other

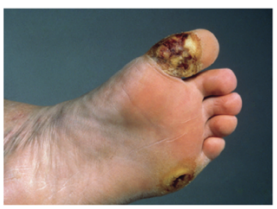
- **Insulin Injection site ➔ scarring** + localised *fat atrophy* and *fat hypertrophy*
- **Liver** (hepatomegaly) ➔ fat infiltration (+/-haemochromatosis due to Injection sites)
- **Kidney ➔** renal bruits/ CKD/dialysis

Request

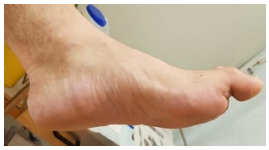
- **Finger prick test (BSL)**
- **Urinalysis**: glucose and protein [Diabetic nephropathy → nephritic syndrome → CKD in late stages]
- **Blood pressure**— **Arm** postural hypotension (standing vs sitting) ➔ diabetic autonomic neuropathy
- Test proximal muscle power (**diabetic amyotrophy**)

Mx (mainly to off-load):

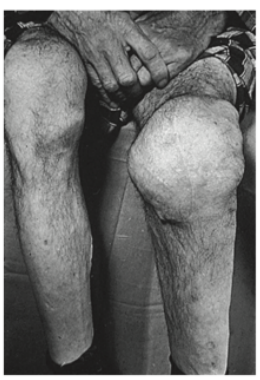
- **Short-term intervention** → CAM boot (reduce pressure off ulcers) or other foot orthoses
- **Long-term** → custom made boots → for charcot arthropathy



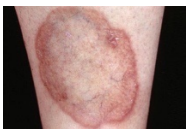
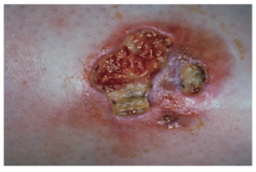
Diabetic (neuropathic) ulcer



Collapsed/loss of foot arch + foot deformity leads to pressure ulcers

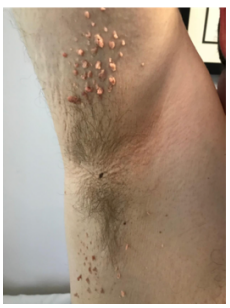


Charcot's joint of left knee

Necrobiosis lipoidica diabeticorum

- Well-demarcated Yellow-brown patches with surrounding erythema slowly enlarge over time
- Shiny, pale + thin w/ telengectasias
- May ulcerate and unknown origin



Skin tags + acanthosis nigracans (must also check for GH excess for acromegaly)

T1DM vs T2DM [*polyuria > 300mL /hr (> 2hrs)

Define

T1DM
- Insulin deficient – causing ketogenesis (utilising fat reserves for energy)

T2DM
Insulin resistance → glycosuria → osmotic diuresis → electrolyte loss + dehydration
- Non-insulin dependent T2DM
- Insulin dependent T2DM – exhausted beta cells in presence of chronic hyperglycemia

RF

T1DM
- FHx of autoimmune
- FHx of T1DM

T2DM
Non-Modifiable
- Older age
- Ethnicity (Black, Chinese, South Asian)
- Family history

Modifiable
- Obesity
- Sedentary lifestyles
- High carbohydrate (particularly refined carbohydrate) diet

Sx

Hypoglycaemia Sx
- **ANS** – drowsy, fits, coma, LOC
- **SNS** - Tremor, diaphoresis, hunger, palpitations (SNS)
- **Chronic** – headache, blurred vision
- Rx: Short-acting CHO (sugar water) + long-acting CHO (biscuits and toasts)
  Last resort: IV dextrose or iM glucagon

Hyperglycaemia Sx:
- Kussmaul
- Fruity breath (Acetone)
- Abdo pain (N/V)
- Polydipsia and polyuria
- UWL
- Altered mental state

- Fatigue
- Polydipsia and polyuria (thirsty and urinat
- Overweight / central adiposity
- Opportunistic infections
- Slow healing
- Glucose in urine (on dipstick)

SUSPECTED T2DM – AUSDRISK
- Age
- Sex (male)
- Ethnicity
- FHx 1st deg (DM)
- Anti-HTN
- Hx of high BSL
- Smoker
- PA
- Obese
- WHR

Comp.

T1DM

Microvascular complications
- Same as T2DM

Macrovascular complications
- Same as T2DM

Infection related complications:
- UTI
- Pneumonia
- Skin and soft tissue infections (esp. fungal/candida)

Diabetic ketoacidosis (1-2 days acute)
- **Trigger** = infection, stress, undiagnosed T1DM, steroids, non-compliance w/ insulin
- Hypovolaemia – AKI, Hyperosmolality
- Electrolyte issues - HypoNa, HypoK
- Neuro issues – Seizures, coma
- **BSL > 11mM → Ketoacidosis + low C-peptide**

T2DM

Microvascular complications
- **Diabetic retinopathy** – NPR vs PR
- **Diabetic nephropathy** – chronic kidney disease – glomerulosclerosis
  - Renal vascular stenosis, secondary hyperaldosteronism
- **Diabetic neuropathy** – diabetic foot ulcers, Charcot's neuroarthropathy
  - **ANS** = Erectile dysfn, gastroparesis, postural HypoTN

Macrovascular complications
- Stroke / TIA
- Atherosclerosis, MI, ischaemic cardiomyopathy
- HTN + OSA
- Peripheral vascular disease - diabetic foot, **mesenteric ischaemia, ischaemic colitis, cellulitis, necrotising fasciitis**

Hyperosmotic Non-ketotic hyperglycaemia (>7 days)
- Glycosuria → osmotic diuresis → electrolyte loss + dehydration
- Severe dehydration / polydipsia
- BLURRED vision
- **BSL > 33mM → absent ketones + normal C-peptide**
- **Complications (same as DKA) → ↑↑VTE**

Trigger for HONK
- infection (e.g. pneumonia),
- stress, + XS cortisol
- stroke,
- trauma , EtOH, drug abuse
- Endo: pregnant, acromegaly

Ix

Dx criteria:
1. **BSL = Hyperglycaemia** (i.e. blood glucose > 11 mmol/l)
2. **UA = Ketosis** (i.e. blood ketones > 3 mmol/l)
3. **ABG = Acidosis** (i.e. pH < 7.3) **+ high anion gap (> 12) → RESP DISTRESS → DEATH**

Supporting Ix

T1DM
- **EUC (osmotic diuresis) -** hypoNa (dehydration – V/D)
- Severe hyperK → becomes hypoK (After insulin)
- **Insulin/ Cpep/ proinsulin levels**
- **Autoantibodies:**
  - **Zn8 transporter**
  - **Anti-GAD**
  - **Anti-islet cell autoantibodies**

T2DM
- FBC, EUC, LFT
- Fasting lipids
- Fasting BSL and OGTT (75g glucose)
- HbA1C
- Urine ACR

Imaging
- USS doppler + duplex
- TTE (RCA = post, LAD = ant.)
- CTA; MRA; CTCA; Ca scores
- PET – sestamibi
- Angiography

	Fasting BSL	OGTT	HbA1C
Impaired fasting glucose (prediabetes)	6.1-6.9 mM		5.7-6.4
Impaired glucose tolerance (prediabetes)		7.8 -11.1 mM	5.7-6.4
Diabetes	> 7mM	> 11mM	> 6.5%

Mx

T1DM

Lifestyle (NEAT)
- **MDT**
  - **Endocrinologists** = ANNUAL check-up – **FBC, EUC (eGFR), LFT, Fasting lipids/BSL, HbA1C, urine ACR**
  - **podiatrist** = ANNUAL foot exam + orthotics
  - **ophthalmologist** = Annual *check → anti-VEGF*
  - **diabetics nurse educator** = **INSULIN PUMP**
  - **Physiotherapist + dietician**
- Lose weight (intermittent faating, low GI high fibre diet, increased physical activity – regular 5x/week of 30mins moderate activity)
- Stop smoking and EtOH'
- **IUTD**
- **Heavy vehicle license, pilot license renewal**

Medications
- SC Insulin – titrated accordingly → **lipodystrophy (injection site) –** when SC fat hardens and does not absorb insulin
- Monitor BSL on waking, at meal and before bed – ***freestyle Libre (PBS funded)***
- Managed complications (micro, macro)

DKA management (FIG – PICK)
1. **Fluids** = IV 0.9% saline 1L STAT → replace w/ 4% dextrose when BSL <15 → 2x large bore cannulas
2. **Reduce BSL = IV insulin** (0.1U/kg/hr = sats receptors)
3. Monitor **glucose** – add dextrose infusion if < 14mM
4. **Potassium - Correct HypoK + metabolic acidosis -** IV KCL (4th hourly) + BSL (hourly)
5. **Chart balance –** fluid balance
6. **Ketones -** monitor
7. **Anti-coag** → dehydrated (↑ coag state)

Pre-op and post-op Mx:
- Omit morning insulin (if 1st on list for short op)
- *Top op:* Small dose basal insulin + 5% dextrose (if early on list)
- IV insulin + dextrose (if long-op fasting prolonged)
- Monitor BSL hrly while NBM

T2DM

Lifestyle (NEAT)
- **MDT**
  - **Endocrinologists** = ANNUAL check-up – **FBC, EUC (eGFR), LFT, Fasting lipids/BSL, HbA1C, urine ACR**
  - **podiatrist** = ANNUAL foot exam + orthotics
  - **ophthalmologist** = Annual *check → anti-VEGF*
  - **cardiologist** = 2-year total CVD risk assessment (if >45 yo or >35 yo +ATSI)
  - **diabetics nurse educator + Physiotherapist + dietician**
- **Lose weight (***intermittent fasting, low GI high fibre diet, increased physical activity – regular 5x/week of 30mins moderate activity***)**
- **Stop smoking and EtOH**
- **Optimise co-morbidities** (HTN, HC, CVD) **and complication → statins, Anti-HTN**
- **IUTD**
- **Heavy vehicle license, pilot license renewal**

Medications
- 1st line = Metformin 1000mg bd PO (with meals)
- 2nd line = Metformin **PLUS** → SGLT2i → GLP-1, DDP4i → SU
- 3rd line = Metformin **PLUS** Insulin
- **Target HbA1C <6.5%**

To optimise glucose control
- Avoid sliding scale insulin
- Basal insulin + prandial insulin (SA insulin – novorapid)

Beware of:
- Hypoaware
- Relative hypoglycaemia (rapidly ↓ chronically high BSL – causes

HHS management
- **Rehydrate -** IV 0.9% saline
- **4mM/hr IV insulin** (Reduce BSL → stop cerebral oedema = ODS + coning)
- **IV KCL**
- **Anti-coag** → dehydrated (↑ coag state)
- **Rx underlying trigger/cause**

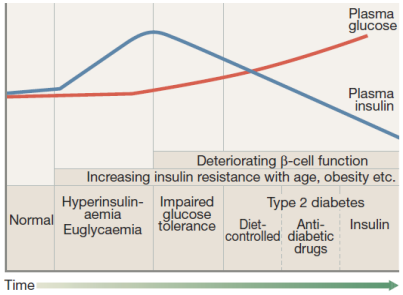
Pre-op and post-op Mx:
- Diet control = monitor BSL (no dextrose needed)
- Oral agents (e.g. metformin) – omit mane dose
- **Stop metformin, SGLT2i, GLP-1, DDP4I** if using IV contrast
- IV insulin infusion (if long op)
- DVT prophylaxis – Clexane

DM Classification

	T1DM (5-10%)	T2DM (90%)	GDM	MODY	Neonatal Diabetes	Whipple's
	• autoimmune destruction of insulin-producing pancreatic β cells ➔ causing marked insulin deficiency • **T1DM – A = autoimmune** • **T1DM – B = idiopathic loss in insulin secretion** • **T1DM – C = post-pancreatectomy**	• ***Insulin resistance*** *= reduced* insulin sensitivity • **cannot** produce sufficient insulin to overcome this "resistance'	• diabetes with first onset or recognition during pregnancy	Most common: • **MODY 2:** β-cell glucose sensing defect-GCK mutation • **MODY 3:** Transcription reg. defect	• GDM mother	• Insulinoma (non-islet cell tumour) • Acute hypoglycaemia \
Epi	• **Onset**: **childhood** & **young adulthood** (**latent autoimmune diabetes of adulthood** (LADA)) • **Most common in Caucasians & higher latitude countries (e.g. Finland)**	• ***Strong genetic predisposition (e.g. monozygote twins – 80-90%)*** • More common in **offspring of T2DM women than T2DM men** Nb: T1Dm can become T2DM	• **Fastest growing type of diabetes in Australia** • ≈ 13% of pregnant women will develop GDM in Australia • Peaked between 24th to 28th week of pregnancy	• 2 - 5 % of diabetes • 90% misdiagnosed as T1/2DM	• Neonatal period → 6 months of life • may relapse	**DDx**: • undiagnosed T2DM, • CKD, • Cirrhosis, • sepsis, • G6PD def. XS alcohol
Assoc.	• **Polygenic predisposition BUT** *80–85% of new cases* with **no known** family hx • Assoc. thyrogastric cluster of autoimmune disorders (e.g. coeliac diseases, thyroiditis, pernicious)	• **Gene defects** affect β-cell function, (e.g. **Transcription factor 7-like 2 (TCF7L2)**)	• Women with GDM ➔ **7x increased risk** of developing T2DM + their offspring • Human placental lactogen = GH analogue = promotes insulin resistance	• ***Autosomal dominant*** *Diagnostic Criteria:* 1. *Age of onset for at least 1 family member < 25 years* 2. *Corrected fasting hyperglycaemia for at least 2 years without insulin* 3. *No ketotic events* 4. *Impaired insulin secretion* 5. **MODY 2)** ➔ many not need treatment as only mild hyperglycemia	1. **Profound insulin deficiency** = marked hyperglycaemia and DKA 2. 50% have **permanent DM** (active mutated genes of subunits of the ***KATP channel ➔ open to hyperpolarise beta cells to decrease insulin secretion =STOPPED***)	**Triad of symptoms:** **1. Hypoglycaemia sx (dizzy, collapse)** **2. BSL < 2mM (VBG)** **3. Symptoms resolve w/ dextrose / glucagon**
Ix	• **HLA DR2 is protective (***DR3/4 present in T1DM in Caucasians)* • **Autoantibodies:** *Anti-GAD, Anti-IA2, Zn transporter 8, islet cell Ab, insulin Ab* *Elevated anti-IA2 = Autoimmune T1DM from very beginning*	• Fasting BSL • OGTT	• Fasting BSL • OGTT			➢ EUC, LFT ➢ Raised serum insuline, c-peptide ➢ 72 hr monitored fasting ➢ CT abdo-pelvis ➢ Autoimmune screen
Environ RF	• **Viruses** (e.g. congenital rubella) • **Chemicals** (e.g. dietary nitrosamines → coffee) • **Diet** (cow's milk) • **Vit D deficiency** • **Hygiene hypothesis** '***More people diagnosed in the winter*** *(due to increase viral infections & Vit D deficiency)*	• **Obesity** (biggest risk factor) • **Diet & Physical activity** • **Alcohol intake** • **Older Age:** • **Ethnicity**: Asians + Afr. American • **GDM** • **PCOS** • **Drugs** (e.g. thiazides and BBs) • **1st deg relatives with diabetes**	• **Obese** (BMI > 30 = 10x risk) • **Previous GDM** • 1st deg relatives with diabetes • **South Asian** *(Indians), Black Caribbean, Middle Eastern*	To check: ➢ Trail of SU (diamicron) to increase insulin secretion – effective Other Ix: ➢ If anti-GAD elevated but IIA-2 is normal	Requires insulin at birth (90% respond to SU)	**Overseas cause** ➢ *falciparum malaria,* ➢ *unripe ackee fruit (Caribbean, West Africa) → toxic hypoglycaemia*

Table 2.1—Staging of type 1 diabetes (4,5)

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria



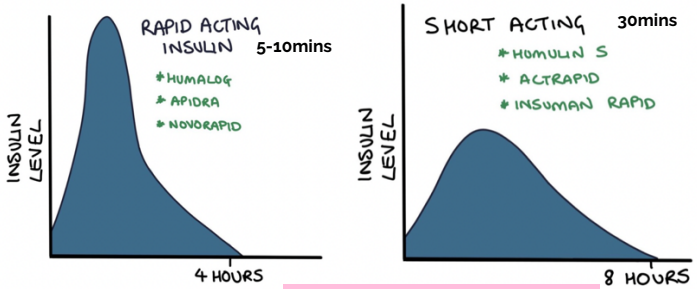
1. Initially, pancreatic beta cells can stabilise rising glucose with increased insulin ➔ hyperinsulinemia with euglycemia
2. Over time, increasing insulin resistance ➔ beta cells cannot compensate for rising glucose ⟶ impaired glucose tolerance ➔ beta-cell function declines

Pharmacological approach to diabetes

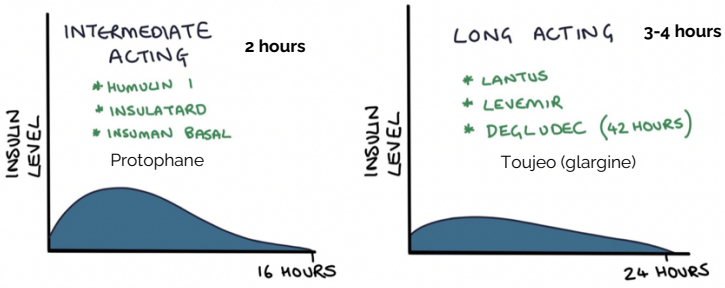
	Insulin	**Sulfonylureas (e.g. *glicazides = diamicron, glimpepiride*)**	Biguanides **(Metformin)**	**GLP-1 analogues)** (Glucagon-like peptide-1) **(*exenatide*)**	**Incretin mimetics Dipeptidyl peptidase-4 (DDP-4) inhibitors (Sita/Saxa-GLIPTIN)**	**Sodium-Glucose co-transporter 2 inhibitors (e.g. Dapagliflozin)**	**Thiazolidinediones (Glitazones)**
Dose Route	Injection	Oral [**T2D**]	Oral [**T2D**]	Injection [**T2D**]	Oral [**T2D**]	Oral [**T2D**]	Oral [**T2D**]
Indication	T1DM or B cell failure in T2DM		**1ST Line for T2DM** (if lifestyle modifications insufficient)	**Incretin mimetics**			
MoA	• Binds to **tyrosine kinase receptor** → activates it leading to intracellular cascade • **Recruit GLUT4** to membrane for glucose cellular uptake	• **Inhibit K-ATP channels** in β cell membrane ➔ depolarise cell • **↑ Ca entry ➔ increase** vesicle release of insulin secretion • **works with glucose*	• Unclear MoA • **Reduce** GNG in **liver** • **increase** SKM glucose uptake and utilisation *(i.e. reduces insulin resistance, thus reduces insulin requirements)*	• **Mimics incretins binding to GLP-1 receptor (GPCR) → inhibit K-ATP → increase insulin release + decrease glucagon** • *Insulinotropic effect is **glucose dependent*** → hence LESS RISK of hypoglycemia • *INCREASE insulin secretion, inhibit glucagon production, slow GiT absorption*	• **Inhibit DDP-4 enzyme to ↓ degradation of incretins (↑ $t_{1/2}$)** • Glucose-dependent insulin secretion is **increased** and glucagon production **reduced** **NB**: • **Less effective** than GLP-1 analogues to lower BGL • **Do not use with GLP-1 agonists** • Used with ***metformin***!	• **Inhibit SGLT2 ➔** reduce glucose reabsorption in kidneys ➔ promote glucose excretion. • **Renoprotective** = ↓renal failure progression • **↓HFrEF**	• **Agonist of a nuclear receptor (PPARγ) ➔**. Regulate genes FOR glucose and lipid metabolism. • **Increases insulin sensitivity of peripheral tissues** • Decreases hepatic glucose output
A/E	• **Hypoglycaemia**	• **Hypoglycaemia*** • **Weight gain** • **↔ risk of CVD and MI**	• **GI disturbances** *(dose-related)* ➔ *N+V + diarrhea, malabsorption of vitamin B_{12} [chronic use]* • **Kidney impairment**: *risk of lactic acidosis* • **Metallic tast**	• **GI disturbances – N+V** (50%), diarrhea, constipation, GORD • **Hypoglycaemia*** • IV site reactions • Dizzy	• **Hypoglycaemia*** (if combined with insulin or sulfonylurea) • **URTi symptoms** • **MSK pain** (avoid with statins) • **Acute pancreatitis**	• **UTI/thrush (females, uncircumcised) + balanitis** • Polyuria/thirst ➔ **Renal impairment (vol. loss → may cause ↓ SP)** • **Hypoglycaemia*** • **Bony fracture (canagiflozin)** • **Euglycemic diabetic ketoacidosis (DKA)**	• **Fluid retention** (Peripheral oedema) • **Weight gain** • MSK pain • Anaemia + HF • **Increased risk of bladder cancer**
CI:	• Alcohol and **BBs (masks hypoglycaemia)** • Pioglitazone (oedema and HF)	• CI : eGFR < 15 • Alcohol and BBs • CYP2C9 Inhibitors (e.g. fluconazole)	***CI** = eGFR < 30 or Cr > 150 or low BMI*		• CI = eGFR < 30 or hx of pancreatitis • CYP3A4 activators or inhibitors (Saxagliptin)	• CI: eGFR < 60 • Diuretics (especially loop diuretics) ➔ Renal failure	CI = Hepatic failure or hx of bladder cancer or HF
HbA1c lowering*	↓↓ to ↓↓↓↓ (if with metformin)	↓↓	↓↓	↓↓ to ↓↓↓	↓ to ↓↓	↓↓ to ↓↓↓	
Hypo-glycaemia	Significant	Significant (esp. older patients)	Unlikely	Unlikely	Unlikely	Unlikely	
Wt	Gain	Gain	Loss	Loss	Neutral	Loss	Gain

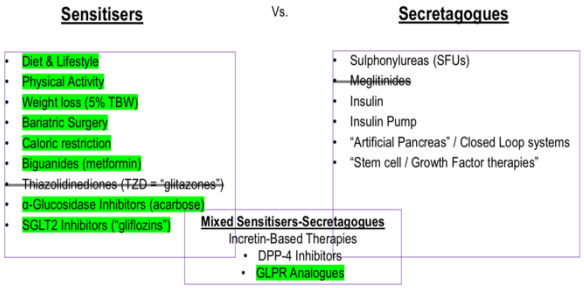
**NB:* Combination with insulin or sulfonylurea can potentiate the risk of hypoglycaemia

- For patients with hyperinsulinemia with insulin resistance (i.e. late-stage T2D)→ treat with **SGLT 2 inhibitor** OR **glitazones** BUT many AEs
- For patients with insulin deficiency or B cell cannot produce insulin ➔ treat with **metformin +/- insulin** [**Sulfonylureas and incretin mimetics ineffective**]



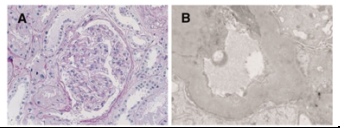
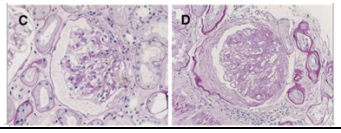
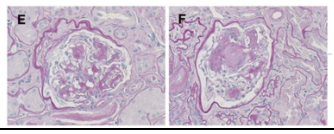
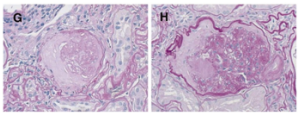
Premixed (5-10mins)
- Novomix 30
- Humalog mix (25 or 50)
- Ryzodeg 70/30





Avoid drugs causing weight gain for heart failure patients

Macro/Microvascular complications of Diabetes

Class	Diabetic Nephropathy Classification	Criteria	
Class I	**GBM Thickening**	*isolated glomerular basement membrane thickening* • *>395 nm (females) > 430nm (males)*	
Class II	**Mesangial Expansion (> 25%)**	*Mesangial expansion ONLY* • **Mild (IIa)** • **Severe (IIb): mesangium > capillary lumen**	
Class III	**Nodular Sclerosis** *(Kimmelstiel–Wilson lesions)*	*Mesangial expansion PLUS ≥ 1 glomerulus with nodular sclerosis*	
Class IV	**Advanced Diabetic Glomerulosclerosis**	*> 50% global glomerulosclerosis + SIGNS of diabetic nephropathy*	

Non-pharmacological approach	Prediabetes	Type 1 Diabetes	Type 2 diabetes *"legacy effect = early intervention leads to sustained benefits"*
Cure?	**Diabetes Prevention Program (DPP)** ➔ Intensive lifestyle intervention (i.e. diet and lifestyle) +/- metformin → reduce risk by 30-60%	All still experimental: • **Islet cell or pancreas transplants** • **Immunosuppressive Therapy (OKT3)** • **Closed loop systems (artificial pancreas)**	• **Bariatric Surgery** (Gastric restrictive procedures, Intestinal bypass procedures) • **Better glycemic control** with fewer antidiabetic medications

*__LEGACY EFFECT__ = Early intervention leads to sustained benefits at 10, 20 years

Rx targets

- *>5-10% TBW loss*
- *Exercise*
- **Target HbA1C < 7%**
- **Optimise BP control** ≤140/90
- *Stop smoking & ≤ 2 standard drinks /day*
- ***Monitor Cholesterol**: TOTAL < 4mM, LDL < 2mM, HDL > 1mM*
- **Screen for micro-albuminemia (UACR)**
  Microalbuminuria >30mg/day
  Macroalbuminuria > 300mg/day :
- ➢ **Vaccinations**

Mx of NEPHROpathy

- **Use ACEi or ARB** [not together] for microalbuminia to minimise AKI
  - ACEi better = reduce mortality, MI, HF
- Avoid glitazones

if eGFR < 60mL/min/1.73m² (CKD 3a)

- ***AVOID*** SGLT2i, NSAIDs, contrast
- ***Reduce DPP-4i*** → reduce dose exc. for:
  - Sitagliptin (used for ESKD)
  - Linagliptin (hepatic metabolism)
- ***Reduce metformin dose*** (lactic acidosis) → stop if eGFR <30
- **Review insulin dosage & sulfonylurea**s (increased BA in renal impairment)

Mx of NEUROpathy

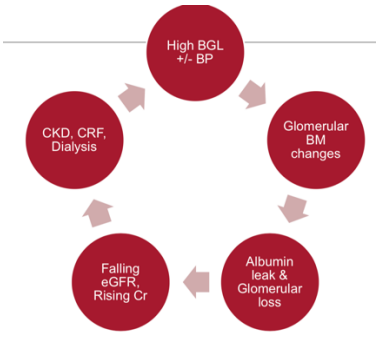
- Foot care (podiatrist)
- Foot assessment (ulcers, charcot's, osteomyelitis)
  - Check dorsalis pedis pulses, ABI, hand-held doppler
- 10g monofilament test
- Reduce pressure or offloading for ulcer healing

MDT needed if:

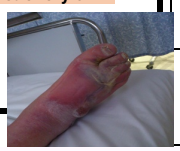
- **Deep ulcers** (e.g. into tendon, or worse bone) → osteomyelitis ➔ X-ray. MRI, bone scan
- **High-risk foot with ulcer**
- **Absence of pulses/or LOW ABI**
- **Ascending cellulitis**
- **Charcot foot** (e.g. unilateral, red, hot swollen aching foot)
- **Signs of infection**

Mx of diabetic RETINOpathy

- Regular ophthalmologist appt
- Anti-VEGF
- Laser photocoagulation



Stratify foot ulceration & amputation risk		Foot care & education tailored to foot risk
Low risk	No risk factors for foot ulceration or ulceration/ amputation	Offer program that includes: • foot care education • Footwear assessment
Intermediate risk	**One risk factor ONLY** (ie neuropathy, peripheral arterial disease [PAD]) **AND NO** previous hx of foot ulceration or amputation	Offer program that includes: • foot care education • Footwear assessment • **Podiatrist every 6/12**
High risk	**≥2 risk factors** (i. e.neuropathy, PAD or foot deformity) **and/or** previous foot ulceration or amputation	
High risk	**ATSI w/ diabetes**	



Category	HbA1c Target (%)	Target For:	Caution
Normal	4.0 – 5.6	Non-diabetics GDM	
Tight	< 6.5	**Young Diabetes Family planning**	T1D hypo unaware, elderly
Standard	< 7.0	**Most diabetes**	T1D hypo unaware, elderly
Safe	< 8.0	**Elderly or Complex Diabetes**	
Substandard	< 9.0	**Elective Surgery** NB: > 9 = higher complication rate	Elective surgery, Hospital length of stay (ALOS) and Surgical Complications

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/1.73 m²)
Stage 1 (prenephropathy)	Normoalbuminuria (<30)	≥90
Stage 2 (incipient nephropathy)	Microalbuminuria (30–299)	≥60-89
Stage 3 (overt nephropathy)	Macroalbuminuria (≥300) or persistent proteinuria (≥0.5)	≥30-59
Stage 4 (kidney failure)	Any albuminuria/proteinuria status	<30
Stage 5 (dialysis therapy)	Any status on continued dialysis therapy	usually <10

:

Reduce HbA1C BY 1% = sig. reduction in microvascular complications and PVD

Improving BP control is better than BSL control (but both needed for optimum outcome)

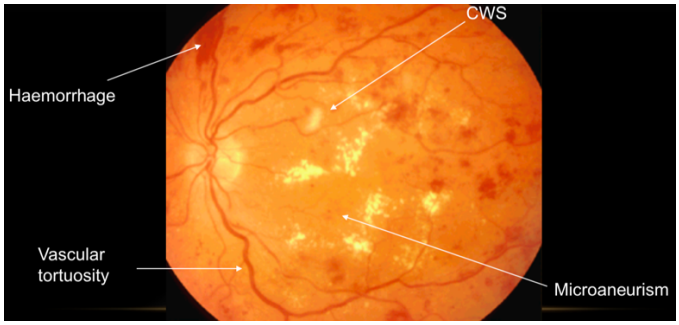
Recognize the importance of diabetic retinopathy as a public health problem

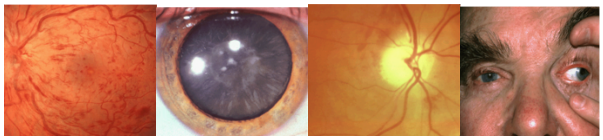
- **DR is 6th leading cause of blindness** (NB: cataract = #1)
  - **Leading cause of blindness in <65 (in Western world)**
  - **30% of diabetics have DR, 5% of diabetics will be blind**
- **DR most common in developed countries**
  - 25% of Baby-boomers will have diabetes (by 70 yo)
  - **Higher prevalence of DR in T1DM** compared to T2DM after 20 years of diagnosis (due to greater BSL fluctuations)

Discuss diabetic retinopathy as a leading cause of blindness in developed countries

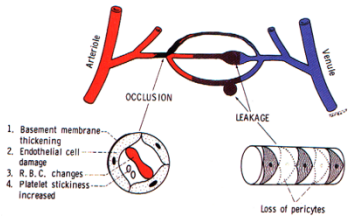
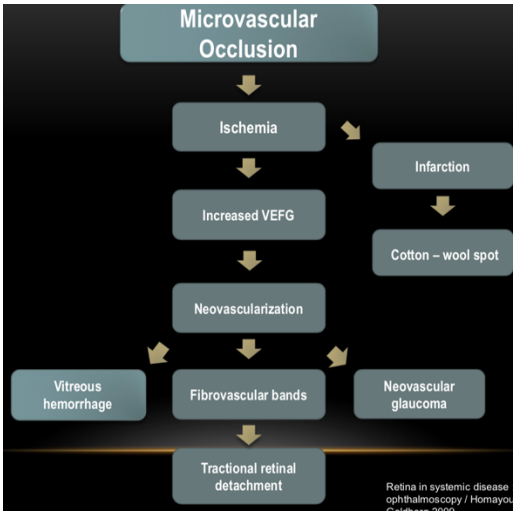
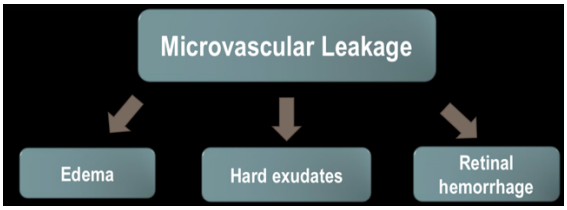
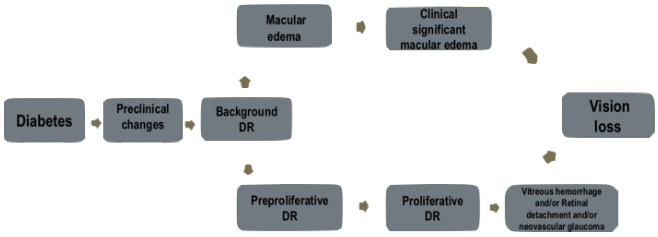
HOW DIABETES CAUSES VISUAL IMPAIRMENT:

- **Diabetic Retinopathy** (inc. Diabetic Macular Oedema, Neovascular Glaucoma) is a micro-vasculopathy due to Progressive dysfunction of the retinal blood vessels caused by chronic hyperglycemia causing:
  1) Retinal capillary ***occlusion***
  2) Retinal capillary ***leakage***
- Cataract – Cortical (Spoke-like)
- **Retinal Vein occlusion**
  - No haemorrhage = "stormy sunset" appearance
- **Retinal Artery Occlusions**
  - Pale retina "cherry red-spot" = painless vision loss
- Ischaemic Optic Neuropathy
- Cranial Nerve Palsies (3,4,6)
- CVA- Cerebrovascular accidents





CRVO | Cortical Cataract | AION | Left MR palsy

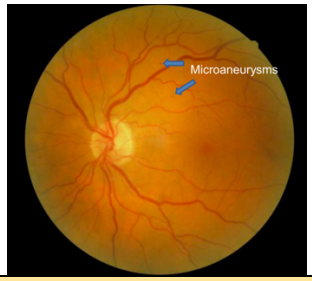
	Retinal capillary occlusion (ischaemia)	Retinal capillary leakage (pericyte loss)
Pathogenesis	1. **Thickened capillary basement membranes** 2. Abnormal proliferation of capillary endothelium 3. Increased platelet adhesion 4. Increased blood viscosity 5. Defective fibrinolysis	1. **Impairment of endothelial tight junctions** 2. Loss of pericytes 3. Weakening of capillary walls 4. Elevated levels of VEGF 
Clinical Progression		 **Development of blindness** 

Identify the risk factors for diabetic retinopathy

Risk factors	Clinical classification + key signs	Clinical Px

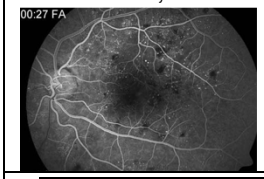
• **Duration of DM**
• **Control of DM** → Will not prevent but delays
• **MetSyn** → HTN, obese, HC
• **Renal Disease**
• **Pregnancy**
• **Smoking**
• **Anaemia**
• Barriers to care
	• Pre-proliferative (Non-proliferative)
	  ○ **Mild**
	  ○ **Moderate**
	  ○ **Severe**
	• Proliferative
	  ○ Advanced diabetic eye disease
	  ○ End-stage diabetic eye disease
		DR = asymptomatic in early stages of either T1DM or T2DM → if untreated can cause **ANY** of the following:
		• Blurred vision
		• Floaters
		• Fluctuating vision
		• Distorted vision
		• Dark areas in the vision
		• Poor night vision
		• Impaired color vision
		• Partial or total loss of vision ➔ blindness

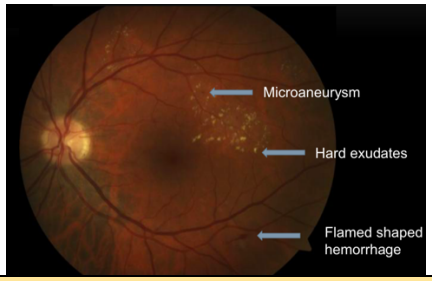
Describe and distinguish between the stages of diabetic retinopathy



Mild NPDR

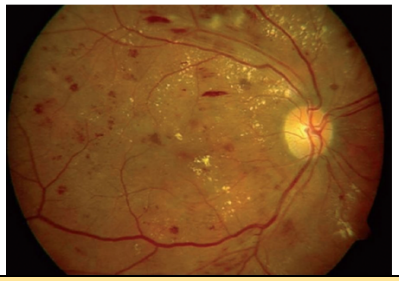
- Microaneurysms





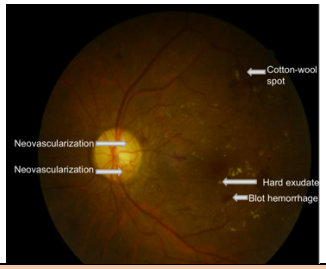
Moderate NPDR

- more microaneurysms
- hard exudates
- flamed shaped haemorrhage (usu. associated with hypertensive retinopathy)



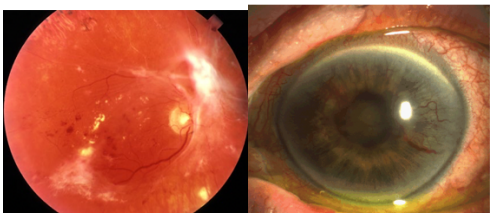
Severe NPDR (any of the below)

- > 20 intraretinal hemorrhages in each quadrants
- Definite venous beading ≥ 2 quadrants
- **Prominent Intraretinal Microvascular Abnormalities (IRMA)** in ≥ 1 quadrants
- **NO signs of proliferative retinopathy**
- **Rx: control risk factors (BP, HC, wt, smoking)**



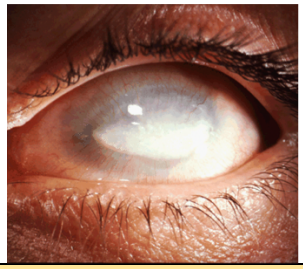
PDR

- CWS + Hard exudates
- **Neovascularisation**
- Blot haemorrhages
- Venous beading & loops → areas of non-perfusion
- **Rx: laser, anti-VEGF**



Advanced diabetic eye disease

- **Pre-retinal fibrosis** (scarring) → pulls on retina → tractional retinal detachment
  - *Operable remove scar tissue → poor prognosis*
- **Rubeosis iridis →** *BV sprout in anterior chamber*



End-stage diabetic eye disease

- **Phthisis**: Shrunken/deflated, soft eye with opaque vascularised cornea
  - no visual potential

Clinically Significant Macular Edema (CSME)

- **Diabetic macular oedema = leading cause of legal blindness in diabetics** (can present anytime but more common in PDR)
- **Due to Thickened retina or hard exudates** WITHIN 500 µm of macula

* Central blur – peripheral vision intact (but poor acuity as no cones)

Understand the role of risk factor control and annual dilated eye exams in the prevention of vision loss

Mx for eye exam schedule

- **Adults**: from Dx of diabetes then yearly
- **Children:** from Puberty then yearly
- **In Pregnancy**: As Early As Possible

Prevention:

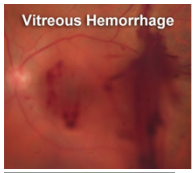
- **Reduce HbA1C** from 7.9% to 7% reduces chance of blindness by 20%
- 90% of diabetic eye disease **easily preventable** by regular exams, Rx and controlling BSL

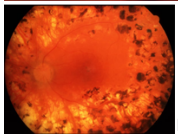
RECOMMENDED EYE EXAMINATION SCHEDULE

Diabetes Type	Recommended Time of First Examination	Recommended Follow-up*
Type 1	3-5 years after diagnosis	Yearly
Type 2	At time of diagnosis	Yearly
Prior to pregnancy (type 1 or type 2)	Prior to conception and early in the first trimester	No retinopathy to mild moderate NPDR every 3-12 months Severe NPDR or worse every 1-3 months.

Rx for diabetic retinopathy

- **Panretinal laser** (ONLY for severe NPDR or PDR) → *starve tissue to reduce VEGF → better vacularise highly metabolic macula*
- **Vitrectomy** for diabetic vitreous haemorrhage or tractional retinal detachment
- **Diabetic neovascular Glaucoma surgery** (i.e. shunt/ tube insertion) bypass drain blockage caused by fibrosis/scarring
- **anti-VEGF** (E.g. avastin, Lucentis/Eylea)

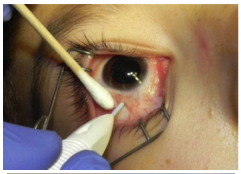




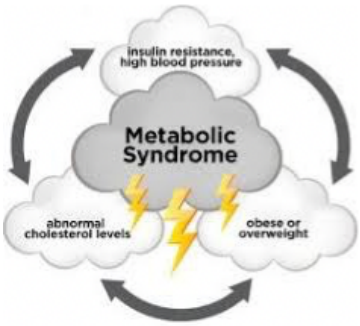
Black spots= burnt retina after 1 year

Rx for diabetic macular oedema

- **Intra-vitreal anti-VEGF** (E.g. avastin, Lucentis/Eylea) → given 1/12
- **Intra-vitreal Dexamethasone → reduce inflammation (given 3/12)**
- *Focal Argon Laser*



Metabolic Syndrome Obesity and associated comorbidities

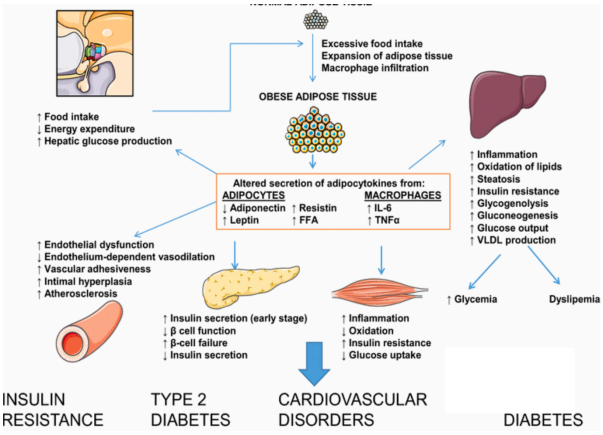


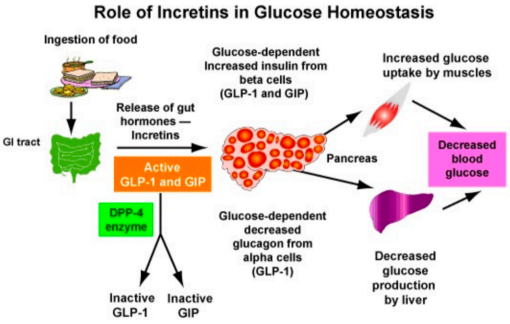
Prevalence:
- **1 in 3 adults** have MetSyn [process starts early – during childhood, maternal imprinting]
- **Expected to increase** [early Recognition of risk factors & early intervention is key]
- MetSyn assoc. with ↑ risk of malignancy, CV disease

Met Syn Criteria
Fasting hyperglycemia (insulin resistance) + 2 or more:
- **HTN** (> 140/90)
- **Dyslipidemia** (high Tg, low HDL)
- **Central adiposity** (BMI > 30 or WHR > 0.9 or > 0.85)
- **Microalbuminuria** (Albumin:creatinine Ratio ≥30)

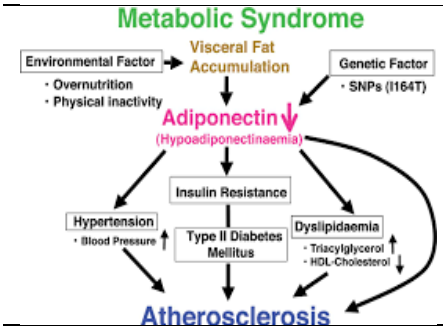
DDxL weight gain causes:
- *Cushing's disease / syndrome*
- *Hypothalamic disease*
- *Acromegaly*
- *Hypothyroid states*
- **Leptin or POMC gene mutations**
- **Other genetic syndromes** – e.g. Prader-Willis, Froehlich
- **Medication** (e.g. *anti-epileptics, steroids, TCAs, OCPs, sulfonylureas, BB, insulin)*

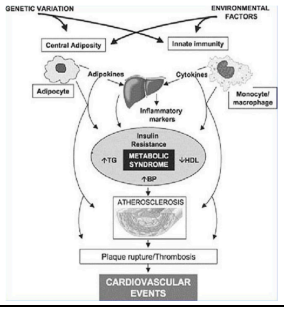
Discuss risk factors and clinical complications associated with obesity and metabolic syndrome

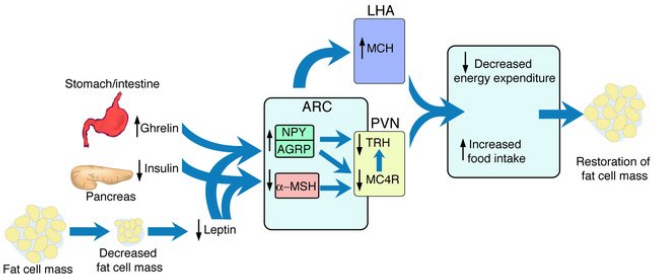




- **Incretins** = GIP (K cells -duo/jej) +GLP-1 (L cells – ileum) – **glucose dependent insulin secretion**
- **Stimulate pancreas** ➔ ↑insulin + ↓ glucagon ➔ ↑ glucose uptake by SKM and decrease GNG



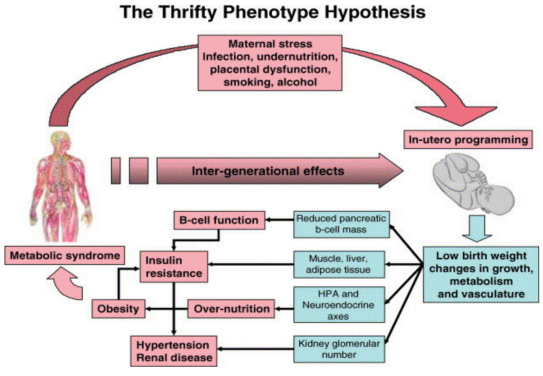




Metabolic syndrome drives inflammatory state:
- Obesity (Excess Adipose tissue) increases **pro-inflammatory cytokines (IL-6)** → drives low grade inflammation (**raised CRP**)
  - Visceral fat is greatest contributor to inflammatory state
- Similarly, genetic and environmental factors stimulate innate immune responses which also drive pro-inflammatory cytokiens which further drive MetSyn
- **Consequence (similar to risk caused by smoking)**: Cirrhosis, NAFLD, insulin resistance (diabetes), CVD (Atherosclerosis)

- **Leptin (adipose tissue) + insulin (pancreas) + incretins (GIT):**
  - Stimulate anorexigenic (POMC/CART) neurons in arcuate nucleus in hypothalamus= ↓ intake
  - Inhibit orexigenic (AgNP/NPY) neurons = ↓ appetite
- **PYY (from colon/ileum)** ➔ Inhibit (AgNP/NPY) neurons = ↓ appetite
- **Grehlin** = Stimulate orexigenic (AgNP/NPY) neurons = ↑ appetite / hunger

Dysregulation of energy intake & expenditure causes obesity:
- **Leptin resistance** ➔ obesity (failure to decrease appetite despite elevated leptin levels reflecting increased fat)
- **Leptin deficiency ➔ loss of function mutation ➔ Rx: leptin injections**
- **T2DM (linked to o**besity) ➔ obesity involves increased [FFA] in SKM ➔ increased [Fatty-acyl-CoA] ➔ activates intracellular cascade to **inhibit** insulin-induced glucose transport (i.e. no glucose uptake = no satiety signals = drives obesity)



Thrifty phenotype hypothesis:
- Over-nutrition, HTN & insulin resistance drives Inter-generational changes in appetite and metabolism likely driving rise in metabolic syndrome
  - Originally, these phenotypes meant to prevent us from starvation
- Impact of insulin sensitivity during growth trajectories driving rise of obesity and MetSyn → CV disease + assoc. co-morbidities

Screening of weight-related complications:
- **Prediabetes, MetSyn, T2DM** → *Ix: HbA1C, fasting glucose*
- **CVD, Dyslipidaemia, HTN**
- **Urinary stress incontinence**
- **PCOS & female infertility**
- **Depression, anxiety, eating disorder**
- **NAFLD** → leading cause of liver failure in Australia
- **OSA, Asthma**
- **Male hypogonadism**
- OA
- **GORD**

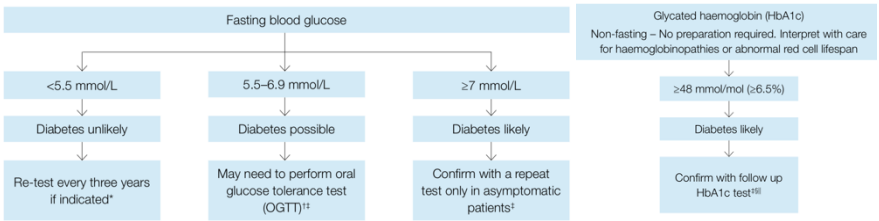
Diabetes Questions

Q1.	A 24 year old woman presents with polyuria and weight loss and is diagnosed with diabetes mellitus. She has a blood glucose level of 18 mmol/L and moderate blood ketones. Which of the following is the strongest indication to commence immediate insulin treatment?	
	A	Age < 25
	B	Blood glucose level > 20 mmol/L
	C	Presence of moderate blood ketones
	D	Weight loss
Q2.	HbA1C is a used to measure glycemic control because:	
	A	It is sensitive to short term intra-day glycaemic fluctuations
	B	It reflects average blood glucose level over the red cell lifespan
	C	It is not affected by disorders of haemoglobin synthesis
	D	It is not affected by haemoglobin level
Q3.	A newly diagnosed 38-year-old type 2 diabetic is commenced on metformin monotherapy at a dose of 1 g tds. HbA1c is 7.2% at diagnosis. He comes for a repeat script and tell you has had episodic diarrhea for 2 weeks. There is no blood or mucous, weight is stable; he is otherwise well. You should advise him to:	
	A	Stop metformin and list it as an allergy
	B	Dose reduce his metformin
	C	Get an urgent colonoscopy
	D	Switch metformin to an alternate oral agent
Q4.	A newly diagnosed 38 year old type 2 diabetic is commenced on metformin monotherapy at a dose of XR 2 g daily without any ill effect. Repeat HbA1c is improved at 7.2%. She is concerned about inability to lose weight and achieve a target HbA1c of 6.5% Which of the following can achieve these aims?:	
	A	Addition of glimepiride
	B	Addition of rosiglitazone
	C	Addition of acarbose
	D	Addition of empagliflozin

Q5.	A newly diagnosed 78-year-old type 2 diabetic has an HbA1c of 8.2% and Stage 3 CKD (eGFR 18 ml/min). Which of the following agents can safely be commenced for her diabetes?	
	A	Linagliptin
	B	Metformin
	C	Empagliflozin
	D	Exenatide
Q6.	A newly diagnosed 48 year old type 2 diabetic is commenced on metformin monotherapy at a dose of XR 2 g daily without any ill effect. Repeat HbA1c is improved at 7.5% He is concerned about family history of coronary heart disease. Addition of which of the following medications has been proven to improve glycemic control added to metformin and lower his cardiac risk?	
	A	Glibenclamide
	B	Vildagliptin
	C	Pioglitazone
	D	Empafligozin
Q7.	Which of the following regimes would be the ideal insulin regime in a newly diagnosed 25-year-old type 1 diabetic man with a normal BMI?	
	A	Metformin
	B	Basal bolus insulin
	C	Basal insulin only
	D	Premix insulin
Q8.	If required to start insulin, which of the following individual diabetics is likely to have the highest total daily insulin requirement?	
	A	Type 1 diabetic with BMI 25 kg/m^2
	B	Type 2 diabetic with BMI 35 kg/m^2
	C	Post pancreatectomy patient with BMI 35 kg/m^2
	D	Cystic fibrosis sufferer with BMI 19 kg/m^2

Answers
1) C
2) B
3) D
4) D
5) D
6) B
7) Basal + prandial
8) C
9) D
10) C

Q9.	Which of the following diabetes drug classes is most likely to cause hypoglycemia?	
	A	Biguanide
	B	DPP4 inhibitor
	C	SGLT2 inhibitor
	D	Sulfonylurea
Q10.	Which of the following diabetes drugs is most likely to cause weight gain?	
	A	Sitagliptin
	B	Liraglutide
	C	Aspart insulin
	D	Metformin



		Definition/Notes	Oral Glucose Tolerance Test (OGTT) (post-stress glucose test)			HbA1C
			Pre (fasting)	2-hr OGTT	1-hr → 2hr OGTT	
Normal		**Normal glucose tolerance**	<5.6	<7.8		≤6.0% (<42mM)
Pre-diabetes	**IFG**	Impaired fasting glucose	5.6-6.9	-		6.0-6.4%
	IGT	Impaired glucose tolerance	<5.6	7.8-11.1	Decrease	6.0-6.4% (42-47mM)
Diabetes (IFG + IGT)	**T1D**	Intrinsic inability to produce insulin S+S: Polyuria, Polydipsia, Ketones	≥ 7	≥11.1	Increase	≥ 6.5% (>47mM)
	T2D	Insulin resistance	**5.6-6.9**	**7.8-11.1**	Decrease	**≥ 6.5%**
	GDM	Gestational diabetes (occurs during pregnancy)	**5.6-6.9**	**7.8-11.1**	Decrease	**≥ 6.5%**

NOTE: prediabetes= Highly likely to develop type 2 diabetes and to have other components of the metabolic syndrome (hypertension, dyslipidaemia, increased risk of atherosclerotic disease)

Case 1: 45-year-old office executive; routine bloods for annual health check.

- Asymptomatic; BMI 28.7 kg/m2;
- Fasting BGL 6.2 mmol/L

Case 2: 25-year-old woman; losing weight (5 kg); polyuria and polydipsia; vaginal thrush.

- Fasting BGL 12.2 mmol/L;
- moderate urine dipstick ketones

Case 3: 45-year-old office executive; routine bloods for annual health check. Known family history of T2D and personal IFG; Asymptomatic; BMI 31.7 kg/m2; 2-hour 75g OGTT

- Fasting BGL 6.2 mmol/L
- 1-hour BGL 15 mmol/L
- 2-hour BGL 11.8 mmol/L

Case 4: 45-year-old office executive; routine bloods for annual health check. Known family history of T2D; Asymptomatic; BMI 28.7 kg/m2

- 2-hour 75g OGTT
- Fasting BGL 4.9 mmol/L
- 1-hour BGL 15 mmol/L
- 2-hour BGL 8.2 mmol/L

Case 5: 45-year-old office executive; routine bloods for annual health check. Known family history of T2D; Asymptomatic; BMI 28.7 kg/m2. 2-hour 75g OGTT

- Fasting BGL 6.1 mmol/L
- 1-hour BGL 12 mmol/L
- 2-hour BGL 8.2 mmol/L
- Glycosylated haemoglobin 6.8%

Case 6: 28 weeks gestation; previous LGA baby (large for gestational age); family history of T2D. 2-hour 75g OGTT

- Fasting BGL 6.1 mmol/L
- 1-hour BGL 9.2 mmol/L
- 2-hour BGL 8.2 mmol/L
- Glycosylated haemoglobin 6.6%

ANSWERS
Case 1: IFG; Case 2: New T1D; Case 3: new T2D; Case 4: IGT; Case 5: T2D; Case 6: GDM

Diabetes Questions

Question 1: Which of the following in regards to the aetiology of diabetes is true?

A. There is no genetic basis for the development of type 1 diabetes
B. HLA DR2 is protective for risk of developing type 1 diabetes
C. Anti-GAD antibodies are a marker for future development of type 2 diabetes
D. Multiple genetic defects are needed to result in Maturity Onset Diabetes of the Youth (MODY)
E. Defects in the glucokinase gene are responsible for type 1 diabetes

Q1:

- True: B, D
- False: A, C, E

Question 2: Tight control of blood sugars in diabetic patients

A. Can prevent macrovascular disease in the short term
B. Can prevent macrovascular disease in the long term
C. Has no effect at all on macrovascular disease
D. Will make macrovascular disease worse in the long term
E. Will increase all cause mortality

Q2:

- True: B
- False: A, C, D, E

Question 1:

Insulin deficiency is associated with

A) Reduced lipolysis
B) Increased ketogenesis
C) Reduced gluconeogenesis
D) Reduced proteolysis
E) Increased glycogen synthesis

Question 2:

The most likely cause of mortality from ketoacidosis after presentation to hospital is?

A) Not enough insulin infused into patient
B) Not enough potassium infused into patient
C) Not enough time nil by mouth
D) Not enough treatment of hyperglycaemia
E) Misdiagnosis

Q1: B
Q2: B

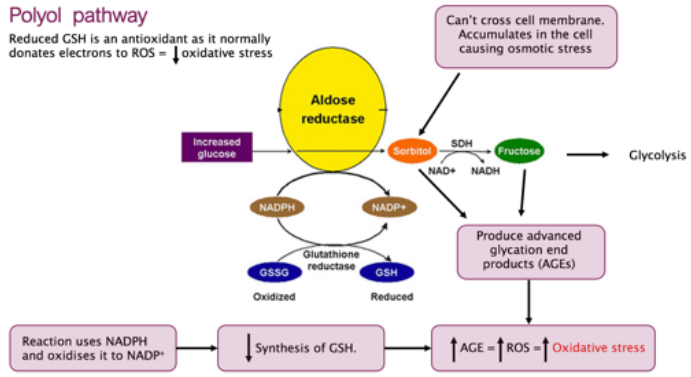
Pathogenesis of hyperglycaemia & vascular complications assoc. with diabetes mellitus

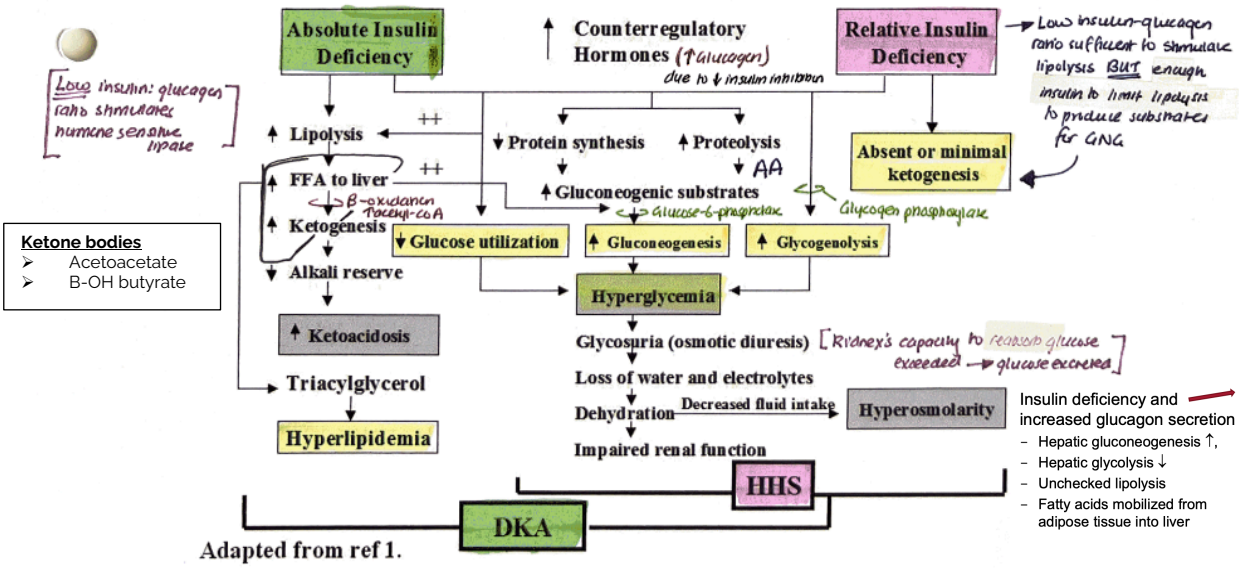
What causes hyperglycemia?

- **Diabetes mellitus** → insulin resistance or deficiency → **Increased** liver gluconeogenesis + glycogenolysis
- **Reduced** glucose cellular uptake in AT, liver and muscle
- **Reduced** glycogenesis in liver
- **Increased** lipolysis of triglycerides and subsequent fatty acid beta-oxidation to form glycerol, which is metabolized into glucose via glyceraldehyde-3-phosphatase

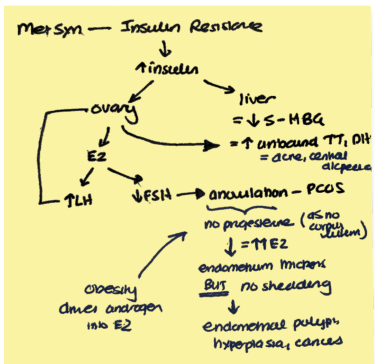
Pathogenesis of vascular complications (Macrovascular vs microvascular)

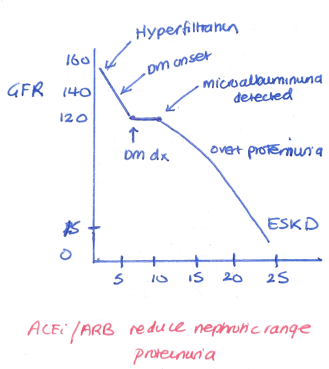
- Glucose undergoes auto-oxidation producing **reactive oxygen species (ROS)**
- Glucose oxidises proteins to form **glycated proteins** ➔ disrupts protein structure and function [**neuropathy:** damage of nerve endings → loss of pain sensation and proprioception → increased susceptibility of untreated repeated trauma → diabetic foot ulcer]
- **Glycated proteins** can be further oxidised to form **advanced glycation end products (AGEs)** ➔ bind to membrane receptors on endothelial cells to induce oxidative stress ➔ damages endothelium + promotes inflammation [**macrovascular**, **non-proliferative retinopathy**, **nephropathy**]
  - renal impairment (hyperfiltration, glycosuria, osmotic diuresis) → diabetic nephropathy (inc. albuminuria, proteinuria) → progressive renal function decline →ESKD
- **Hyperglycaemia increases the NADH:NAD+ ratio** ➔ decreases NADPH:NADP+ ratio ➔ pushes glucose into polyol pathway
  - Glucose is reduced to **sorbitol** which cannot cross cell membranes and accumulates in the cell → **Osmotic stress** → **nerve damage** [**neuropathy**] + [**retinopathy**: accumulated sorbitol causes osmosis of water into lens causing lens shape change → blurry vision)
  - Polyol pathway also **reduces GSH synthesis** ➔ **produces AGE** ➔ oxidative stress

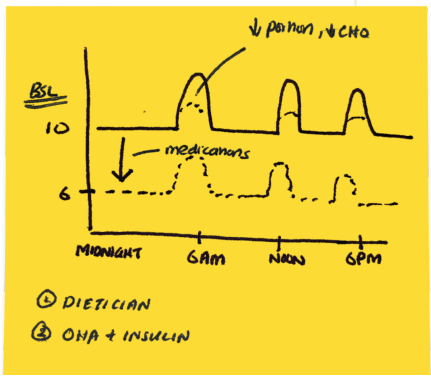




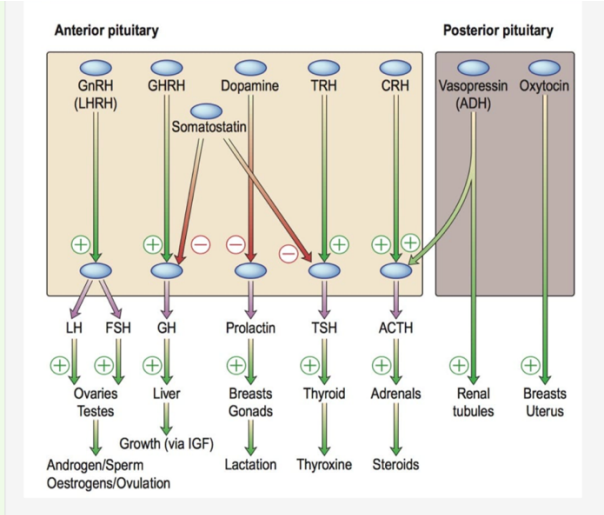
Higher concentration of circulating hepatic insulin partly accounts for the absence of significant ketosis in patients with HHS.
Patients presenting with HHS have *lower* concentrations of free fatty acids, cortisol, growth hormone, and glucagon than do those presenting with DKA

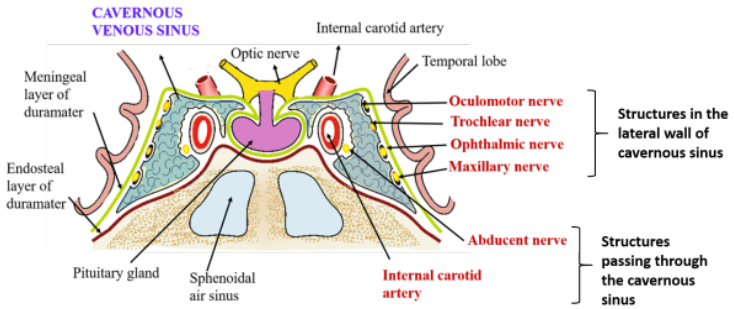






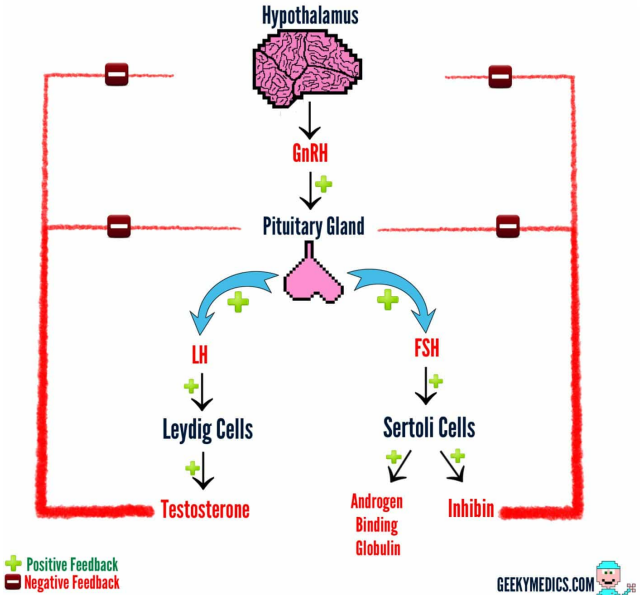
HPA AXIS

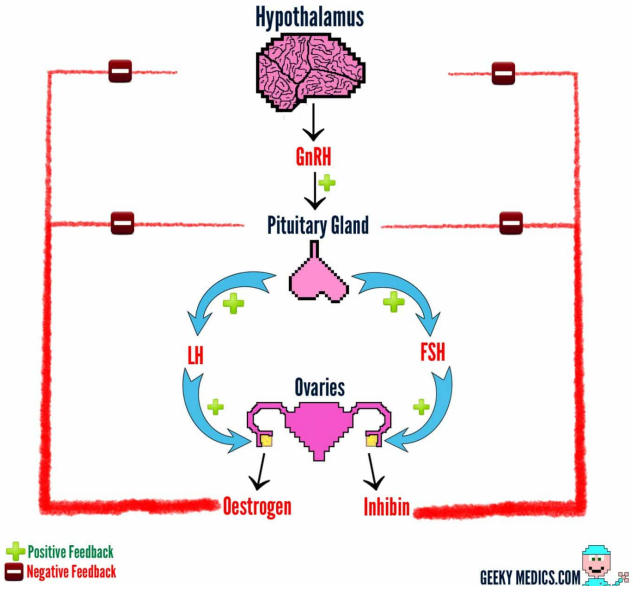




Panhypopituitarism:
GH → PrL → LH/FSH → TSH → ACTH

HPG Axis – Males vs females





CUSHING + ADDISON'S

Cushing's

Define

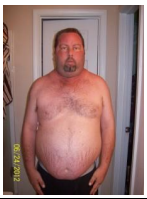
XS cortisol

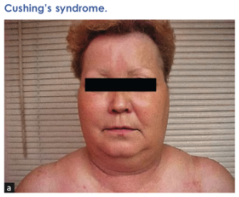
Cause

			Dex Suppression Test	
	ACTH	Cortisol	ACTH	Cortisol
Cushing's disease (Pituitary adenoma)	High	High	Suppressed	Suppressed
Pseudo-cushing's (psych stress, shift worker)	High	High	Suppressed	Suppressed
Ectopic ACTH Paraneoplastic Cushing's (SCLC)	High	High	Not suppressed	Not suppressed
Adrenal adenoma (cortisol-secreting tumour)	Low	High	Suppressed	Not suppressed
Exogenous steroid	Low	Low	Suppressed	Suppressed

RF

- HTN,
- Cardiac hypertrophy
- T2DM (hyperglycaemia)
- Depression
- Insomnia





Sx

Physical signs

- **Round "moon" face**
- **Abdo striae**
- **Buffalo hump** (fat pad on upper back)
- **Proximal limb muscle wasting** - squat test = Gower's sign (difficulty walking upstairs)
- **Easy bruising + Florid striae**
- **Acne & Hirsutism** → elevated androgens
- **Central obesity** = Unintentional weight gain
- **Thinned skin**

Short-term:

- High BSL
- Insomnia

Long-term:

- OP – bony tenderness
- Easy bruising
- Poor skin healing
- Muscle weakness
- Cataracts (XS BSL)
- Irregular menstrual cycle & amenorrhoea

Ix

- **FBC** (raised white cells)
- **EUC** (hypoK if ***aldosterone*** is secreted by an ***adrenal adenoma***)
- **MRI brain** for ***pituitary adenoma***
- **Chest CT for** small cell lung cancer
- **CT adrenal for** adrenal tumours

Dexamethasone Suppression Test

Given at night (10pm), measured in the morning (9am)

Low Dose Test: 1mg dexamethasone	Low cortisol → Normal High/normal cortisol → Cushing's Syndrome
High Dose Test: 8mg dexamethasone	Low cortisol → Cushing's Disease High/norm cort → ACTH low → Adrenal Cushings ACTH high → Ectopic ACTH

Alternative - 24-hour urinary free cortisol can be used to diagnose Cushing's syndrome but does NOT indicate the **underlying cause** and is **cumbersome** to carry out.

Mx

Remove the underlying cause (surgically remove the tumour)

- ***Trans-sphenoidal*** (through the nose) removal of pituitary adenoma
- Surgical removal of adrenal tumour
- Surgical removal of tumour producing ectopic ACTH

*Alternative to surgery = remove both adrenals + lifelong steroid hormones

Adrenal Insufficiency

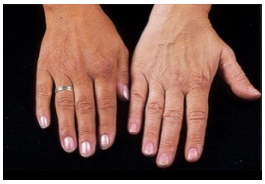
Define

Adrenal glands do not produce enough steroid hormones (esp. cortisol and aldosterone)

Cause

	ACTH	Cortisol
Primary adrenal insuff. (autoimmune cause,)	**High**	**Low**
Secondary adrenal insuff (Pituitary cause - Sheehan's syndrome) – no ACTH stimulation	**Low**	**Low**
Tertiary adrenal insuff (Withdrawing of long-term steroid usage)	**Normal**	**Low**

RF



Sx

- Fatigue
- Nausea
- Cramps
- Abdo pain
- Reduced libido
- Amenorrhoea / oligomenorrhoea
- UWL
- Cachexia (hyperK)
- Polyuria/nocturia + polydipsia (Na + water loss = low aldosterone)

Primary adrenal insuff

- **Vitiligo / Hyperpigmentation of skin creases** (due to relase of a-MSH to stimulate melanin production)
- **HypoTN – postural dizziness**

Ix

- **EUC** (hypoNa or hyperK) – due to low aldosterone
- **Short-synacthen test** (gold standard) to diagnose adrenal insufficiency
- **ACTH levels** – SEE results above
- **Adrenal autoantibodies** (80% of autoimmune adrenal insufficiency) → adrenal cortex antibodies and 21-0H antibodies
- **CT / MRI adrenals** (adrenal tumour, haemorrhage or other structural pathology).
- **MRI pituitary**
- **ECG –** check for arrythmias

Short synacthen test (ACTH stimulation test)

- Give synthetic ACTH – measure blood cortisol at baselin , 30 and 60 minutes after administration
- Failure of cortisol to rise (< 2x the baseline) indicates primary adrenal insufficiency (Addison's disease).

Mx

Initial Mx:

1. ***Hydrocortisone*** (glucocorticoid) - replace ***cortisol***.
2. ***Fludrocortisone*** (mineralocorticoid)-replace ***aldosterone***
3. ***IV dextrose***
4. **Emergency ID tag show** dependent on steroids for life. Doses should not be missed as they are essential to life.
5. **DOUBLE Doses** during acute illness until they have recovered to match the normal steroid response to illness.

Addisonian crisis (aka adrenal crisis) = life-threatening

- Reduced LOC
- HypoTN = hyperK + hypoBSL
- **Trigger** = infection, trauam, acute illnesss or sudden withdrawal of steroids
- ICU monitoring
- **Parenteral steroids** (e.g. IV hydrocortisone 100mg STAT then 100mg qid)
- IVF
- Correct BSL, electrolytes and fluid balance

THYROID DISEASE

Define

Hyperthyroidism: Elevated thyroid hormone levels

Hypothyroidism: Reduced thyroid hormone levels

Cause

Hyperthyroidism

Grave's (autoimmune)	anti-TSHr, exophthalmos, symmetrically enlarged, lid lag, chemosis, ophthalmoplegia
TMG (> 50) "plummer's disease"	➢ asymmetrically enlarged **firm** goitre ➢ AGED > 50YO [**Rx: anti-thyroid + RAI**]
Subacute (De Quervain's) thyroiditis	hyper → hypothyroid) –recent URTi/ GITI (↑ESR) ➢ **Neck pain radiating to face** [**Rx: NSAID or STEROID**]
Jod Basedow	*giving iodine to hypothyroid → hyperthyroid state*
Drug-induced thyroiditis	**Amiodarone (inhibits T4 → T3 to reduce iodine uptake)** • **Type 1 = excess iodine (↑ T3/4) [Rx: anti-thyroid]** • **Type 2 = hypothyroid [Rx: STEROID]**
Pregnancy or post-partum thyroiditis	• **Choriocarcinoma (malignant)** = female uterus womb -→ abdo pain + menorrhagia • **Hydatidiform mole (pre-malignant)** = rare mass during early pregnancy • Partial (69XXY) or Complete (46XX)
Malignancy Solitary toxic thyroid nodule	• **Follicular** (solitary mass + extracapsular invasion → malignant vs benign → **biopsy needed, NOT FNA**) • **Anaplastic** (hoarseness, stridor → pleomorphic giant cells – 100% mortality rate) • **Hurtle cell** (rare + rough, granulated) • **Papillary ca.** = middle-aged females w/ **"**orphan annie nuclei" + psammoma bodies, • **Medullary carcinoma = ↑ Calcitonin = Men2A (parafollicular C cells – amyloid between cells)**

Hypothyroidism

Hashimoto's (1st world) (autoimmune)	• DDx: **Nutritional (3rd world)** • **GOITRE – Hurthle cell change**
Nutritional deficiency (3rd world)	Fortification of staple foods using iodine
Subacute (De Quervain's) granulomatous thyroiditis	➢ 30-50yo Females –recent URTi/ GITI (↑ESR) – neck rad to face ➢ hyper → hypothyroid → NO UPTAKE ➢ [**Rx: NSAID or STEROID**]
Wolff-Chaikoff	(↓ T4 when taking iodine
Iatrogenic	• ***Antithyroid meds*** *(carbimazole, PTU) OR* • **Lithium** = inhibits thyroid hormone production causing goitre and hypothyroid • **Amiodarone – inhibit thyroid hormone production** • ***radioactive iodine OR*** • ***post-thyroidectomy***
Pregnancy or post-partum thyroiditis	**lymphocytic thyroiditis**
Secondary hypothyroidism (CENTRAL)	• Tumour • Infection • Vascular (sheehan syndrome) • Radiation

Sx

- **Heat intolerance**
- **UWL**
- **Sweaty warm**
- **Palpitations** – tachycardia, AF
- **Hyperdefecation** (diarrhoea)
- **Oligo/amenorrhoea**
- **Anxious, tremor**, irritable
- **Proximal myopathy** →squat test
- **Sexual dysfunction**

Specific:

- **Thyroid ophthalmopathy** – Bilateral **Exophthalmos**, conjunctiva injection, periorbital swelling, thyroid stare, upper eyelid lag
- **Thyroid acropachy** – digital clubbing, periosteal bone growth
- **Grave's dermopathy**
  Elephantiac like feet = "orange peel"
  ↑ Glycosaminoglycans = pretibial myxodema (non-pitting)

- **Cold intolerance**
- **Pale puffy face + increased wt**.
- ↓ basal met. Rate = ↓ O2 consumed = **coarse dry skin, alopecia,**
- **high LDL, TC**
- ↓ SNS = ↓ **sweat, HR, constipation**
- ↓ sarcolemma gene transcription = ↓ CO, **proximal myopathy**
- ↑ PrL (due to ↑ TRH) → **gynecomastia + reduced libido**
- **Menorrhagia**

Signs

- **Goitre** (after atrophy of thyroid gland)
- **Fluid retention** (oedema, pleural effusion, ascites)

Ix

Bloods

➢ FBC, EUC, LFT, CRP
➢ TFT – TSH, free T3, free T4

Antibodies

➢ ***Antithyroid Peroxidase (anti-TPO) Antibodies*** = autoimmune antibodies against thyroid gland (***Grave's Disease*** and ***Hashimoto's Thyroiditis***)
➢ ***Antithyroglobulin Antibodies*** are antibodies against ***thyroglobulin*** – present in normal, ***Grave's Disease***, ***Hashimoto's Thyroiditis*** and ***thyroid cancer***.
➢ ***TSH Receptor Antibodies*** = autoantibodies that mimic TSH, bind to the ***TSH receptor*** and stimulate thyroid hormone release (**Grave's**)

Imaging

- **Thyroid USS – DDx: thyroid nodules, cysts and solid nodules →** also help to guide biopsy of a thyroid lesion.

Radioisotope scan (*IV radioactive iodine – gamma camera detection****)***

- Diffuse high uptake is found in ***Grave's Disease***
- Focal high uptake is found in ***toxic multinodular goitre*** and ***adenomas***
- "Cold" areas (i.e. abnormally low uptake) can indicate ***thyroid cancer***

Compression/mass effect

1) **Stridor** (tracheal obstruction)
2) **Dysphagia** (for solids)
3) **RLN compression** = hoarseness
4) **Pemberton's sign**

Mx

1. **Carbimazole (12-18/12) - titrate carefully → 4-8 WEEKS** (may need careful balance with levothyroxine to achieve remission in 18/12)
   a. Or PTU (if carbimazole not tolerated or 1st trimester)
   b. ***STOP PTU*** if signs of agranulocytosis, fulminant hepatitis
2. **BB (non-selective – propranolol)** (first 6-8 wks) to control flushing + tremor OR *dilatezem* if not tolerated (e.g. asthma)
3. **Radioactive iodine (single-dose) → no surgery but takes 6/12 to destroy overactive thyroid cells →** need lifelong levothyroxine
4. **Thyroidectomy** → lifelong levothyroxine

Beware of Thyroid Storm (thyrotoxic crisis)

- Trigger: *acute iodine load in Grave's / thyroiditis (CTPA)*
- **Febrile + HR + palpitations + confusion + N/V**
- Resus: **Admit → IVF (0.9% NS) → anti-arrhythmic +NSBB (propranolol)**
- Post resus Rx: Anti-thyroid → thyroidectomy → lifelong levothyroxine

1st line

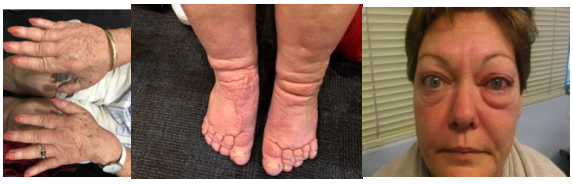
➢ *Levothyroxine (synthetic T4 metabolised into T3 in body) → take on **empty** stomach*
➢ *FU in 4 wks – measure TSH levels monthly*

Beware of Myxodema Coma

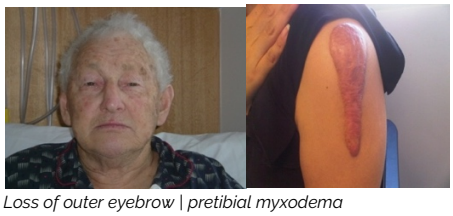
- *Triggered by stress, illness, trauma*
- *Low GCS, hypoNa, S3*
- *Bradycardia, pitting oedema*

Rx

- *ICU + IV fluids + IV CS*
- *Controlled IV T4 + ECG monitoring for AF*



Thyroid acropachy | elephantiatic-like feet | proptosis

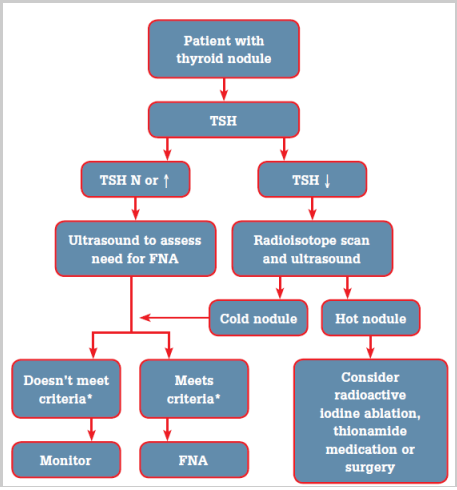


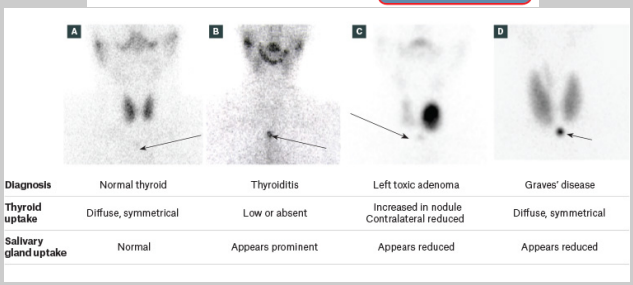
Loss of outer eyebrow | pretibial myxodema

COMMON BENIGN AND MALIGNANT PATHOLOGIES I THYROID GLAND

BENIGN	MALIGNANT	Rx
➢ **MNG** ➢ **Hashimoto's** (chronic lymphocytic) thyroiditis ➢ **Cysts** (simple, haemorrhagic) ➢ Follicular adenomas ➢ **NIFTP** (*non-invasive follicular tumour with papillary like nuclear features)* ➢ Hurthle Cell adenoma	➢ **Papillary thyroid carcinoma** (PTC – extracapsular invasion) ➢ **Follicular thyroid carcinoma** (malignant) ➢ **MTC= CHECK calcitonin levels** ➢ Hurthle Cell carcinoma ➢ Primary thyroid lymphoma ➢ 2nd mets = breast, RCC, others ➢ **Anaplastic thyroid carcinoma [BAD]**	➢ Active surveillance ➢ **Radioactive iodine** ➔ if vascular invasion ➢ **External beam radiotherapy** ➔ metastasis ➢ Completion thyroidectomy +/- neck dissection

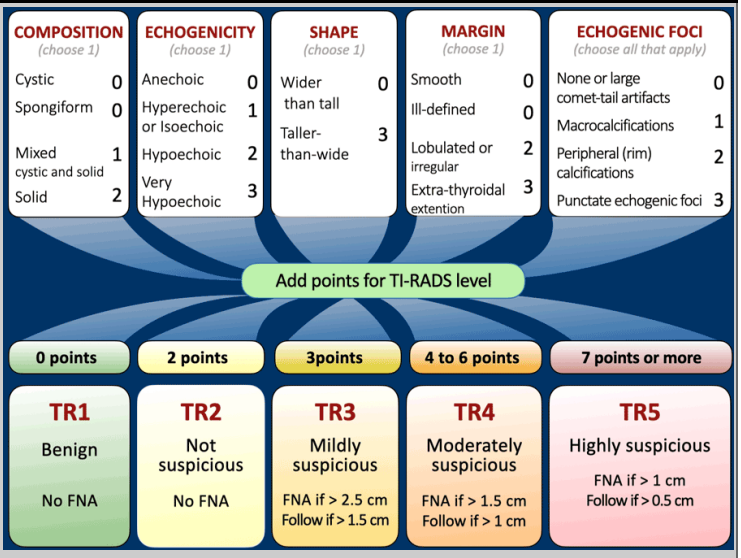
Ix pathway





*__Hashimoto's & de quervains'__ = typically no uptake
**__Reidel's thyroiditis__ = fibrosis = also no uptake

Ultrasound – TI-RADS



FNA BIOPSY

Bethesda category	Cytopathologic category	Approximate expected frequency	Malignancy rate	Suggested treatment (Prior to availability of molecular testing)
I	Non-diagnostic/Inadequate	5-11%	1-4%	Repeat FNA
II	Benign	55-74%	0-3%	US follow-up
III	Atypia/follicular lesion of undetermined significance	5-15%	5-15%	Repeat FNA or US follow-up or Lobectomy
IV	Follicular neoplasm/ suspicious for FN	2-25%	15-30%	Lobectomy
V	Suspicious for malignancy	1-6%	60-75%	Lobectomy or Thyroidectomy
VI	Malignant	2-5%	97-99%	Near-total thyroidectomy

FNA: Fine-needle aspiration, FN: Follicular neoplasm, US: Ultrasonographic

Why would you conduct a partial or hemithyroidectomy?

- Firstly need ENT referral
- Cost-benefit ratio = if thyroid removed is actually benign → patient would have to take thyroxine for the rest of their life
  - CHECK TSH levels (should decrease to normal)
  - Dose titration

COMMON ENDOCRINE PRESENTATIONS

Acromegaly

Define

XS growth hormone

Cause

- Central pituitary adenoma
- Secondary – paraneoplastic pancreas or lung
- **Gigantism** (children) – before epiphyseal plate colusre
- **Acromegaly** (Adults) – insulin sensitivity

Sx

Space Occupying Lesion
- Headaches
- Visual field defect ("bitemporal hemianopia")

Overgrowth of tissues (MSK/neuro)
- Prominent forehead and brow ("frontal bossing")
- Large tongue ("macroglossia")
- Large hands and feet (spade like hands) – **carpal tunnel syndrome**
- Large protruding jaw ("prognathism")

Extra-organ manifestations:
- Arthritis from imbalanced growth of joints - kyphosis
- Hypertrophic heart – **HTN → papilloedema + arrythmias**
- Type 2 diabetes (**skin tags, acanthosis nigricans)**
- Colorectal cancer
- Small testes – due to ↓ GnRH caused by growing tumour

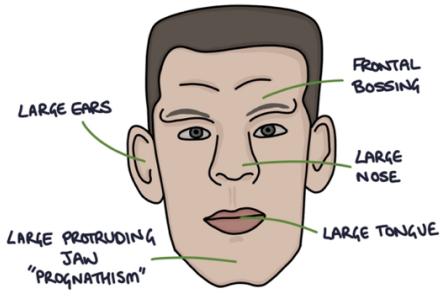
Signs for active raised GH
- Development of new skin tags (insulin resistance)
- Profuse sweating

Ix
- **IGR-1 assay** = raised
- **OGTT -** GH not suppressed (when normally high BSL suppresses GH)
- **MRI brain for** the pituitary tumour
  - If signs of prolactinoma, bitemporal heminopia
- **Refer to ophthal for** formal visual field testing

Mx

Medication
- **Pegvisomant** (GH antagonist given subcutaneously and daily)
- **Somatostatin analogues** to block GH release (e.g. octreotide)
- **Dopamine agonists** to block GH release (e.g. bromocriptine) – less potent than Somatostatin analogues

Surgery:
- **Trans-sphenoidal** (surgical removal of the pituitary adenoma
- **Secondary acromegaly** – ectopic hormones from . pancreatic or lung cancer
- **Rx: surgical removal of these cancers**



Hyperparathyroidism

Define

XS PTH by **chief cells** leading to hypercalcemia

Cause

Primary	Parathyroid adenoma
Secondary	Vitamin D def. or chronic renal failure
Tertiary	Chronic secondary HPTH – hyperplasia (uncontrolled growth of PTH glands)

Sx

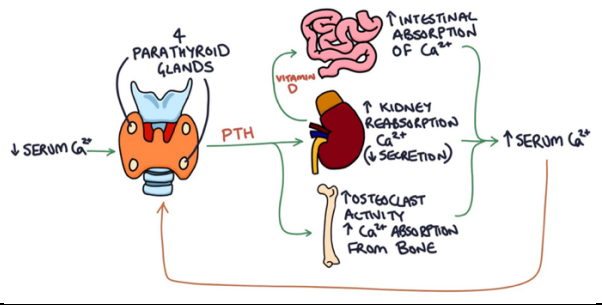
Hypercalcemia symptoms
- **Polyuria, polydipsia**
- **Renal stones**
- **Painful bones**
- **Abdominal groans** = abdo pain, constipation, nausea and vomiting
- **Psychiatric moans** = fatigue, depression and psychosis

General Ix for hyperCa
- **FBC (***heam issue***) → EUC (eGFR)**
- **CMP + PTH** Hyperparathyroidism?)
- **Vit D levels** (Vit D toxicity), Vit A
- **Cancer**? – (PTH independent) → PTHrP, calcitriol, PSA
- **Sarcoidosis (ACE serum)**
- **MM** screen – EFLC / EPG
- **DEXA Bones scan**
- **KUB USS** → *renal stones, hydronephrosis*
- **Genetic screen – MEN2**

Ix

	Primary	Secondary	Tertiary
PTH	High	High	High
Ca	High	Low/normal	High
PO4	LOW	HIGH	HIGH
Mx	Surgical resection	Correct vit D def. Renal transplant	Surgical resection of hyperplasia

Increase excretion of Ca:
- **Hydration – Saline to induce** Diuresis
- **Furosemide – calciuresis**
- **Bisphosphonate**- Pamidronate
- ***Steroids** -sarcoidosis
- **SURGERY – parathyroidectomy**
  - Hoarseness – unilateral RLN palsy
  - SOB – bilateral RLN
  - Dysphagia
  - Haematoma
  - Hypoparathyroidism → Vit D and Ca supp.



Hyperaldosteronism

Define

XS aldosterone (minerolcorticoid) → XS fluid retention and HTN

Cause

Primary	Secondary
➢ ***Bilateral adrenal hyperplasia*** **(most common)**	➢ ***Renal artery stenosis***
➢ ***Adrenal adenoma*** **secreting aldosterone (*Conn's Syndrome*)**	➢ Renal artery obstruction
➢ Familial hyperaldosteronism **type 1 and type 2 (rare)**	➢ Heart failure
➢ Adrenal carcinoma **(rare)**	

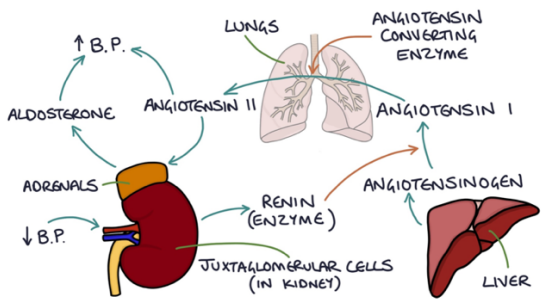
Sx

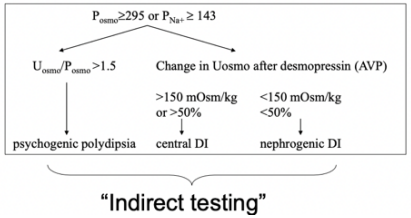
General:
- Uncontrolled HTN - most common cause of secondary HTN
- Chest pain, SOB,
- reduced exercise tolerance
- HTN unresponsive to anti-HTN

Ix
- Vitals = BP
- **EUC (hypoK)**
- VBG (alkalosis)
- Renin-aldosterone ratio
- CT / MRI – look for adrenal tumour
- ***Confirm RAS OR OBSTRUCTION → doppler ultrasound***, ***CT angiogram*** or ***magnetic resonance angiography*** (***MRA***).

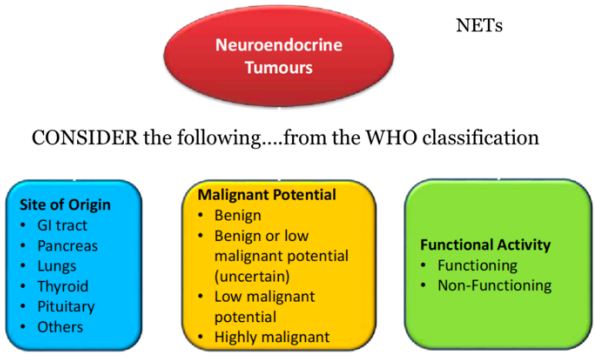
Mx

	Primary	Secondary
Renin	Low	High
Ranin- aldo ratio	High	Normal
General Mx	➢ *Stop all anti-HTN* ➢ *Start LA hydralazine + CaB* ➢ *Test renin:aldo in 6/52* *Aldosterone antagonists:* ➢ Eplerenone or spironolactone ➢ CI: hyperK, hypoNa, dehydration	
Specific Mx (Rx cause)	Surgical removal of adenoma	Percutaneous renal artery angioplasty (via femoral artery)



	SIADH	DIABETES INSIPIDIS		PHEOCHROMOCYTOMA
Define	XS ADH / vasopressin release	Lack of ADH - prevents kidneys from concentration urine		XS catecholamine release by chromaffin cells in adrenal medulla
Cause	➢ Post-operative from major surgery ➢ Infection, particularly atypical pneumonia and lung abscesses ➢ Head injury ➢ Medications (thiazide diuretics, carbamazepine, vincristine, cyclophosphamide, antipsychotics, SSRIs, NSAIDSs,) ➢ Paraneoplastic Malignancy (e.g. SCLC) ➢ Meningitis	**Nephrogenic**	Collecting ducts do not respond to ADH	➢ **Drugs** (lithium for mood stabilisation) ➢ **Mutations** (AVPR2 gene on X chromosome) ➢ **Intrinsic kidney disease** ➢ **Electrolyte issue** (hypoK, hyper Ca)	25% are familial and assoc. with ***multiple endocrine neoplasia type 2*** (***MEN 2***). **10% rule** to describe patterns of tumour: ● 100% MALIGNANT ● 10% bilateral ● 10% cancerous ● 10% outside the adrenal gland (paraganglioma)
		Cranial	Hypothalamus does not produce ADH	➢ Brain tumour ➢ Head injury ➢ Brain malformation ➢ Brain infection (meningitis, encephalitis, TB) ➢ Brain surgery or RT	
Sx	➢ Headache ➢ Fatigue ➢ Muscle aches and cramps ➢ Confusion ➢ ***Severe hyponatraemia*** ➔ seizures and reduced consciousness ➢ FLUID RETENTION = HTN, CCF, oedema MAY APPEAR CLINICALLY **EUVOLAEMIC → hence other** causes of hyponatraemia need to be excluded: • Negative ***short synacthen test*** to exclude ***adrenal insufficiency*** ○ No history of diuretic use ○ No diarrhoea, vomiting, burns, fistula or excessive sweating ○ No excessive water intake ○ No ***chronic kidney disease*** or ***acute kidney injury***	• ***Polyuria*** (excessive urine production) • ***Polydipsia*** (excessive thirst) • Dehydration • Postural hypotension • ***Hypernatraemia***		• Anxiety • Sweating • Headache • Hypertension – uncontrolled • Palpitations, tachycardia and ***paroxysmal atrial fibrillation*** • ***Looks pale + impending sense of doom***	
Ix	➢ FBC ➢ EUC - hypoNa ➢ Serum and urine osmolarity ➢ ***Short synacthen test*** to exclude ***adrenal insufficiency*** ➢ CXR = pneumonia, lung abscess and lung cancer ➢ CT abdo/pelvis and MRI brain = identify possible malignancy	➢ **Low** urine osmolality ➢ **High** serum osmolality + high sodium ➢ Water deprivation test (desmopressin stimulation test) for **8 hours** ➢ **Pituitary MRI** = *Stalk thickening + Loss of posterior bright spot* DDx: based on **urine osmolarity** After deprivation / After ADH (DDAVP) Nephrogenic: **Low** / **Low** Cranial: **Low** / High Primary polydispsia: High / High		• Vitals (HR, BP) • FBC, EUC, LFT, CRP *Gold-standard:* • **24 hour** urine ***catecholamines*** ***(****since levels fluctuate over the day and adrenaline has a very short half life****)*** • Plasma free ***metanephrines*** ***(****breakdown product of adrenaline = longer half life****)*** • Renal venous sampling (prodding adrenal gland – secrete and detect catecholamines) *Genetic screen:* ➢ *MEN2b, NF1, SDHD, VHL*	
Mx	**Acute Mx** ➢ **Stop offending drug** ➢ **Fluid restrict 500mL -1L** ➢ Correct Na slowly to prevent ***central pontine myelinolysis*** (osmotic demyelination syndrome) ➔ ***OCCURS DUE TO RAPID NA correction (esp. for severe hypoNa < 120mM)*** ○ **1st phase** = confused, N/V and headache ○ **2nd phase** = pontine demyelination → spastic quadriparesis, pseudobulbar palsy, beaviourla changes ○ **Prevention essential** = high mortality rate ○ Aim for a change in sodium of < 10 mmol/l per 24 hours to prevent osmotic shift of water out of brain cells **Specific medications:** ➢ **Tolvaptan**. "***Vaptans***" are ***ADH receptor blockers***. → specialist endocrinologist and require close monitoring, for example 6 hourly sodium levels. ➢ **Demeclocycline** is a ***tetracycline antibiotic*** = *inhibits ADH (old med -not used now)*	**Desmopressin** • Intranasal (rhinyl or metered dose) • **Vasopressin PO** = 20x that of IN ▪ 200-400 ug x 2-4 times daily • Nephrogenic DI requires higher doses and closer monitoring  "Indirect testing"		**Initial Treatment**: (ABCD) 1) **Alpha blockers** (i.e. ***phenoxybenzamine***) – minimise prazosin as can damage bV resulting in stroke, HF and kidney failure 2) **Non-selective Beta blockers (metoprolol)** once established on alpha blockers (to prevent refractory HTN caused by uncontrolled alpha-mediated vasoconstriction) 3) **Circulatory –** peri-operative fluid loading 4) ***Adrenalectomy*** to remove tumour is the definitive management Patients should have symptoms controlled medically prior to surgery to reduce the risk of the anaesthetic and surgery.

Neuroendocrine Disease



NET cell, characterised by secretory functions

- Syndromes: VIPoma, glucagonoma, insulinoma....
- MEN 1& 2, medullary thyroid ca
- Variable behaviour based on cell derivative

Carcinoid syndrome: Inc.; symptoms of

- flushing,
- diarrhoea,
- wheeze/asthma-like syndrome,
- right heart failure
- Pellagra (dermatitis, diarrhoea, dementia)

Table 1. WHO 2010 Classification and Suggested Grading

Classification		Grade	Mitotic count (per 10 HPF)	Ki-67 index (%)
Well-differentiated	NET	G1: low grade	<2	<2
		G2: intermediate grade	2–20	3–20
Poorly-differentiated	NEC	G3: high grade	>20	>20

Describe biochemical & hormonal markers and imaging techniques used for Dx and Mx of neuroendocrine tumours

- **Nuclear medicine;** using radioactive traces for Dx or Rx
- **Diagnostic procedures;** image tracer distribution in body
- **Therapeutic procedures** deliver targeted radio-labelled tracers that can also be imaged

NET	Gene	NET manifestation	Key manifestation
MEN 1	MEN 1	• Parathyroid • Gastroenteropancreatic – *gastrinoma, insulinoma, VIPoma* • Anterior pituitary • Lung an dthymus	Adrenocortical tumours
MEN2A	RET	• MTC (90-100%) • Adrenal medulla • Parathyroid (20%)	
MEN2B	RET	• MTC (100%) • Adrenal medulla (50%)	Marfinoid habitus Mucosal neuromas
MEN4	CDKN18	• Parathyroid • Pancreas • Pituitary	
NF1	NF1 (aut-dom) – Chr 17	• Adrenal medulla • Lymphoma, neural crest tumour	Neurofibroma Café au lait
NF2	Chr22 mutation (no EGFR suppress)	• Schwannoma (acoustic neuromas)	
VHL	VHL (tumour suppressor gene)	• Adrenal medulla and SNS ganglia	Haemangioma RCC, cysts
Tuberous sclerosis	TSC1/2	• Pancreas	Hamartomas
Familial PGL	SDHA-D, SDHAF2	• SNS and PSNS paraganglia • Adrenal medulla	GIST, RCC
Polycythaemia paraganglioma syndrome	EPAS1	• SNS ganglia • Adrenal medulla • Duodenum	Polycythaemia

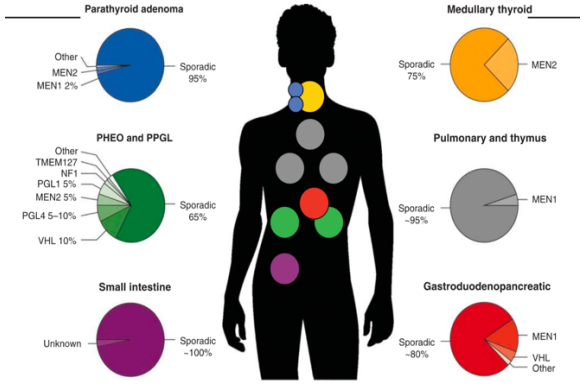


Figure 1
Overview of genes with recurrent mutations in NETs and their distribution accordingly to anatomical location.

Multiple endocrine neoplasia type 2 = Sipple's syndrome

- Derived from the **gain-of function** mutation **RET gene**
- MOST NETs = idiopathic

Scans	Mechanism	Indication for use
Bone Scan	• Tracer binds to bones – labelled with **Tc-99m** (≈ 4hrs) • +/- used for pt with NET – but NET spread to bone less freq. than other ca	Detects bone tumours • Outpatients
MIBG scan [*Metaiodobenzyl-**guanidine Labelled With I 131***]	• Taken up by NET which produce ○ **Serotonin – carcinoids** ○ **Adrenaline – pheos** • Varied protocols (4 hr, 24hr +/- whole body +/- SPECT/SPECT- CT)	• Detect & characterise NET lesions – MTC, carcinoid, pheos, neuroblastomas • Can exploit same tracer ***at higher doses for therapy***
PET [hybrid PET/CT scan]	• **FDG PET – ^{18}F- Fluorodeoxyglucose** ➔ how much glucose used by tumours • Need good glucose control | cannot read in dark (false activity) • Need euglycemic for diabetes • **Ga-68 PET DOTATE SCAN** –somatostatin analogues labelled with **^{68}Ga octreotide**, dotatate etc ➔ somatostatin receptors (NETs) • Same as octreoscan but faster, higher resolution & sensitivity	Useful in selected pt with NET (e.g. tumour on CT/ MRI but **Octreoscan** –ve or assess aggressiveness or Rx response, fasted, 2 hour procedure
Radionuclide Rx for NET	• *Regional*: **Yttrium-90 microspheres injected IV** • *Systemic*: PRRT, (Peptide receptor radionuclide therapy) e.g. Analogue tracers of somatostatin (**^{177}Lu-octreotate**)	• Regional; **Yttrium-90** injected in liver artery, accumulates in tumour lesions in that organ • Systemic: PRRT → accumulate in tumour

BEWARE OF POLYGLANDULAR SYDNROME

Type 1 PGS	Type 2 PGS	Type 3 PGS	Type 4 PGS
➢ **Mucocutaneous** candida ➢ **Addison** ➢ **Hypoparathyroidism** (PTH, CMP)	➢ **Addison** – short synacthen test ➢ **T1DM** – anti-GAD, IIA, Zn8 transporter ➢ **Thyroid Disease** (Grave's, Hashimoto) → TrAB, anti-TPO, Tg	➢ **Thyroid autoimmune disease** assoc. with other autoimmune conditions ➢ NO Addison, hypoparathyroidism	Combination of organ specific autoimmune diseases

Describe common clinical syndromes associated with neuroendocrine disease

*__Carcinoid syndrome__ = secretory diarrhoea, wheezing and **episode cutaneous flushing (***triggered by eating, alcohol, liver palpate)*

- ***Carcinoid tumours*** *usu. GI tract and asymptomatic as hepatic metabolism of serotonin secreted by tumour*
- *Ix: DOTATE scan (elevated serotonin)*
- ***Complications*** ➔ *elevated serotonin metabolite (5-HIAA) and vit B3 (niacin) def. → pellagra (3 D's)*

Tumour	ACTHoma	Gastrinoma	Glucagonoma	GRFoma	Insulinoma	Somatostatinoma	VIPoma (WDHA)
% of functional NETS		16-30%	< 10%		35-40%	< 5%	< 10%
Hormone	ACTH	Gastrin	Glucagon (a cells)	GH releasing factor	• Fast insulin (>5) • Glucose (<40) • C-peptide (0.6) • Pro-insulin (	Somatostatin (D cells)	• *VIP = vasodilator + neurotransmitter* • *Relax SMC = ↑GI motility* • Modulates insulin activity
Location	Pancreas	Pancreas (60%) Duodenum (30%) Zollinger-Ellison?	Pancreas	Lung (55%) Pancreas (30%) Jejunum (7%)	Pancreas	Pancreas (56%) Duodenum/ jejunum (44%)	Pancreas (90%) Other (10%)
S+S	Cushing's syndrome	Refractory PUD, Duodenum, diarrhoea	Dermatitis w/ migratory necrotic erythema, diarrhoea, DVT, anaemia	Acromegaly	Episodic hypoglycaemia	Glucose intolerance, Steatorrhea, UWL, gallstones	Chronic watery diarrhoea, hypokalaemia, achlorhydria (low HCl)

Pancreatic NETS localisation

- AIM: planning surgery & distinguish from nesidioblastosis

Often multiple modalities required:

Cross-sectional imaging (USS → uptake scan → CT → MRI → EUS)

Functional imaging:

- SRS: In-111-octreotide
- PET: Ga68-Octreotide
  - No uptake = poor differentiation, no receptor expression

Selective arterial Ca stimulating testing (SACST)

- Assumptions: Ca: insulin secretagogue and tumour has single positive supply
- Positive: HVI x2
- False +ve liver = retrograde HA → GDA OR variant anatomy

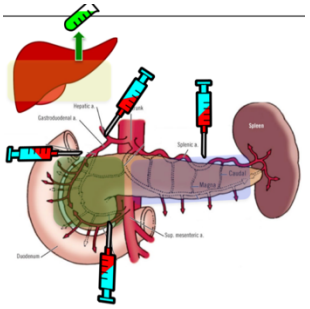
Multi-region SACST – differentials:

- Check timing of symptoms
- Screen for c-peptide/insulin, sulfonylurea levels

Features	Multifocal Insulinoma	Nesidioblastosis
SACST	Focal	Diffuse
Hypo timing	Fasting	Prandial
Localisation	POS/NEG	NEG
		Hyperinsulinemia Hypoglycaemia Functional B cell issue in children

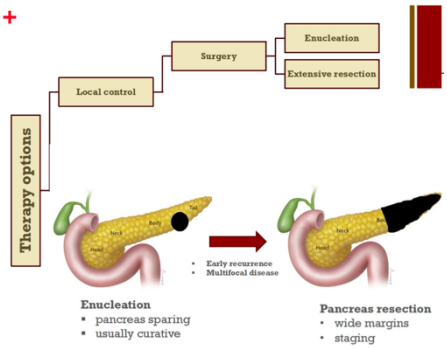
USS → functional uptake → CT → MRI → EUS

Modality	Result
Selective mesenteric angiogram	Visualise Tumour neovascularity
MRI pancreas	Lesion esp. around the head
EUS *(endoscopic USS)*	• Uncinate lesions, small 2-3cm lesions • LN and vascular invasion not seen on CT
In-111 Octreotide	Any focal uptake – bind to somatostatin receptors
Intra-arterial Ca Stim Testing	Tumour localisation



- Positive: HVI x2

Head/Neck	SMA, GDA
Body/Tail	SA
Liver met	HA

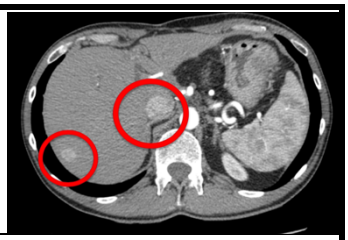


Briefly discuss some therapeutic options in neuroendocrine disease

Glucagonoma	• SSA Lanreotide (somatostatin analogue) 90mg four weekly & Creon
	• FU check:
	  ○ **Chromogranin A & fasting gut hormones** (check for cancer relapse)
	  ○ **LFT, EUC**
	  ○ **CT scan → 2 homogenous hypodense lesions in the liver**
	  ○ If DVT develops → **long-term clexane (LMWH)**

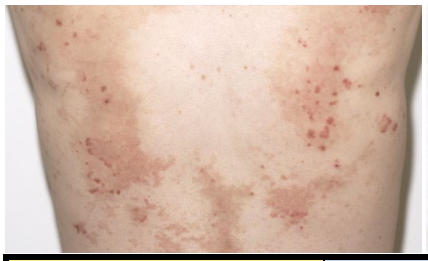
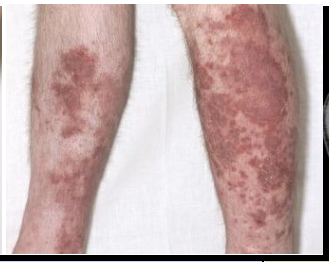
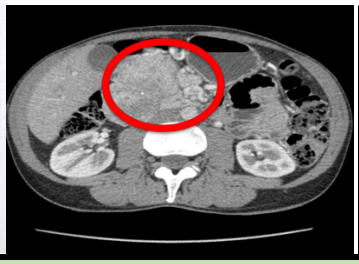
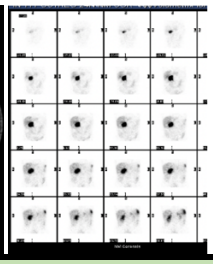
RECURRENT Medullary Thyroid Ca	• Surgery if possible
	  • RT for bone metastases for symptom control but no survival benefit
	  • Chemo has poor response rates (<20%) → TKI? → target RET proto-oncogene
	  • GLP1- agonist = increaser risk
	  • Check elevated calcitonin = reduced calcium

Papillary Thyroid Cancer	• **Most common thyroid cancer** • Thyrogen ablation – not advised if metastatic • May reduce RAI toxicity but does not protect from oedema or metastasis



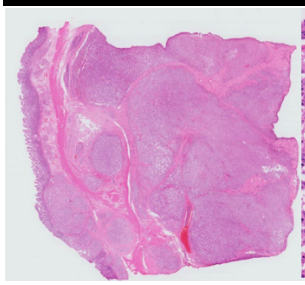
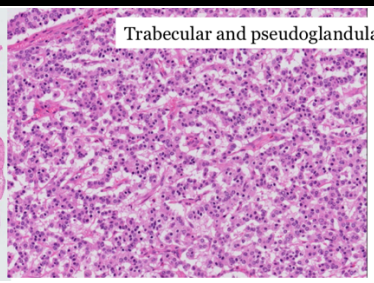
Glucagonoma *(rare NET→a2 islet cells)*

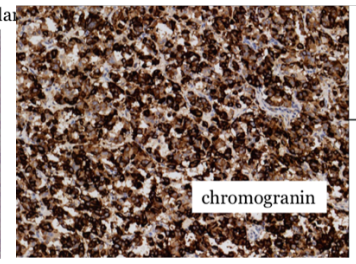
- Non-specific signs: weight loss, diarrhoea and stomatitis
  - (4D'S) **Diabetes, dermatitis, DMT and depression**
- Cutaneous lesions in this phase of the disease OFTEN confused with non-specific dermatitis, which occurs more often in patients with DM

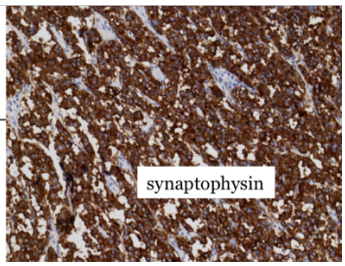





Symptoms	Examination	Investigations

• Gradual weight loss over years
• Presumed with IBS
 	
Negative signs:
• NO DVT,
• NO aneamia
• NO previous endocrine tumours
• NO jaundice, Abd pain
• NO polyuria, polydispsia or autoimmune disease
	• Low BMI
	• Midline surgical scar in epigastrium
	• **Soft palpable fullness in** epigastrium
	
	Describe the rash!
	• **Erythematous raised patches over epigastrium with poorly-demarcated irregular borders**
	• **Rash is diffusely spread across the trunk and back**
	• Multiple confluent erythematous areas
	• **Cutaneous eruption** (skin rash)
		• FBC, EUC, Fasting BGL, Hba1C (normal)
		• **Skin biopsy (non-diagnostic)** excl:
		  ○ Spongiotic dermatitis & eosinophilia
		• **Gut hormones (***i.e. pancreatic enzymes)*
		  ○ Glucagon (elevated)
		  ○ Chromogranin A (elevated) = generic NET marker (pt must not be on PPI to work)
		• **CT abdomen →** *epigastric heterogenous lobulated mass 7cm arising from pancreas compressing surrounding structure*
		  ○ Non-empty stomach
		• **Octreotide Scan (positive) →** somatostatin receptors (confirm)
		• **Histopathology**:
		  ○ well differentiated pancreatic NET involving resection margin
		  ○ trabecular and pseudo-glandular
		  ○ Stained for Ki67, chromogranin, synaptotrypsin, glucagon
		
		Rx: Lanreotide (somatostatin analogue) + **Creon** (commercial mixture of pancreatic enzymes e.g. amylase, lipase in CF)
		• If DVT develops → long-term clexane (LMWH)





Parathyroid Adenoma **(DDx: Hypercalcemia -2.15-2.55mM)**

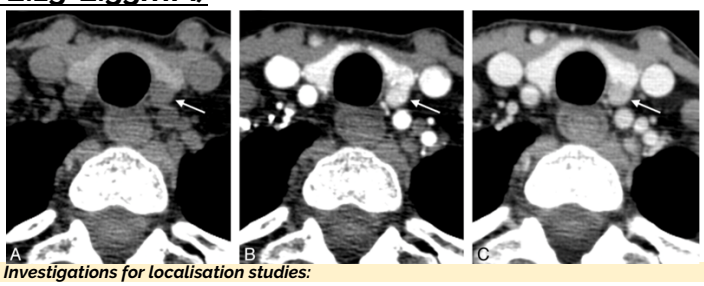
- *Bones* = ↑↑ osteolysis and fractures
- *Stone* = Renal colic and hypercalcemic stones (Hx of low eGFR)
- *Abd groans*= Fatigue, N+V, constipation, polyuria, pancreatitis, PUD
- *Psych moans* = Confusion, hallucinations, depression, brain fog
- *Hyporeflexia weakness + nephrogenic Diabetes insipidis*
- ↑↑ nocturnal BP (24hr monitoring)
- ***Arrhythmia*** (**serum ≈ 3mM**) (short QT (low Ca, Mg, K)→ prolonged PR → wide QRS → AV block → CHB → cardiac arrest)

DDx: (90% malignancy OR hyperparathyroidisms)

- **Solid organ Malignancy** (breast, lung, prostate, thyroid, kidney, haematological malignancy – NHL, HL)
- ***Primary HPTH*** = Single adenomas (75-85%)
  ↑↑ ***serum Ca*** + ↑↑***serum PTH (corrected for vitamin D i.e. > 50)***
- ***2º HPTH*** = **CKD**
- Endocrine (Addison's, Pheo, hyperthyroidism)
- Paget's (bowed legs = non-malignant increased bone turnover)
- Familial hypocalciuric hypercalcemia (FHH) = mutant Ca-sensing receptor gene
- Dehydration
- Resp. (TB, sarcoidosis)
- Drugs (lithium, thiazides, vitamin D excess)
- Fictitious (not albumin corrected, prolonged cuff time)

Rx hypercalcemia:

- vol. expansion + hydrate (replace lost fluid and force diuresis)
- Dialysis for CVS or renal impairment
- Calcitonin/EDTA bisphosphonate to reduce bone resorption (48hrs ONLY)
- Avoid thiazides, furosemide (worsen)



Investigations for localisation studies:

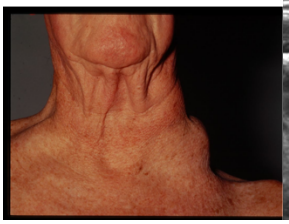
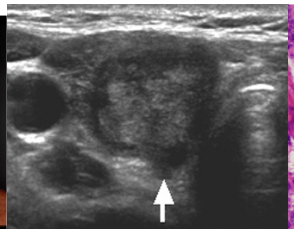
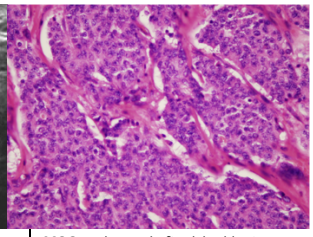
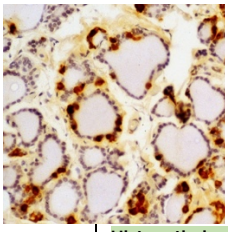
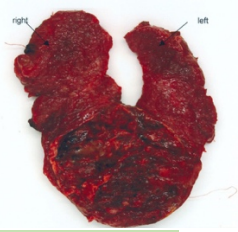
1. ***US neck***
2. ***Tc-99^{m} Sestamibi***
3. ***4DCT imaging*** → (if unable to localise on USS or ***Tc-99^{m})*** *uses hypervascular nature of adenomas to identify them by enhancement (relative thyroid)*
   - *CT scan showing well-circumscribed slightly heterogenous lesion on the right side*
   - *Pre-contrast → contrast → delayed phase (washout of parathyroid adenoma)*

Advantage of 4DCT:	Disadvantage of 4DCT:
• Identifies > 50% abnormal parathyroids • Prompts bilateral neck exploration	57x HIGHER radiation dose than sestamibi (Tc-99^{m})

COMPLICATIONS OF PARATHYROIDCETOMY:

- ***Haematoma – " check drain"***
- ***Hoarseness –*** *unilateral RLN palsy*
- ***SOB/Stridor –*** *bilateral RLN palsy*
- ***HypoCa –*** *periorbital numbness*

Medullary thyroid cancer (MTC) – classic thyroid NET

Single unilateral left-sided mass in the anterior lateral neck w. coarse texture and no discolouration with no transillumination

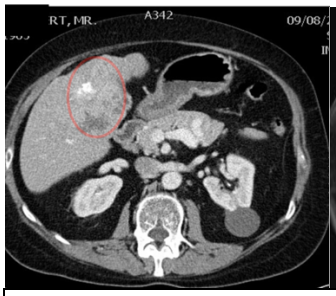
- ***DDx: thyroid cancer (1° origin), lymphoma***

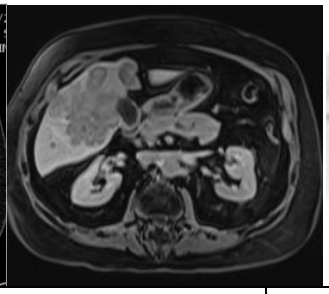
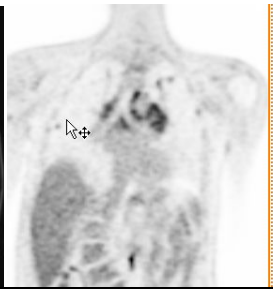
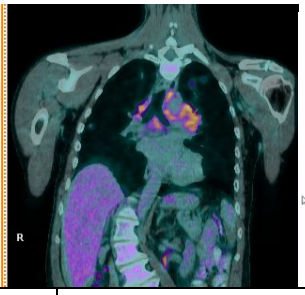
USS → large left-sided heterogenous lesions lateral to trachea compressing the internal jugular vein

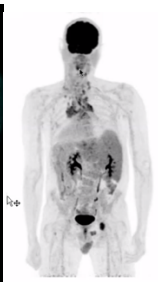
Histopathology – orphan annie cells

- Amyloid between cells (polyglonal-shaped)
- Parafollicular cell neoplasm

Clinical Px	Investigations for recurrent MTC	Localisation of MTC
Mass effect: • HOARSENESS • Dysphagia . cough • SOB, stridor *Hypercalcemia signs* • Arthralgia • Bone pain • Constipation • Enlarged lump in thyroid region	• Hormone secreting tumour: **Calcitonin doubling time useful** ○ If calcitonin <400ng/L, likely no visible tumour • Familial **MTC➔** MEN2A/B ➔ "Rearranged during Transfection" (**RET**) **proto-oncogene ➔** increases hyperplasia of specialised cells in "C-cells" • Biopsy - **parafollicular C cells – amyloid between cells** • **RET gene mutation → MEN2A or MEN2B?** **Nb:** NO hypocalcemia as tissues resistant to calcitonin	• **USS (MOST USEFUL for thyroid ca)** • **CT to characterise** • PET for neck but not all sites encompassed • Bone scan and/or MRI for axial skeleton • CT chest and abdo • MRI superior to CT for liver ***Rx: targeted therapy with TKIs? → due to RET proto-oncogene and suppress cancer growth**



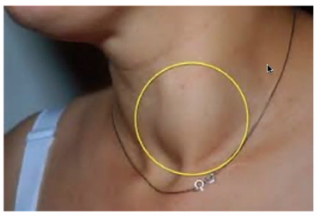
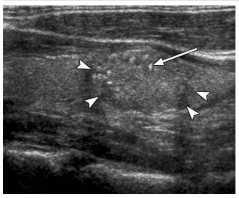
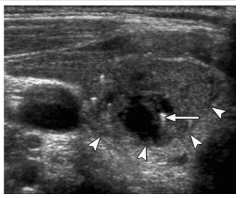


2 lesions in the lump → This is a CT scan showing 1 hypodense and 1 small hyperdense poorly demarcated calcification (vascular supply to tumour is lost)

T1 MRI – multiple hypointense lesions in the liver

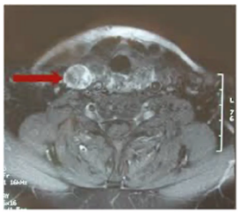
PET-CT scan → diffuse metastatic disease in mediastinal region

Papillary Thyroid Cancer [most common thyroid cancer]

a. b.

- Microcalcifications present (arrows)
- NB: *Positive Tg should be assessed with neck US +/- FNAB, prior to 2nd ablative RAI dose and post-abln RAI scan*



- *Dermatology*: Single unilateral large circular mass in the left anterior neck with no pigmentation, redness of smooth texture
- *USS*: heterogeneously hyper and hypoechoic regions within a central lesion with irregular border
- *Radiological description*: is there mass compression? / airway compromise?, confirm location?, hoarseness/stridor?)

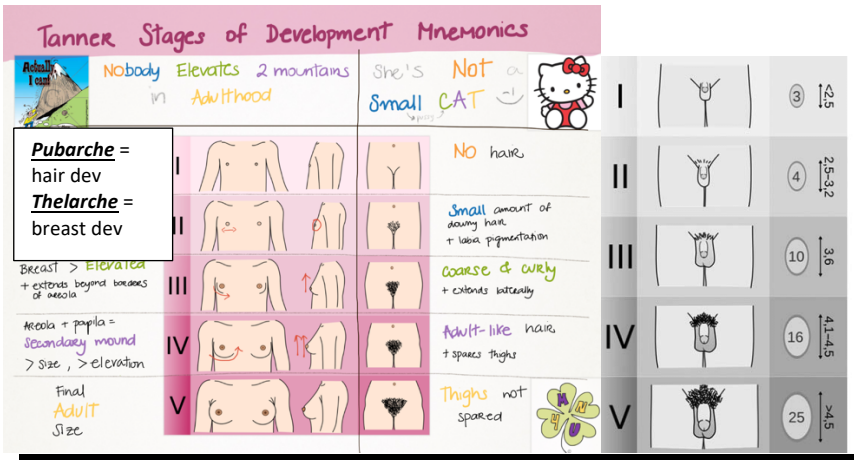
CLINICAL Px	Exam
• Solitary palpable thyroid mass • PTC tendency to metastasize early to local LN [20% pt] • NO HORMONE PRODUCTION	**Imaging of the neck involves BOTH** • Thyroid exam **AND** • Regional LN for presence of mets

ATA risk	A	B	C	D
Codon	768,790,791 891,912,804 844,912,532 533,321	609,611,618, 620, 630	634	918 883
MTC aggressiveness	High	Higher	Higher	Highest
Thyroidect.	>5 ?criteria	? criteria	<5 years	ASAP
MTC onset	adult	5 years	< 5 years	<1 year
Phaeo. screening	20 yrs then occasionally	20 yrs then yearly	8 yrs, yearly	8 yrs, yearly
Hyperpara.	20 yrs	20 yrs	8 yrs, yearly	
Syndrome	FMTC/MEN2 A	MEN 2A/FMTC	MEN2A	MEN2B

Ix

	Sensitivity		
Neck US	70-85%	*for malignant nodes* • *Short-axis > 5mm* • *Internal echoes* • *Diffuse/peripheral blood flow* • *Cystic LN* • *Non-echogenic hilum*	Scan if (every 6/12) • ***Thyroglobulin (Tg) +ve*** • *Tg negative* ***BUT TgAbs +ve***
Radioactive iodine (RAI) uptake scan	0-25%	**What is the significance of thyroglossal duct remnant RAI uptake?** Suggestive of functional thyroid activity → potential to develop into cancerous lesion (e.g. papillary thyroid carcinoma)	
Stim Tg	80-90%		
Stim Tg + Neck USS	95-100%		
High-res CT		follicular Ca and distan/pulm. METS?	
PET	staging in *high-risk patients* and *hurthle cell Ca pts* • **PET positivity = RAI negativity**		
Thyrogen scanning	***MBS criteria***: previous negative scan, psychiatric, hypopituitarism or cardiac issues		
Histology	***Orphan Annie nuclei -→****optically clear nuclei, psammoma bodies*		

Gender Dysphoria, Transformation and Intersex Disorders



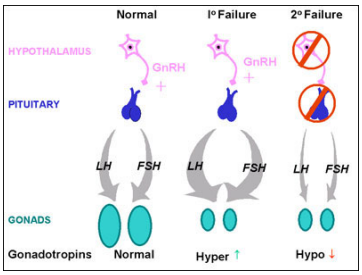
Stage I: prepubertal; testicular size less than 4 cc in volume and 2.5 cm in longest dimension

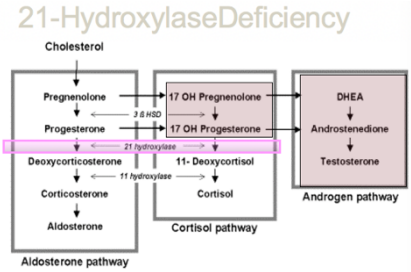
Stage II: enlargement of scrotum and testes; scrotal skin reddens and changes in texture; growth of testes to 4 cc or greater in volume

Stage III: enlargement of penis (length at first); further growth of testes

Stage IV: increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker

Stage V: adult genitalia





	LH or FSH	TT, E2	Cause	Symptoms + Ix	Rx
Hypergonadotrophic (primary/peripheral) **hypogonadism**	**High**	**Low**	• **Primary testicular failure** • **Congenital** (e.g. Klinefelter, Turner's, Noonan, crypto-orchidism, XX gonadal and XY gonadal dysgenesis) • **Acquired** (infection (mumps), chemo/RT, trauma, gonad removal, autoimmune)  **Turner (F)** *(short + low E2) webbed neck Large carrying angle Epicanthic folds* **Klinefelter (M)** *(tall, thin, low TT) small testes, tall, gynacomastia* 	**Delayed puberty** *[absent 1st signs of pubertal development usu. > 16 y.o.]* • Low libido + energy • Reduced bone density & lean muscle mass • Infertility and amenorrhoea	**HRT**: • Boys = TT • Girls = E2
Hypogonadotrophic (secondary/central) **hypogonadism**	**Low**	**Low**	• **Constitutional delay** [GnRH deficiency esp. Hispanics] • **Congenital** (*Kallman's – defective migration of GnRH cells → oligospermia or amenorrhea + impaired sense of smell*) ○ **Prolactinoma** • **Acquired (obesity** → PCOS, **opioids, underweight** (AN), • **Malnutrition** (E.g. AN, CHO restriction, T1D, coeliac, CKD) • **Severe stress/exercise** • **HP-disease** (surgery, RT, tumours, infiltrative – sarcoid, deposition - haemochromatosis, inflammatory – vasculitis)	• FBC, EUC, CMP, LFT • **TT/E2 + LH/FSH** • 17OH progesterone • Growth chart, bone age • **Full pituitary profile** (GH, TSH, IGF-1, TT, Cortisol, PrL) • Pituitary MRI, Abdo US	
Hypergonadism *"obvious in women, subtle in men"* **Risk factors:** • *Female* • *Ethnic (black, Hispanic)* • *Obesity* • *HRT use*	**High**	**High**	• **Idiopathic precocious puberty** (growth spurt – dx of exclusion) • **Virilising Gonadal Tumours** [Ovarian, Leydig and germ cell tumours] • **Hypothyroidism (↑TSH ➔ GRANULOSA CELLS ➔ XS E2)** • **Adrenal issue (PERIPHERAL)** ○ ***androgen secreting adrenocortical carcinoma*** ○ ***CAH*** *(e.g.* **21-OH Deficiency (90%) - HIGHLY** elevated 17-OH progesterone due to *recombination of CYP21 and CYP21P genes in* ***Chr. 6*** ○ Most common cause of female virilisation due to ↑ androgen production by hyperplastic adrenal glands ○ **Males**: Genital enlargement + hair and skin abnormalities ○ **Females**: facial hirsutism, central alopecia, **clitoromegaly**, labioscrotal fusion, 1° amenorrhoea • **Damaging HP disorders (CENTRAL)** ○ *tumour, infection (TB meningitis), trauma, RT* ○ **McCune Albright syndrome** → TRIAD: precocious puberty + fibrous dysplasia + café au lait spots [↑osteolytic lesions = fracture risk]	• **Precocious puberty** *< 8 y.o. in girls & <9 y.o. in boys* • Subfertility or Infertility • Amenorrhea & Virilisation in women • Sex hormones: TT/E2 + LH/FSH • Full pituitary profile • 17OH progesterone	**DELAY puberty** via: • GnRH analogues • Monitor wt/ht

Consider adult onset - hypogonadism

- Menopause in women ➔ estrogen def. ➔ vasomotor issues ➔ hot flush, headache, light-headed, syncope, vaginal dryness, vision issue,
- Men slower ➔ loss of libido & shaving less

Intersex disorders

- **CAH (aberrant shunting of adrenals)** ➔ Most obvious in women (excess hirsutism)
- **Androgen insensitivity syndromes** [receptor defects] –
  - 46XY **but Female phenotype**
  - **Internal male genitalia (no uterus, fallopian tubes, ovaries, upper vagina)**
  - **Raised LH and raised E2**
  - **Rx: specialist MDT**
    - BILATERAL ORCHIDECTOMY (remove testes – reduce risk of testicular tumours)
    - Oestrogen therapy
    - Vaginal dilators or vaginal surgery – to expand vaginal length
- **Drugs** ➔ **Spironolactone** (aldosterone antagonist) → risk of incomplete virilization of male fetus

Klinefelter PP:

- Dysgenesis of seminiferous tubules
- Reduced inhibin B = reduced -ve feedback ➔ elevated LH/FSH → increased E2
- Tall stature and small testes

DDx for precocious puberty vs exogenous HRT:

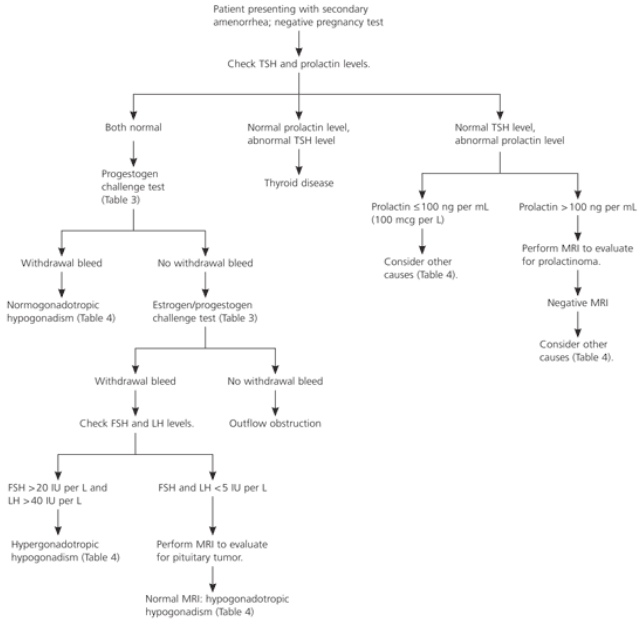
- Bone age scan of wrist, hand, digits (precocious is > 2 y than chronological) – **left hand – epiphysis**
- Constitutional activation of HPA or peripheral exogenous source (central vs peripheral)
- Check sex hormones (TT, E2, FSH, LH) , DHEA, 17-OH progresterone

Gender dysphoria:

- Persistent feelings of not matching one's biological phenotypic gender (**feeling female when 46XY)**
- *Evaluation for adults*
  - Stage 1 therapy = formally diagnosed by psychiatrist confirming gender dysphoria
  - Stage 2 therapy = hormonal evaluation
  - Stage 3 therapy = surgical reassignment (e.g. **top-surgery:** bilateral vasectomy, breast implants | **bottom-surgery**: remove testes/penis)
- *For children = need consent of 2 parents*
  - Need to show competence (Gillick competence) e.g. **trans-girl** (risk of growing breasts & increased risk of clotting – E2 therapy), **trans-boy** (facial hair growth → goserelin/zoladex – GnRH agonists)
- *3 factors for successful gender reassignment*
  - Persistent identification to opposite gender
  - Openly dressing in clothes of other gender

Openly discuss dysphoria with family and friends

	Description	S+S	Ix	Rx
Tumour	Most common = non-functioning		• Mildly elevated PL (stalk interruption	
	Craniopharyngioma [**Affects young]**	• **Bitemporal hemianopia** • Diabetes insipidus • **Hypopituitarism**	• Low GH > Prl > LH/FSH > TSH > ACTH	**Surgical removal**
Lymphocytic Hypophysitis	Autoimmune (esp. women)	• Raised PrL • Diabetes Insipidis	• ACTH deficiency	**HRT**
Pituitary Apoplexy	• Haemorrhagic infarction of a pituitary adenoma/tumour • **RF** = diabetes, radiation, warfarin	• **Severe Headache [1-2 days]** • **N + V + vertigo** • **Bitemp. Superior quadrantopia**	• Glucocorticoid deficiency • CT pituitary – hyperdense bleed in pituitary	**Neurosurgical emergency** ➔ Trans-sphenoid decompression
Empty sella syndrome	• empty sella by CSF filling the dural herniation	• Clinically silent infarction	• Normal pituitary function • Incidental MRI finding	• Removal of mass
Septo-Optic dysplasia	• Hypothalamic dysfunction and hypopituitarism • **HESX1 gene mutation**	• **Optic atrophy** • **Micropenis** • **Cleft palate** • **Ear deformities**	• Diabetes insipidus • GH deficiency and short stature (sometimes TSH deficiency)	**N/A**
Kallman Syndrome,	• Defective hypothalamic GnRH synthesis ➔ ***prevents progression through puberty***	• **anosmia** • color blindness, • optic atrophy, • nerve deafness,	• Low LH and FSH levels • low concentrations of sex steroids	• **Male (micropenis)** : HcG or testosterone • **Female (amenorrhea)**: cyclic E2 and progestin
Laurence-Moon-Bardet-Biedl Syndrome,	• **Rare autosomal recessive** • **(GnRH deficiency)**	• **Retinal degenerate (blind by adult)** • Mental retardation + obesity	**Low GnRH**	
Frohlich Syndrome	• Adipose Genital Dystrophy • hypothalamic lesions	• **obesity**	• Low LH and FSH levels • Low leptin ➔ obesity	
Nelson's syndrome	• Cushing's disease + hyperpigmented skin + mucus membranes **post-adrenalectomy**  Hyperpigmentation with Nelson's syndrome	**Enlarged ACTH tumour causes HIGH levels of ACTH:** • Na + fluid retention = oedema • **Hypokalemia**	**SAME + pigmentation** Test via: 1. 24 hr urine free cortisol 2. Loss of diurnal pattern 3. Serum ACTH 4. **Dex suppression test**	•
Conn's syndrome (primary aldosteronism)	• **Adrenal adenoma** – autonomous secretion • **Bilateral adrenal hyperplasia** (eg ARM mutation) *DDx*: ➢ Renal artery stenosis (young females- hereditary)	• **HTN** (10%) • **fatigue, numbness,** • **Frequency + thirst** • **muscle cramps, and muscle weakness**	**High Aldosterone-renin ratio** • (NOTE: *may be affected by anti-hypertensives ➔ hence withdraw prior to test)* **CT** abdo to confirm adenoma *(exclude BAH- benign adrenal hyperplasia)*	• **1st line spironolactone [***AE = gynacomastia, menstrual irregularity)* • **2nd line** = selective mineralocorticoid receptor blocker • **Surgery is definitive** but with morbidity
Congenital Adrenal Hyperplasia (CAH)	adrenal insufficiency of: • **21-hydroxylase enzyme** • **11b-Oh deficiency** • **17a-OH deficiency**	• **abnormal growth for both sexes** ➔ *"tall children but short adults because of early bone maturation"* • **female hirsutism** • **males** = precocious dev.	• **Tanner staging** **Check:** • ***17 OH progesterone levels*** *(should be elevated)* • ***Cortisol and aldosterone levels (17a-OH)***	
Pheochromocytoma	• adrenal medulla tumour • SNS overdrive (NA,A) • 10% extradrenal, • 10% bilateral, • 100% malignant but 10% metastise	• Headache, sweating, palpitation • Impending doom • Pale face (ghost like) • Unresolved HTN	• Repeat 24-hr Urinalysis ➔ free catecholamines + metanpehrines (e.g. NA/.A)	• **Fluid replacement** • **Alpha blocker** then BB before surgery + avoid refractory HTN • **Surgical removal**
PCOS	**Hyperandrogenism**: • hyperinsulinemia: Increase unbound androgens [↑↑ **TT or DHEAS or Androstenedione**] & ↓↓↓ **binding proteins in liver (SHBG)** + ↑↑ **Free androgen index (FAI)** • **Clinical**: Hirsutism (80%), acne (20%), central alopecia (10%), **Acanthosis Nigricans** (insulin resistance = overproduction of insulin + decreased HDL) **Amenorrhoea**: • **Amenorrhea (LH:FSH >2 ➔ anovulation) & irregular menses** ○ **No ovulation = no corpus luteum = No progesterone release** • **Leads to**: infertility, endometrial hyperplasia/cancer ○ Elevated E2 levels [due to lack of progesterone] → endometrial proliferation with no shedding → higher risk of polyps/hyperplasia ○ Obesity = increased adipose tissue = increased androgen into estrogen **US Polycystic ovaries**: • **> 12 follicles or increased ovarian volume [>10mL]** ○ No dominant follicles			• **Metformin (lose wt and increase insulins sensitivity)** • **Reudce wt** • **Treat Hirsutism/ acne/ hair loss** → Anti-androgen OCP (Slinda), laser hair removal • **Protect endometrium** → Administer HRT/OCP • **Infertility – Advise weight loss**



21-year-old woman with secondary amenorrhea. Blood levels of gonadotropins (FSH and LH) are lower than 10 IU/ml. Prolactine and TSH are within normal range. This patient does not have a period after having a progesterone challenge test, but she menstruates when she has oestrogen and progesterone challenge test (COCP). This patient is likely to suffer from:

1-PCOS
2-Premature ovarian failure
3-Turner syndrome
4-Central amenorrhea

Type 1 central amenorrhoea

Which one of the following assertions in regards to PCOS is true:

1- It accounts to approximately 20% cases of anovulatory infertility
2- Its expression is not affected by changes in body weight
3- It is associated with an increased risk of insulin-dependent diabetes mellitus
4- The hypersecretion of luteinising hormone (LH) is associated with a reduce chance of continuing a pregnancy
5- All the above are correct

21-year-old woman with secondary amenorrhea. Blood levels of gonadotropins (FSH and LH) are higher than 50 IU/ml. Prolactine and TSH are within normal range. This patient does not have a period after having a progesterone challenge test, but she menstruates when she has oestrogen and progesterone challenge test (COCP). This patient is likely to suffer from:

1-PCOS
2-Premature ovarian failure
3-Turner syndrome
4-Central amenorrhea
5- 1 and 5 are correct

Define the Rotterdam criteria to diagnose PCOS.

Stem *Benjamin is a 30-year-old lawyer presenting with concerns for* ***hair loss*** *over the past 12 months. This is the first consultation with a GP since the initial COVID restrictions in 2020.* ***What would you ask, examine, investigate and manage or refer****?*

Additional Stem *Benjamin returns 5 years later with difficulties achieving and maintaining an* **erection**. *He has recently started a new relationship.* ***What would you ask, examine, investigate and manage or refer****?*

	Androgen def.	Male baldness (*androgenic alopecia*)	Erectile dysfunction
Sx	• Hx of cryptorchidism, testes surgery • Issues w/ puberty, virilisation, fertility • Pubertal development or virilisation. • Genitourinary infection. • ***Coexistent illness*** (e.g. pit. disease, thalassaemia, haemochromatosis). • ***Sexual dysfunction*** • Drug use (medical or recreational). • Unable to conceive • Embarrassment – nil facial hair, small testes (not feeling masculine)	• Gradual onset of hair thinning after puberty (esp. crown and vertex of crown) • Low self-esteem – entire conversation focused on baldness **Check**: ➢ FHx of hair loss ➢ Duration/qty and area of hair loss ➢ Impact of QoL ➢ Assoc. Sx – rash, B Sx, infections, travel ➢ RF for male baldness = obesity	**Medical** • **Lifestyle changes** (diet, reduced PA) • **General health** • **Chronic diseases** (CM, CHF) • **Genetics** • **Current meds, herbals, OTCs, SSRI** • SHx – smoking, EtOH **Sexual** Define nature of sexual dysfn • No Spontaneous AM erections • ED = no ejaculation • Reduced libido • Loss of hair • Gynecomastia • STI issues – d/c and ulcers **Psychogenic** • Depression & performance anxiety • Relationship difficulties (e.g. sexual abuse, Domestic violence)
Signs Exam	**Pre-pub**: Small testes **Pub**: • " + delayed 2nd sex char. (hair, scrotal size, penis) • Gynecomastia • Reduced muscle mass **Post-pub**: • Low mood • Poor concentration • Hot flush and sweats	***Check for scaling, inflammation or scarring***: ➢ Psoriasis, ➢ folliculitis ➢ Cicatricial alopecia – (scarring) inflammatory condition that destroys hair follicles leading permanent hair loss	• Vitals (BP) • Genito-urinary: penis (plaques), testes (size). • Cardiovascular: BP, HR, waist circumference, cardiac examination, carotid bruits. • Neurological: focused neuro examination (e.g. peripheral neuropathy). • DRE – enlarged prostate? (if suspected – FUN WISE sx) • **Mental health exam** – current stresses, previous MH, impact of ED on relationship
DDx	***Primary hypogonadism (testes)*** • Chr. Abnormal (Klinefelter) • Undescended testes • Trauma • Infection (e.g. mumps, orchitis) • Systemic diseases (e.g. hemochromatosis, thalassemia) • RT, chemo, orchidectomy • Meds (spironolactone, ketoconazole) ***Secondary hypogonadism (CNS)*** • Kallman's • Micro/macroadenoma (prolactinoma) • Pituitary trauma or disease, RT, surgery	**If LOCALISED of focal hair loss:** 1) Scarring alopecia ***Infectious*** *= folliculitis, tinea, scalp cellulitis* ***Skin disease****= SLE, lichen, aplasia cutis* 2) Non-scarring alopecia **Intact hair shafts –** *alopecia areata (+ nail pitting), Alopecia syphilitic* **Broken hair shafts** – tinea capitis, post-op alopecia **If DIFFUSE hair loss:** 3) Scarring alopecia= **SLE, or lichen planopilaris** 4) Non-scarring alopecia ***Male pattern baldness*** *(androgenic alopecia)* ***Chemo****therapy /cytotoxic drugs* ***Endocrine*** *(hypothyroidism, hypopit, Sheehan)* ***Diet*** *(Fe, Zn, Cu or Vit D def. or Vit A XS)* ***Drugs*** *(COCP, Li)* ***Stress*** *(post-op, infection, anxiety)*	**Vascular issues**: • CVD • HTN • Atherosclerosis • T2DM - ANS **Iatrogenic**: • **Post-op** • **traumatic** • **Med side effect** BB, ARB, opiates, SSRI, anti-psychotics, antihistamines - cetirizine, cocaine) **Neurogenic**: • SCI, head trauma • Stroke, • Parkinson's • MS • Epilepsy • DM **Structural**: • Peyronie's disease • Congenital chordee • Hypospadias • Old age **Endocrine**: • Klinefelter • Thyroid • Pituitary • Congenital or acquired **Psych**: Stress Anxiety Mental health **Organic**: Gradual loss of AM erection
Comp.	• Increased fat mass + reduced muscle • High OP risk = High # risk	• Higher risk of scalp exposure to sun = ++ SCC and BCC and melanoma risk • Early onset AGA = early onset CAD, MetSyn	• Psychological = low mood, low self-esteem, irritability, loss of masculinity /identity (infertile)
Ix:	*General:* • FBC + Fe studies (thal, haemochromatosis) • Serum PrL • Karyotyping (Klinefelter) • MRI (pituitary/hypothalamic lesion) *Specific:* • Total serum TT • FSH/LH *≥2 measurements of above to diagnose androgen def.	*Physical Exam* ➢ Vitals *General:* • FBC + Fe studies (ferritin) • Hyperandrogenism studies (PrL, FSH, LH, DHEAS) • ANA • Vit D levels • TSH	*General:* • FBC + Fe studies (**thalassemia or haemochromatosis**) • Fasting lipids • Fasting BSL (HbA1C) - ?**diabetes** • LH/FSH (**hypogonadism**) • E2/TT (**as long as TT > 5 = enough to get erection**) + DHEA, FAI • PSA, PrL *Unless indicated:* • **TFT** – *hypothyroid* • **Karyotyping** – *Klinefelter* • **Brain MRI**- pituitary adenoma (signs of bitemp. Hemianopia, headaches)
DKA-E	*Androgen def. due to poor testicular function due to testes or pituitary gland* • *5 in 1000 men* • *I/C/E*	1 in 2 men > 40 yo	• ***Educate to address psychological issues*** linked with ED, such as relationship difficulties, sexual performance concerns, anxiety and depression "many men have these issues" • ***Normal for many men over the age of 80*** • ***Discuss sexual misinformation***: esp. sufficient arousal and lubrication, and set realistic expectations
Non-pharm	None	Conservative Mx: ➢ Wear a wig or hair extensions (safest) ➢ Protection of scalp - suncreen	**1st line = Address modifiable risk factors** ➢ **Stop meds** (e.g. anti-HTN, anti-depressants, anti-psych causing erectile dysfn ➢ **Lifestyle** = stop smoking, alcohol, improve diet and exercise, ➢ **Check compliance** = diabetes and CVS meds
Pharm	***Testosterone replacement therapy (TRT)*** • Injectable →Oral →Gel, cream, patch ***CI of TFT*** • known prostate or breast cancer • Haematocrit > 55%	No treatment will completely reverse process (varying response to treatments) ➢ ***Topical minoxidil 2-5****% (least effective)* ➢ ***Oral finasteride 1mg daily*** *= improves hair growth and reduce hair loss* ***A/E*** *= sexual dysfn, +++ gynecomastia and monitor PSA baseline for prostate cancer* ➢ ***Oral dutasteride 0.5mg daily*** (indicated for BPH but can also be used for hair loss)	**Administration / CI** 1. **PDE5 inhibitors (sildanefil)**: • MUST be trialled 7-8x + take on empty stomach • Requires sexual stimulation to work / • A/E = headache, flushing, dysperpsia, myalgia • CI = LA or SA nitrates 2. **IV vasoactive drug (alprostadil)**: • Max usage 3x/week / • priapism 3. **Vacuum rings (urologist referral)**: • those who do not want drugs or CI for drugs / • numbness • painful ejac.
Surgery	➢ pituitary tumour resection	Hair transplant	**Penile prosthesis**: • Irreversible surgery that eliminated normal function of corpus cavernosa **Vascular surgery**: • Arterial bypass and venous ligation to increase arterial inflow and decrease outflow
Refer	PBS prescription for TFT needs referral from: ➢ Endocrinologist (paeds if < 14.5 years) ➢ Urologist ➢ Registered member of Australian chapter of sexual health medicine	➢ Refer patients to Better Health Channel website for more info ➢ Adequate sun protection ➢ Psychologist for counselling	***Indicators for referral***: • Level of GP training/experience. • Patient request. ***Refer to endocrinologist***: • Complex endocrine disorders ***Refer to urologist***: • Pelvic or perineal trauma, Penile deformities, Treatment failure (e.g. poor or non-responders to meds) ***Refer to psychologist (if organic)***: • *complex issues (couples counselling)*
F/U	➢ Times regular bloods = TT, LH, FSH ➢ 1-2 year DEXA scans ➢ FBC checked 3/12 after Rx then yearly		