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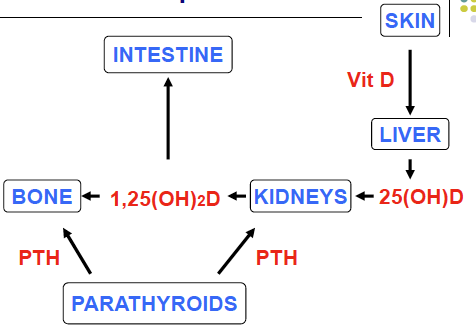
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# Calcium, Phosphate and Vitamin D Disorders

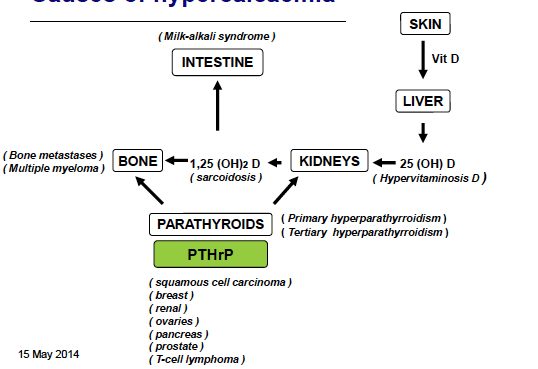
**Calcium Homeostasis**

* Coordinating mechanisms



* Calcium sensing receptor
  + Member of superfamily of G-coupled membrane proteins
  + Response to hypercalcaemia in the parathyroid gland
    - Normally exerts a tonic inhibitory action on parathyroid hormone secretion (when calcium within normal range)*.* Ie Ca increase corresponds to decrease PTH
      * Role for cinacalcet – a calcimimetic
      * IC50 – [Ca] at which 50% of PTH secretion is inhibited.
        + Increased IC50, higher Ca level at which PTH inhibited 🡪 benign familial hypercalcemic hypocalciuria (No Rx req, A/D condition)
        + Hypercalcaemia with normal Ca excretion (may be low), PTH normal
        + Decreased IC50 – Familial autosomal dominant hypocalcaemia: Normal PTH, increased urinary calcium excretion 🡪 nephrolithiasis, maintain Ca in normal to low range to prevent recurrent urinary stones
  + Response to hypercalcaemia in the renal tubules
    - Activation of calcium sensing receptor by hypercalcaemia promotes calciuria via inhibition of ADH action
  + Calcimimetics
    - Mimic extracellular Ca, binds to receptor, reduces PTH secretion, treats primary and secondary hyperparathyroidism
    - Cinacalcet, maintains normocalcaemia in primary hyperPTH

**Causes of Hypercalcaemia –** Remember thiazides, lithium can cause hyperCa

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**Primary Hyperparathyroidism**

* Presentation: mainly asymptomatic, mildly elevated Ca with normal or elevated PTH
* Natural Hx
  + [Ca] did not increase until year 13, PTH did not decrease, creatinine did not worsen, disease progression seen in 38% pts, 100% if symptomatic, BMD changes occurred after 8y with ~ 10% decline thereafter
* Rx – surgery vs medical vs observation
  + Surgery appropriate in most pts with asymptomatic hyperparathyroidism, because hyperCa often associated with mild neurocognitive effects. Further evidence supporting this is that Sx causes decreases in fractures, reduced kidney stones
    - Guidelines exist for selecting pts: absolute [Ca] + skeletal [fragility fracture OR T score <-2.5] + Renal [CrCl <60, increased 24hr Ca excretion + nephrocalcinosis]
  + Medical: cinacalcet, only for those who wont tolerate Sx, bisphosphonates for those at high osteoporosis risk 🡪 they don’t change [Ca]
  + Observation: natural Hx 🡪 no change in [Ca] over 13y

**Role of 1,25(OH)2D**

* Hereditary Vitamin D Resistance Syndromes
  + mutation of vitamin D receptor within the nucleus of the cell
    - Osteomalacia, hypocalcaemia, secondary hyperPTH, normal 25 vitamin D, increased 1,25 vit D
  + Inactivating mutations to 1-alpha OHase
    - Osteomalacia, hypoCa, secondary hyperPTH, markedly decreased 1,25 OH vit D
* Idiopathic infantile hyperCa
  + 1,25 🡪 1,24,25 vit D (inactive) by 24 OHase, inactivating mutation causes Hypercalcaemia with decreased PTH, increased 1,25 vit D
* Regulation of 1-alpha hydroxylase in renal tubules
  + Stimulated by PTH, hypocalcaemia, hypophosphatemia and decrease in FGF23
  + Inhibited by 1,25(OH2)D3, hypercalcaemia, hyperphosphatemia and an increase in FGF23
* Causes of hypercalcaemia associated with an elevated 1,25-dihydroxyvitamin D: any granulomatous disease classically sarcoidosi
* Relationship between serum 25(OH)D and PTH concentrations
  + Several studies have shown that parathyroid hormone (PTH) levels plateau to a minimum steady state level as serum 25(OH)D levels approach and rise above approximately 75 nmol/L
* Vit D deficiency
  + 51% of Australian women aged 60-79 had vitamin D inadequacy (< 50nmol/L during winter)
* Vitamin D, calcium, BMD and fracture
  + There is good evidence that vitamin D3 plus calcium results in small increases in BMD of the spine, total body, femoral neck and total hip
  + There may be a small benefit on primary fracture prevention and preventing bone loss for those who have inadequate serum levels of 25(OH)D but only when vitamin D supplements are combined with calcium supplements
  + Widespread use of vitamin D for osteoporosis prevention in community dwelling adults without specific risk factors for vitamin D deficiency is probably inappropriate
* Recommendations for management of vitamin D deficiency states
* Endocrine society clinical practice guidelines 2011
  + Adults: 1500-2000 units per day
    - Obese or malabsorption or medications affecting vitamin D metabolism: 3000-6000 units per day

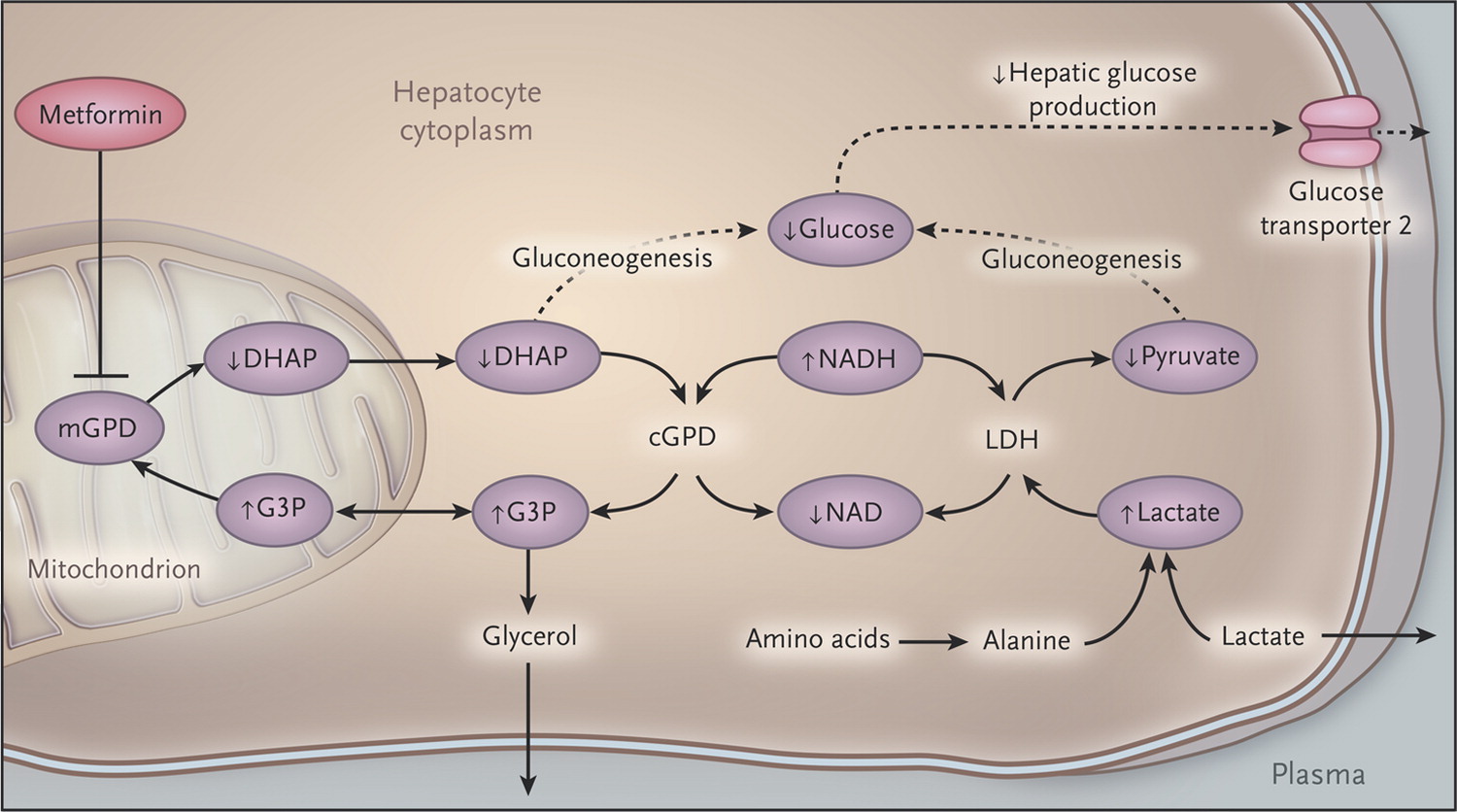
**Phosphate Homeostasis**

* Major regulatory site: renal tubules re-absorbs 85-90% phosphate filtered through the glomeruli, reabsorbed through Na-phosphate co-transporter
  + Low PO4 🡪 increase expression of transporter
  + High PO4 🡪 high FGF23 🡪 internalization of transporter 🡪 phosphaturia. ALSO FGF-23 🡪 decreases 1,25 Vit D 🡪 decreases intestinal absorption of Ca + PO4 ALSO Increase PTH 🡪 phosphaturia
  + FGF23 🡪 acts independently of PTH, decreases Na-PO4 transporter expression, decreases 1,25OHD by decreasing 1-alpha hydroxylase

# Basic Science of Type 2 Diabetes

**Glucose Regulation**

* Fasting:
  + Brain will be using 30% of glucose used by the body -> hence glucose levels would drop when fasting unless you made glucose to maintain those levels
* Amount of insulin made at the time of a meal
  + Exactly proportional to amount eaten, quickly glucose has entered the system, and how significant the glucose load is.
* Diabetes only occurs when there is an absence of insulin
  + Either insulin in the right amount
  + Or at the right speed
  + Or proportional to the right sensitivity
* Mechanisms that underlie development of hyperglycaemia are much more complex
  + Beta cell failure
    - Diabetic pts lost >80% of fx
    - Decreased disposition index 🡪 beta cell produces right amount of insulin to match the meal with regards to given insulin sensitivity. Therefore if low sensitivity high bet-cell insulin utput required to maintain glycaemia
    - Weight gain decreases disposition index prior to development of T2DM
    - Reduced beta cell mass in type 2, and pre-diabetes have lost 50% of mass, and cannot make new beta cells plus functional loss that can be reversed (remission in bariatric surgery in obese pt + early diabetics)
    - Fat spilling from liver into pancreas causing metabolic inhibition of insulin secretion, meaning obese pts are in a fat induced coma
    - Remission of type 2 DM after bariatric surgeries correlates with increased beta cell fx
  + Reduced incretin effect
    - Incretin secretion occurs through L cells in distal intestine and colon, release implies large food load
    - 50% reduction in T2DM
    - Presumed Moa of by-pass Sx, deliver more food to distal intestine to trigger incretin effect
  + Reduced insulin sensitivity (liver, muscle and fat)
    - Interestingly not for all insulin pathways
  + Increased renal glucose re-absorption
    - SGLT2 = high capacity low affinity transporter 🡪 90% reabsorption of glucose in proximal tubules
    - Because glucose load higher, kidney upregulates transporters to reabsorb more glucose, threshold increases for spill over by 2.2mmol
  + Anarchnic gluconeogenesis
    - Dysregulated gluconeogenesis (normally would occur only during fasting), inappropriate fasting glulose despite plasma insulin 2 – 3x higher
    - Presumed pathogenesis through loss of ability to regulate glucagon control via GLP-1 inhibition, somatostatin inhibition and insulin inhibition
* Metformin’s MOA:



# Management of Diabetes

**DKA and HHS: Definitions**

* DKA:

1. Hyperglycaemia (serum glucose > 14 mmol/L)
2. Ketosis (performed on fingerprick testing)
3. pH < 7.3 (bicarbonate < 20mmol/L)

* HHS criteria

1. Hyperglycaemia (serum glucose > 30mmol/L)
2. Minimal ketosis (are unwell so may not be eating and may have an element of ketosis)
3. Serum osmol > 320 mOsm/kg
   * Coma present in 1 in 3
   * Mortality 3x higher with DKA

* Significant overlap between conditions
  + DKA serum glucose usually < 44 mmol/l
  + HHS serum glucose usually > 56 mmol/L

**Complications of Hyperglycaemic Pathologies**

* Dehydration – electrolyte disturbances leading to circulatory instability and arrhythmias
* Vascular thrombosis: coronary, bowel, cerebral, DVT/PE, limb
* Sepsis
* Aspiration
* Non-cardiogenic pulmonary oedema
* Cerebral oedema
  + Mainly children with DKA (0.5-1% almost all patient < age 20 years)
  + Mortality 25%
  + Usually occurs within 24 hours of treatment
  + Recommendations (based on clinical judgment, no trial evidence)
    - Gradual Na and H2O replacement
    - Gradual reduction in blood glucose (3mmol/hr ok if high risk)
    - Add dextrose once achieve BGL targets
  + Treatment options
    - Mannitol 0.25-1.0g/kg
    - ?Dexamethasone
* Precipitants of DKA and HHS
  + Infection (50%)
  + Inadequate insulin
  + Other
    - MI, stroke

**Management**

* Monitoring
  + Glucose hourly
  + Ketones – blood beta-hydroxybutyrate (blood glucometers) - **BEST because insulin causes beta-hydroxybutyrate -> acetoacetate**
  + EUC 2-4 hourly (ABG if arterial line)
* Fluid replacement
  + IV fluid rehydration (normal saline) to correct deficits over 24 hours
    - DKA fluid loss 3-6 L
    - HHS fluid loss 8-10L
  + Lowers BGL alone (increased renal perfusion with increased urine production)
  + Monitor for cerebral oedema
* K+ supplementaiton (K + < 5mmol)
  + Mechanisms hypokalaemia
    - Urinaly loss (osmotic diuresis)
    - Hypovolaemia induced hyperaldosteronism (extracellular shift K+ initially may lead to hyperkalaemia initially)
* Low dose IV insulin infusion
  + IV 0.1U/kg bolus followed by infusion 0.1U/kg per hour (hyperosmolar state use infusion rates lower than this, approximately 1-2 U/hour)
  + Mainly decreases hepatic gluconeogenesis
  + Decreases ketone production (decrease lipolysis and glucagon)
  + DKA serum BG < 11.1 swap to IV dextrose and halve insulin infusion rate (HHS serum BG < 15) to avoid cerebral oedema
* Phosphate:
  + Not routinely replaced
  + Consider if cardiac dysfunction or respiratory depression if phosphate < 1 mmol/L
* DVT prophylaxis
* Resolution
  + Blood glucose < 11 DKA or < 15 HHS
  + Serum anion gap < 12 meq/l
  + Serum bicarbonate > 18 mmol/L
  + pH > 7.3
  + Usually see normal anion gap acidosis with resolution of DKA
  + IV insulin infusion and SC insulin should overlap for 2 hours
  + If patient unable to eat best to continue IV insulin

**DKA in Type 2 DM**

* Well described in patients of African-American descent
* Develop a ketosis prone form of diabetes
* Rapid beta cell dysfunction that reverses with treatment
* Re-characterising DKA in T2DM
  + Should try to characterize an individual who presents with DKA based on their auto-immunity and their beta cell function
    - A = presence of auto-antibodies
    - ß- = low beta cell function, based on C-peptide levels
    - From Northern Hospital data
      * Group A+, ß- (28%): auto-antibodies without beta cell function -> unrecognized T1DM
      * Group A-, ß- (36%): potentially burnt out T2DM
      * Group A-, ß+ (36%): more reversible form of DKA, acute glucose toxicity interfering with beta cell function ability to produce insulin. This group of patients can get off insulin,

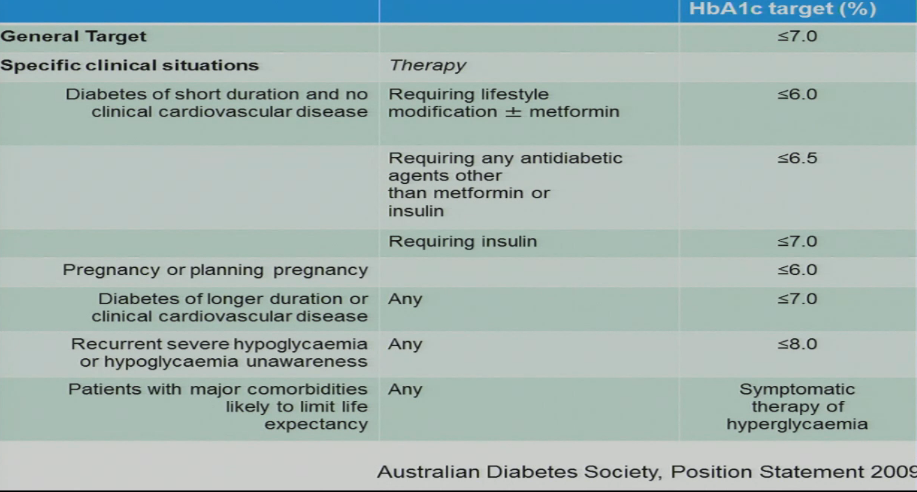
**Inpatient Glycaemia**

* Three areas
  + Critical care
  + General ward
  + Perioperative management
* Glycaemic targets in critical care
  + Conflicting data regarding intensive vs. conventional treatment
    - DIGAMI study: 11% mortality benefit in aggressive arm
    - NICE SUGAR: increased mortality and hypoglycaemia in aggressive arm
  + Portland study: 30% RR of deep sternal wound infection in patients post CABG with intensive BSL treatment – **post CABG patients will often be on insulin infusions**
* General ward
  + **Unrecognized hyperglycaemia/diabetes in hospital is associated with increased mortality after discharge – it is not known if this is causative or an association**
  + No evidence for current targets used for inpatients (5-10.0)
  + 1 in 3 inpatients have diabetes and 10% have unrecognized diabetes
* Perioperative periods
  + Pre-operative
    - Improved glycaemic control likely to translate to better post-operative glycaemic control (however no end-point studies)
  + Principles peri-operative diabetes management
    - Optimizing glycaemic control reduces infection, wound and metabolic complications
    - The cornerstones of glycaemic control are
      * Intensive monitoring BSLs: aim 4-10mmol/L. Should monitor every 2 hours
      * IV fluids: patients on insulin should receive IV dextrose to minimize hypoglycaemia
      * Insulin: patients on insulin require insulin even if fasting, sliding scales are a guide and should be reviewed daily
  + Hypoglycaemic drugs

|  |  |  |  |
| --- | --- | --- | --- |
| **Class** | **Generic** | **Trade** | **Recommendation** |
| Biguanides | Metformin | Diabex  Diaformin  Nidem | Ideally withhold 24 hours for major surgery |
| Sulphonylureas | Gliclazide  Glipizide  Glibenclamide  Glimepiride | Diamicron  Glyade  Minidiab  Daonil  Amaryl | Withhold day of surgery |
| Glitazones (thiazolidinediones) | Rosiglitazone  Pioglitazone | Avandia  Actos | Withhold day of surgery |
| Alpha 1 glucosidase inhibitors | Acarbose | Glucobay | Withold day of surgery |
| Incretin mimetic DDPIV  GLP-1 agonist | Sitagliptin  Exenatide | Januvia  Byetta | Witthold day of surgery |

* + Insulin types

|  |  |  |
| --- | --- | --- |
| **Type** | **Generic Name** | **Trade Name** |
| Ultrashort (4 hours) | Lispro insulin  Aspart insulin | Humalog  Novorapid |
| Short (6 hours) | Regular insulin | Actrapid  Humulin R |
| Intermediate (14 hours) | Isophane insulin | Protaphane  Humulin NPH |
| Long/basal (up to 24 hours) | Glargine insulin  Detemir insulin | Lantus  Levemir |
| Pre-mixed | Regular/Isophane  Lispro/Protamine | Mixtard 30/70  Mixtard 50/50  Mixtard 20/80  Humulin 30/70  Humalog mix 25 |

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# Lecture 40: Diabetic Complications

**Introduction:**

* Of adult population: 7.6% of adults had diabetes in 2000 (1/2 of these did not know they had diabetes prior to survey)
* Consequences of diabetes mellitus
  + 2-3 fold increase in cardiovascular mortality (cause of death in T2DM in 70-80%)
  + The leading cause of new causes of ESRF
  + The leading cuase of new cases of blindness in working-aged adults
  + The leading cause of non-traumatic lower extremity amputations

**Monogenic diabetes**

* Most common = MODY 3 = HNF1alpha, family Hx +, autosomal dominant, highly sensitive to SFU, need ¼ normal dose,
* MODY2 = glucokinase mutation, mild fasting hyperglycaemia, mild elevated HBA1c, very rarely have complications, controversy about treating these patients. They also have little response to drugs and insulin

**Diagnosis of diabetes**

* Can use HBA1c >6.5%, but only if there are no conditions such as chronic renal dysfx, anemia, haemoglobinopathies, recent blood transfusion (effects RBC half life)
* If other parameters elevated (fasting >7.0, 2hrs OGT >11.1 and random + symptoms >11.1) AND HBA1c <6.5, believe the elevated sugars
* If asymptomatic (of hyperBGL), repeat test to confirm
* Do NOT use HBa1c to Dx gestational diabetes or type 1 DM

**Pre-diabetes**

* 50% with pre-diabetes with progress to full blown diabetes
* Dx: Fasting BGL >5.6 but <7.0 OR OGT >7.8 and <11.1, only need one test and don’t need to be symptomatic
* Rx: Lifestyle > Metformin > placebo in Lancet study; Rosiglitazone > placebo in prevention of full blown diabetes as per DREAM study
* ORIGIN trial 🡪 hyperglycaemia is independent risk factor for cardiovascular events
* Medications that have got evidence to support use: rosiglitazone, metformin, acarbose, insulin glargine

**Type 1 Diabetes Mellitus – Glycaemic Control**

* DCCT Trial, 1993
  + Hba1c achieved correlated with the risk of microvascular complications – exponential risk
  + Target currently: HbA1c of 7
* DCCT Conclusions
  + The cumulative incidence of retinopathy is 50% less with intenstive therapy compared with conventional management
  + Intensive insulin therapy reduced the risk of macro-albuminuria (54%) and microalbuminuria (39%)
  + Reduced the risk of developing clinical neuropathy by 60-69%
  + Not enough cases of cardiovascular events in this trial to make any conclusions
* DDCT/EDIC
  + Followed up the patients from DDCT for approximately 7 years
  + Individuals who had received the intensive therapy in the DCCT trial, although their HbA1c had returned to the same as those in the conventional arm there was a 50% reduction in non-fatal MI, stroke or CVD death **LEGACY EFFECT**
  + This was not related to use of statins, ACE, aspirin etc

**Type 2 Diabetes Mellitus – Glycaemic Control**

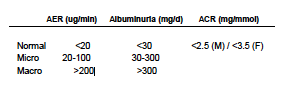
* Best agent for glycaemic control once T2DM Diagnosed?
  + Rosiglitazone, in accordance to ADOPT trial comparing rosiglitazone vs glibenclamide vs metformin. Rosiglitazone > metformin > glibenclamide, in terms of HbA1c
* PPAR-gamma receptor activators
  + Rosiglitazone and pioglitazone
  + SE = fluid retention and weight gain and CCF, Controversy about rosiglitazone and risk of AMI, 2007 meta-analysis suggested p=0.003 for association, pioglitazone in the clear
  + All thiazolidenidiones increase fracture risk
* GLP-1 analogues
  + Increase effect of insulin, decrease glucagon, decrease HBa1c, decrease weight and appetite
  + Low risk of hypos unless used with SE
  + Severe SE = nausea
* DPP4 inhibitors – the ‘gliptins’
  + Increase t(1/2) of GLP1
  + Tablet form, byetta is sc injection
  + Less nausea than GLP-1
  + Weaker HBA1c drop cf GLP1, no weight loss effect and potentially more CHF hospitalizations (reported in Circulation 2014) but in NEJM 2015 no difference found and non-inferiority confirmed. Acute pancreatitis was more common but numerically very small, as was pancreatic cancer
* SGLT2 inhibitors
  + Inhibit the high affinity low capacity transporter in renal proximal tubule
  + NEJM2015 – Empagliflozin compared to placebo decreased primary outcome, death from cardiovascular cause, death from any cause and hospitalization from heart failure
  + BUT… SE include non hyerglycaemic ketoacidocis
* Surgical Rx
  + 2 studies to support superiority, with remissions achieved and glycaemic control of rou-en-Y (HBA1C decrease)
* UKPDS trial
  + Also demonstrated an exponential increase in microvascular complications as you go up HbA1c levels
  + In contrast to this – linear increase in myocardial infarction and this actually continues into the normal range with no flattening of the curve.
  + **Microvascular endpoints p <0.01 in reduction with intensive control**
  + Intensive glycaemic control (T2DM)
    - Did not reach statistical significance with regards to MI **p = 0.052, stroke p=0.52**
  + Follow-up of these patients after median 8.5 years of follow-up (**legacy effect** of earlier glucose control)
    - MI rates became significant with improved glycaemic control
* Comparison of intensive glycaemic control studies in type 2 diabetes
  + No trials demonstrated any benefit in terms of macrovascular outcomes
  + Increased mortality in the intensively treated group in ACCORD study thought to be related to severe hypoglycaemia
  + NEJM 2015: Follow up of glycaemic control and cardiovascular outcomes in type 2 Diabetes: Long term follow-up of veterans affair trial, which showed there was no significant difference during the intensive treatment of cardiovascular outcomes, but after showed reduction in MACE but no reduction in all cause nor cardiovascular mortality

**Type 2 Diabetes Mellitus – Blood Pressure Control**

* Linear relationship for both macro and microvascular complications for hypertension
* Liner relationship for macrovascular but exponential relationship for microvascular outcomes
* UKPDS: **Blood pressure control 🡪 no legacy effect after Rx 🡪 benefit only during treatment**
* HOPE study: ramipril vs. placebo with subgroup of patients with type 2 DM:
  + Significant risk reduction with regards to CVD, MI, diabetes complications and any nephropathy
* ONTARGET: No difference between ramipril and telmisartan with regards to primary outcome (combined cardiovascular outcome)
  + No benefit of combining the two and associated with more adverse events
* ADVANCE:
  + Had blood pressure arm
  + Added in combination of perindpril-indapamide
  + Addition of this combination: 14% relative risk reduction in all cause mortality with modest reduction in BP.
* ACCOMPLISH Study:
  + Addition of amlodipine or hydrochlorothiazide to benazepril (ACEI) in type 2 diabetics with inadequately controlled BP on benazepril
  + No difference in terms of systolic and diastolic BP between the two agents
  + But significant decrease in deaths from cardiovascular cuases with addition of amlodipine rather than hydrochlorothiazide
* ACCORD:
  + Aimed to achieve normal blood pressure (in addition to normoglycaemia) – achieved a SBP of 119mmHg with a difference between the two arms of 14mmHg
  + **No conclusive evidence that a strategy targeting normal SBP, compared with a standard SBP goal, reduces a composite of major CVD events in high risk patients with type 2 diabetes, in the setting of good glycaemic control**
  + There was a higher risk of SAE in the intensive BP group, **but also a 41% lower stroke rate.** The stroke effect is consistent with other BP trials.
  + SBP goal < 120mmHg may reduce strokes in patients with diabetes like those in ACCORD (NNT = 89 for five years)
  + The number of major coronary disease events was far higher than the number of strokes

**Nephropathy trials in types 1 and 2 diabetes**

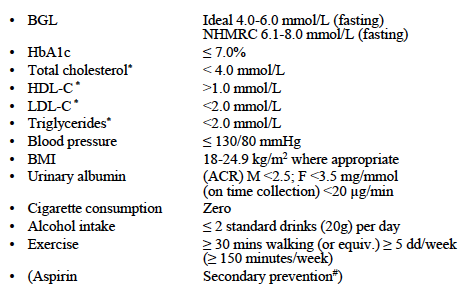
* Evolution of diabetic neuropathy
  + Note may be a period of hyperfiltration in some patients
  + Deterioration of GFR correlates with transition from microalbuminuria to macroalbuminuria
* Diabetic nephropathy annual screening recommendations
  + Measure albumin excretion rate annually in timed overnight or 24 hour urine sample OR
  + Measure albumin: creatinine ratio in spot urine



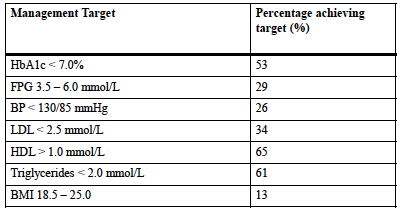
* Clinical end points
  + IDNTL irbesartan reduced the incidence of the composite end point (doubling of sCr, ESRD or death) by 20% vs. placebo and 23% vs. amlodipine in patients with type 2 diabetes, hypertension and proteinuria
  + RENAAL (losartan): the only trial demonstrating a significant reduction in risk of ESRF (RRR = 28%, p = 0.002) in patients with type 2 diabetes and proteinuria. Significantly reduced risk of HF hospitalization in this group of patients
  + **No significant reduction in macrovascular complications in either RENAAL or IDNT**
  + **Slow progression from microalbuminuria 🡪 macroalbuminuria 🡪 ESKD but does not prevent it**
* **Goals: Reduce BP <130/80, in pts with CKD, add diuretic because subclinical fluid overload can exacerbate hypertension 🡪 end point is to up titrate until symptomatic or BUN going up**
  + Hyperfiltration may be an earlier manifestation of kidney disease before there is a decline in eGFR
    - MDRD would suggest these patients have a lower eGFR than estimated via nuclear methods
  + Even though these patients have high GFR they actually have a much faster rate of decline than baseline
    - May intervene earlier

**Cardiovascular trials in type 2 diabetes**

* Causes of mortality in men with and without diabetes
* High risk of CV events in type 2 diabetes
  + Suggest diabetes as a cardiovascular risk equivalent
  + Risk of myocardial infarction is equal in non-diabetics who have had MI and diabetics who have not had an MI
* **Primary prevention studies with statins in DM**
  + Simvastatin 40mg daily reduced the risk of heart attack, stroke and of revascularisation by about one-third (intention to treat)
    - Effective irrespective of cholesterol level (or age, sex, or other treatments)
* Secondary prevention in diabetes – TNT
  + Treating to New Targets – Diabetes Substudy: Atorvastatin 90mg versus 10mg daily
    - Main study in 10,000 patients with established coronary heart disease and LDL cholesterol of 3.4-6.5 mmol/L
    - Post hoc analysis of 1501 diabetics (15% of diabetes)
    - Study end: LDL 2.0mmol/L (80mg) vs. 2.5mmol/L (10mg)
    - Diabetes patients: **25% decreased rate of cardiovascular events, trend towards reduced CV mortality matched by increase non-CV mortality!**
  + Fenofibrate intervention and event lowering in diabetes (FIELD)
    - **Non significant primary endpoint** but when they looked at total cardiovascular events there was a **significant reduction in total CVD with a HR of 0.89** in the fenofibrate group compared with placebo giving a NNT of 70
  + ACCORD Lipid Trial: also looked at fenofibrate, **no significant benefit in additing fenofibrate to simvastatin**
    - Subgroup analysis suggesting heterogeneity in response to combination therapy by gender and by presence of significant dyslipidemia
      * Seemed to be some benefit for men, in particular for those with high triglycerides and low HDL cholesterol
* Diabetes Australia Goals for Management 2012/2013



* What patients achieve targets



**Empagliflozin in diabetic individuals with overt cardiovascular disease (September 2015)**

The cardiovascular effects of diabetes drugs have been evaluated in a growing number of trials. In a trial designed to evaluate the sodium-glucose co-transporter 2 (SGLT-2) inhibitor empagliflozin and cardiovascular outcomes in patients with type 2 diabetes and established cardiovascular disease (CVD), 7028 patients were randomly assigned to empagliflozin or placebo once daily [[1](http://www.uptodate.com/contents/whats-new-in-endocrinology-and-diabetes-mellitus/abstract/1)]. The majority of patients were taking metformin, antihypertensives, and lipid-lowering agents, and approximately half in each group were taking insulin.

After three years, the primary outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in fewer patients assigned to empagliflozin than to placebo (10.5 versus 12.1 percent), driven by a significant reduction in risk of death from cardiovascular causes (3.7 versus 5.9 percent). The difference in glycemia between the groups was minimal (glycated hemoglobin [A1C] 7.8 versus 8.2 percent), suggesting that extra-glycemic effects of the drug were responsible for the CVD outcome. **Whether empagliflozin or other SGLT-2 inhibitors will have similar CVD effects in persons with type 2 diabetes who do not have overt CVD is unknown.**(See ["Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'SGLT2 inhibitors'](http://www.uptodate.com/contents/management-of-persistent-hyperglycemia-in-type-2-diabetes-mellitus?source=see_link&sectionName=SGLT2+inhibitors&anchor=H457938#H457938).)

**Bariatric surgery for diabetic patients and glycemic control (September 2015)**

Bariatric surgical treatment of obese patients with diabetes results in significant sustained weight loss (20 to 30 percent after one to two years) and, in parallel, large improvements in blood glucose control. However, there are few data on long-term success rates in maintaining weight loss and glucose control. In a report of five-year outcomes (53 patients) from a randomized trial evaluating gastric bypass, biliopancreatic diversion, or medical therapy (pharmacologic therapy, education, lifestyle modification) in 60 patients with obesity and type 2 diabetes, diabetes remission (A1C <6.5 percent without diabetes medication) was maintained in only 56 percent of patients in the surgical groups who had experienced remission at two years [[2](http://www.uptodate.com/contents/whats-new-in-endocrinology-and-diabetes-mellitus/abstract/2)]. Compared with the medical group, patients treated surgically had significantly lower diabetes and cardiovascular medication use, serum total and LDL cholesterol, and weight, although weight regain occurred in both surgical groups (+6.09 and +4.56 kg, respectively). The study was not powered to assess long-term diabetes complications. Longer-term follow-up of microvascular and macrovascular complications and mortality are required before laparoscopic banding or other bariatric surgery procedures can be routinely recommended for the treatment of persistent hyperglycemia in obesity-related type 2 diabetes. (See ["Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Surgical treatment of obesity'](http://www.uptodate.com/contents/management-of-persistent-hyperglycemia-in-type-2-diabetes-mellitus?source=see_link&sectionName=SURGICAL+TREATMENT+OF+OBESITY&anchor=H1665282#H1665282).)

**Diabetic retinopathy**

* Aneurysms, hypertension, micro-infarcts cause areas of ischaemia 🡪 Release VEGF, EPO, hypoxia induced factor 🡪 proliferation of new vessels with a significant risk of leakage = rationale for laser Rx, and bevacizumab injections into eye for proliferative retinopathy

# Bariatric Surgery

Currently, there are three types of bariatric surgeries being performed:

1. Malablsorptive, where weight loss is due to absorptive dysfunction caused by the reconstruction of the small intestines – the biliopancreatic diversion is considered a malabsoptive procedure.
2. Restrictive procedures, such as banding, simply limit the size of the stomach. The patient loses weight because they will feel full or satiated after consuming very little food.
3. In combination procedures, such as a Roux-en-Y Gastric bypass, the size of stomach is reduced by creating a small pouch, but the small intestines are also altered to limit absorption, particularly the absorption of foods high in fat and in carbohydrates.

Roux-en-y: in 1977 the roux-en-y configuration introduced to replace the loop gastro jejunostomy. The bypassed section is re connected to the intestine forming a “Y” shape. This modification improved the technique by: lessening the tension on the jejunal loop, eliminating bile reflux in the pouch, and added a malasorptive component.

Dumping syndrome

* When undigested (hyperosmolar) contents of stomach move too rapidly to SI
* Symptoms: abdominal cramps, nausea and diarrhoea, flushing, palpitations, lightheadedness
* Hypoglycemia may follow as dumping of food triggers pancreas to release excessive insulin
* exacerbated by high energy, high GI foods

Gastric Banding

- An adjustable silicone band placed immediately beneath gastro oesophagogastric jc, so supraband pouch of stomach cannot accommodate meals. The patient loses weight because they will feel full or satiated after consuming very little food.

* Mechanism of action: with optimal band adjustment pressure of 20-30 mm Hg produced which after a standard meal induces powerful intermeal satiation. Distention of small pouch may activate gastric sensory receptors that via the vagus nerve induce satiety (animal studies). Alternatively direct pressure or contact of the band on the gastric wall might induce satiety
* This procedure affects range of food that can be consumed & conditions eating behaviour
* Rapid weight gain with reduced satiety reported 1-2 days after band removal



This is consistent with other larger bariatric studies; **equivocal improvements often seen in HTN, Dyslipidemia but substantial improvements frequently seen for Type 2 Diabetes13.**

**Indications**

* Morbid obesity (BMI > 40 kg/m2), significant co-morbidity AND BMI >35, all non surg methods tried and no weight loss, pt fit for anaesthesia and Sx, pt commits to long term f/u

# Obesity

**Measurement of Body Mass**

* Prevalence (% has actually increased since 2003):
  + 67.5% of men overweight + obese, 52.1% women
  + Obesity increases mortality, visceral fat 🡪 worst outcome, in terms of RR for mortality, waist circumference > waist-hip ratio

**Consequences and Manifestations of Obesity**

* Metabolic
  + Type 2 DM (obesity is the main driver of type 2 DM, fat provides significant insulin resistance)
  + Dyslipidemia
  + Hyperuricaemia
* Cardiovascular: hypertension, increased risk of coronary heart disease
* Respiratory
  + Obstructive sleep apnoea
* Orthopaedic: back pain, osteoarthritis
* Dermatological: acanthosis nigricans, skin tags, intertrigo
* Gastrointestinal: NASH, reflux, oesophagitis, gall stones
  + Gallstones are probably related to dieting rather than obesity
* Psychosocial: social isolation and discrimination, decreased self-esteem, binge-eating disorder and bulimia
* Reproductive system: obesity is most common cause of PCOS
* Renal system: proteinuria improves with weight loss in obesity
* Other: increased risk of breast and other cancers, increased intracranial pressure

**What Causes Obesity?**

* Medical Causes of Weight Gain: cushings, hypothalamic, prada-willi etc
* Regulatory mechanism of weight
  + In arcuate nucleus:
    - Neuropeptide Y cells which also express agouti-related peptide -> both hormones may you hungry
    - POMC cells: cleave MSH from ACTH -> removes hunger. Also produce CART (cocaine and amphetamicine regulated transcript) which inhibit food intake
  + Only one hormone that makes you hungry: ghrelin. Gastric bypass suppresses ghrelin. CCK is a satiety factor, triggered by gut distension, relayed to brainstem via vagus 🡪 meal termination
  + Note insulin inhibits hunger, but when administered subcutaneously is associated with weight gain. If administered centrally inhibits hunger.
    - Levemir is weight neutral as attached to a fatty acid molecule which improves brain penetration
  + Liraglutide: long acting glucoagon-like peptide 1 agonist (attached to fatty acid molecule)
    - Inhibits food intake better than exenatide
  + Only leptin does not go up and down with meals!
* Weight is homeostatically regulated 🡪 change in energy expenditure acts to minimize weight change
  + Animals maintained steady state when overfed or underfed
  + In humans, it seems that steady state weight is achieved in those that are force fed high calorie by increasing their spontaneous activity ie figity
* Weight is genetically determined 🡪 identical twin studies
* Mutations that are monogenic 🡪 MCR-4, OB [leptin deficiency]

**Management of Obesity:**

* Weight loss (rapidly)
  + RCT evidence: Rapid weight loss program (12 weeks) vs. gradual weight loss program (36 hours), VLED had more people achieve target weight because of compliance, popular diets work about the same, efficacy mitigated by compliance [hunger primordial and driven by hormonal adaptation]
* Pharmacotherapy:
  + Available in Australia [] = off label use
    - Phentermine (Duromine): suppresses hunger but can only use for 3 months
    - Orlistat: does not suppress hunger 🡪 malabsorption
    - [Topiramate – Topamax)]: available for epilepsy, migraine and neuropathic pain but causes weight loss
* Bariatric surgery [discussed elsewhere] – most successful long term, considered in pts with BMI >35 + co-morbidities [lipid profile, Trigs, HDL, LDL improve, hypercholesterolaemia no improvement], aus do sleeve gastrectomy commonly
  + Mortality reduction only through observational studies, no RCT showing mortality benefit

# Osteoporosis Prevention and Treatment

* Bone biology and osteoporosis: Cells include osteoclast [from mononuclear cells, reabsorb bone], osteoblast [from mesenchymal cells – synthesise osteoid and mineralize bone, inhibit osteoclast activity] and osteocytes [derived from osteoblast trapped in osteoid, mechanosensing role, secrete FGF23 and sclerostin 🡪 binds to LRP5 on osteoblast 🡪 inactivate it through inhibition of Wnt signalling]
  + Microstructure of bone 🡪 mineral 65% [hydroxyapatite = calcium phosphate + OH] + matrix 35% [Type 1 collagen]
  + Macrostructure of bone 🡪 Cortical bone = dense outer shell, 80% skeletal mass, 95% cortical = radial head’ Trabecular bone = 20% mass, delicate trabeculae plates, sponge like, 75% vertebrae = trabeculae, fem head = 50:50 cortical/ trabeculae
  + Bone modeling 🡪 uncoupled synthesis of bone during growth
  + Remodeling 🡪 mineral homeostasis + reparation of microstructural damage with resorption + re-synthesis
    - Mechanism 🡪 osteoclasts activated to resorb [RANK-L potent signal, OPG = decoy of RANK-L, cathepsin K involved in bone resorption] 🡪 osteoclastic apoptosis 🡪 osteoblast synthesise osteoid 🡪 mineralization
  + Bone mass 🡪 peaks age 25 then declines
* Osteoporosis pathology 🡪 breakdown of horizontal + vertebral trabeculae + thinning of cortical bone with incr porosity
  + Glucocorticoid induced osteoporosis 🡪 fracture at higher BMD, and osteoporosis occurs more commonly in Trabecular bone [eg vertebrae]
  + In post menopause, oestrogen normally decreases RANKL, therefore lack of oestrogen 🡪 increase RANKL 🡪 survival + activation of osteoclast 🡪 negative bone balance
* Secondary osteoporosis
  + Hyperthyroidism, CKD, CLD, vitamin D deficiency, hyperparathyroidism, hypogonadism, Drugs [corticosteroids, anti-epileptics, GnRH agonists, aromatase inhibitors]
* Secondary Prevention [NNT = 20]
  + Previous fracture = most important risk factor for more osteoporotic fractures!
  + All minimal trauma fractures + asymptomatic vertebral fracture [1/3 only detected, defined when height <80% width] 🡪 Rx. NOTE fracture cascade 🡪 increasing risk of future fracture with incident fracture, also increasing mortality
    - Must be Vit D and Ca replete [1200mg/d = average intake = 2 caltrate tabs] + anti-resorptive OR anabolic Rx
* Primary Prevention [NNT >100]
  + Cut-off = Treat those with 10yr fracture prob = 10%, estimated based mainly on BMD, age [Aus = >70], falls = garvan.
  + Generally BMD <-2.5SD based on T score, for glucocorticoids BMD cut-off = <-1.5. Fracture risk starts at time of initiation, no safe dose, age is most important effect modifier and osteoporosis more sign
* Non-pharmacological Rx
  + Falls prevention, hip protectors have evidence only in clinical trial setting but real life have low compliance
* Pharmacological Rx
  + Ca + Vit D 🡪 1200mg req, Rx Vitamin D only if deficient, in institutionalised adults, if <60nM 🡪 Rx as get falls reduction
  + Bisphosphonates: PO [Alendronate, risedronate, IV = Zoledronate] 🡪 reduces hip and non-hip fractures, but vertebrae > non-vertebrae b/c prevents trabeculae resorption particularly, NOTE zoledronic acid, once yearly IV infusion, caused increase in serious AF! Also GFR >35, Vit D and Ca replete. Delay Rx by 2/52 if fracture.
    - ONJ 🡪 caused by impaired healing after tooth extraction with exposed bone 8/52 after extraction, usually after minimum 2y duration Rx, mainly mandible, last stage mx = Sx debridement
    - Atypical femoral fracture 🡪 stress fracture, usually after 7yr, prodrome of mid thigh pain, SE Asians higher risk, subtrochanteric fracture, simple typically not comminuted.
      * Risk ceases after 1 yr cessation 🡪 further argument for bisphosphonate holiday in those at low risk
    - Possibility of holiday 🡪 FIT study with alendronate suggested that BMD peak occurs 4-5 y and plateus, and if you take bisphosphonates off, BMD about the same until about 1y. Decision to stop should be based on fracture risk after decision to stop Rx considered [Age, BMD, falls etc]
  + Raloxifene 🡪 PBS for older women, reduces vertebral fractures, no prevention non-vertebral fractures
  + Hormone Replacement Rx 🡪 reduces hip fracture [HR 0.76], increases breast Ca, stroke, PE, CAD
  + Denosumab 🡪 Ab against RANK-L [replicating effect of OPG], increases BMD vertebral + non vertebral, decreases fracture rates throughout skeleton, ONJ cases rare [eTG]. ALSO large increases in BMD lost pretty quickly after cessation [cf bisphosphonates]. On PBS as first line Rx. Note cannot combine with others
  + Strontium 🡪 Dual anti-resorptive + increase tissue material strength, note same column as Ca on periodic table. Increased BMD = decreased fracture rate, Black box for myocardial infarction, VTE + causes diarrhoea
  + Teriparatide 🡪 synthetic PTH, if intermittent causes increases osteoblast activity, after 18/12 stimulates osteoclast activity by increased RAK-L and decreased OPG from PTH receptor on osteoblast, gives 18/12 anabolic window. PBS reserved for severe osteoporosis [BMD <-3 AND >=2 Minimal trauma fractures AND 1 fracture despite 12/12 anti-resorptive AND must be only agent AND only for 18/12], black-box warning for osteosarcoma

# Lecture 43 – Pituitary and Adrenal Disorders

**Acromegaly (GH)**

* Physiology of GH: Effector is IGF-1, GH released pulsatile from ant pit, released stimulated by GHRH, inhibited by stomatostatin, SRIF, insulin. Feedback inhibition via IGF1 and GH
* Acromegaly: Dx usually delayed by 12y
  + Acral changes/enlargement: progressive – face/jaw and hands/feet
  + Visceral/metabolic changes: cardiomegaly, HTN, DM, sleep apnoea, arthritis
  + Increased incidence of colon Ca malignancy x4
* Diagnosis:
  + Hormonal 🡪 IGF-1, lab specific and age corrected, no variation with meals, but false positives and negatives exist, OGTT 🡪 75g load, then GH every 30min for 2h, normal response is to suppress and will be <1ng/ml, in acromegaly can inc, dec or no change but will NOT suppress <1ng/ml
    - Don’t ever do random GH level
  + Structural 🡪 MRI
  + Assess end-organ damage 🡪 ECHO, ECG, visual fields, sleep study, other pit hormones, colonoscopy
* Rx
  + Surgical first 🡪 transphenoidal, with 24hr potop GH <1ng/ml 98% predictive of cure, low mortality 1%
  + Medical 🡪 somatostatin receptor ligands: longer acting, inhibit GH secretion, octreotide, lantreotide, pasireotide. Ideal to have high affinity for subtype 5 receptor which is what pasireotide does. SE = gallstones/ sludge
    - New Rx = pegvisomant 🡪 prevents dimerization of GH R 🡪 prevents IGF-1 production, use in addition to uncontrolled GH release in somatostatin Rx pts
    - Dopamine agonists cabergoline and bromocriptine can be used as they suppress GH release
  + Monitoring response 🡪 difficult to assess: normalization of IGF-1 or OGTT <1ng/ml
  + Follow-up 🡪 Life long f/u, aggressive Rx of metabolic RF, GH level is the single most important determinant of mortality in acromegaly

**GH deficiency**

* Characterised by inc fat, dec muscle, decreased BMD, decreased QOL
* Dx:
  + Screen with IGF-1 (low useful but false negatives)
  + High sen/specificity with ITT
* Rx:
  + Benefits 🡪 increased skeletal integrity + inc QOL
  + Start low, aim normalize IGF-1

**Cushing’s Syndrome**

* Eitiology: Cushings disease (66%), adrenal adenoma > ectopic ACTH > adrenal carcinoma > nodular adrenal hyperplasia
* Clinical suspicion: centripetal adiposity + incr weight upper back + limb/ buttock wasting + proximal myopathy + HTN + osteoporosis + DM + hirsuitism + livid wide striae
* Dx:
  + Lots of difficulty and controversy
  + Screening tests (1) 24hr urine free cortisol [look for >3x, if not >3x then need to re-test] (2) late night cortisol = loss of diurnal variation (3) overnight dexamethasone suppression test = impaired corticosteroid negative feedback + dexamethasone does not interfere with assay
  + Confirmatory tests [can repeat or do two diff ones as per MKSAP] (1) 24hr urine cortisol (2) o/n DM suppression test [give 1mg 2300, take cortisol 0800, suppress to <50]
  + Differentiate cause:
    - Plasma ACTH [low 🡪 adrenal; high 🡪 pituitary, ectopic, v high 🡪 ectopic]
    - High dose DMS test 🡪 suppresses cushings disease ~ >90% supression, not ectopic ACTH
    - Dexamethasone infusion test 🡪 as above
    - Petrosal sampling, basal and after CRH. If 1.5:1 grad pre, then 3:1 post CRH, then pit source, may lateralise
    - Localise: MRI, CXR, CT adrenals
* Rx
* If adrenal 🡪 surgery
* Pituitary 🡪 surgery + replacement therapy VS pasireotide
* Ectopic 🡪 Sx if possible, consider adrenelectomy, also medical Rx 🡪 ketoconazole

**Hyperprolactinaemia (Prolactinaemia)**

* Physiology: Anterior pit hormone, inhibitory control via dopamine, thyroid hormones, GnRH fragments, stimulatory control via TRH. Effects include breast development and reproductive effects
* Pulsatile secretion, max at night, min at 8am
* Presentations, very common
  + Amenorrhoea 🡪 osteoporosis/ galactorrhoea/hypogonadism/ sexual dysfx
* Causes of hyperprolactinaemia
  + Drug causes: phenothiazones, olazepine/ risperidone, metoclopramide
  + Other causes: Post-partum, CRF, seizure, hypothyroidism, chronic renal failure (accumulates), hest wall trauma (eg herpes zoster)
  + Pituitary/hypothalamic cause: pit tumour (most common is adenoma, microadenoma most common), stalk trauma as dopamine comes down pit stalk
  + Macroprolactinaemia: prolactin aggregates in plasma – false elevation = pseudohypoprolactinaemia
* Rx
  + Can monitor if menstrual cycles present or postmenopause and tolerable galactorrhoea
  + Microprolactinoma, extent of prolactin indicates size of tumour, only caused by tumour if prol >300ng/ml
    - Medical treatment with dopaminergic agent: bromocriptine, cabergoline (shrinks 93%), quinagolide
  + Macroprolactinoma
    - Medical therapy with cabergoline (SE = nausea, hypotension, valve disease, better tolerated than bromocriptine, bromocriptine used if pregnancy anticipated as more safety data)
    - Surgery if feasible and if specifically indicated after medical therapy. Relatively poor cure rates
    - Adjunctive radiotherapy – last resort

**Hypopituitarism:**

* Panhypopituitarism, prtial, caused by tumour, even hypothalamic tumour, trauma, sheehans, pituitary apoplexy, autoimmune hypophysitis, empty sella syndrome
* Partial hypopituitarism
* Presentations: tired, pale, poor stress response, postural hypotension, cold intolerance, amenorrhoea
* Therapy
  + Treat cause if required
  + Replacement hormonal therapy: usual first priority is to treat hypoadrenalism and hypothyroidism
  + Thyroid deficiency: oral thyroxine (days/weeks for full effect)
  + Sex steroid deficiency

**Diabetes Insipidus:**

* Related to AVP = ADH physiological derangement: ADH synthesized in hypothalamus, increased osmolarity and decreased MAP potent triggers, transported down pit stalk to posterior pit.
  + Other stimulus for release = N+V, pain, hypoglycaemia, angiotensin II
  + Action: binds to V2 receptors 🡪 increase water re-absorption through AQP, binds to V1 receptors 🡪 vasoconstriction, activates factor VIII, stimulates arousal
* Causes of central
  + Any disruption to stalk 🡪 pathological sieve
* Causes of nephrogenic
  + hypoK, hyperCa, sickle cell, post-relief urinary tract obstruction, Li [use amiloride to prevent]
* Imaging of hypothalamus with MRI (central does not have post pit bright spot and has normal thickness of pit stalk)
* Investigation: water deprivation test. No drinking from midnight, measure hrly paired urine and serum osmolality, complete test when (wt loss ~ 3-5% OR urine osmol <30mosm cf serum osmol; normal test if urine osmol > 2x serum osmol), then DDAVP, measure 1h after to see response
  + Interpretation: Normal = urine osmol 2 – 4x >serum osmol
  + Central DI when urine osmol <30 of serum osmol AND response to DDAVP >50% incr in urine osmol
  + Nephro DI when urine osmol <30 of serum osmol AND response to DDAVP <50% inc in urine osmol
  + If urine osmol > serum osmol but not by 2x, then may be partial central (when urine osmol increases >10% DDAVP) or partial nephrogenic or primary polydipsia (when urine osmol <10% inc to DDAVP)
  + In primary polydipsia and partial nephrogenic, DDAVP does not ameliorate thirst or polydipsia but causes development of hypoNa
* Treatment:
  + If temporary and mild: ensure access to fluids
  + If severe and permanent: desmopressin nasal spray/tablets

**SIADH**

* Non-osmotic release of ADH, ectopic, lung infections, stress, drugs (SSRI, SNRI, carbamazepine, opioids, anaesthetic agents, dec O2 + inc CO2, TCA, amiodarone, cyclophosphamide, vincristine)
* Euvolemic hypoNa in absence of hypocortisolism, hypothyroidism, diuretic use
* Dx: Must (1) exclude other cause (2) clinical euvolemia (3) urine osmol maximally dilute ie <100mOsm (4) renal Na wasting with urine Na >40
* Rx: Acute, aim no more than 0.5mM/hr increase, aim [Na] >120, use hypertonic saline +/- diuretics, Chronic 0.5 – 1.0L fluid restriction +/- salt tablets, aim Na inc <= 8mM/24h
* Tolvaptan: selective V2 antagonist higher receptor affinity compared to ADH, TGA approved for CCF induced hypoNa AND SIADH. Avoid use in liver disease because inc mortality in cirrhosis

**Primary Adrenal Failure/Insufficiency**

* Fatal if untreated, Near normal lifestyle and longevity unaffected except by misadventure
* Signs and symptoms – wasted, pigmented and hypotensive (if very rapid destruction – no pigmentation), abdo pain, N, V, in shock, postural BP
* Chronic most common sx = fatigue/ anorexia/ weight loss > pigmentation>hypotension + tachy > lab derrangement
* Labs: hypoNa, hyperK, low HCO3, hypoBGL, fever due to lack of cytokine inhibition, elevated plasma renin (good way to f/u Rx), can get eosinophilia and neutropenia
* Aetiology of primary adrenal failure
  + Acute haemorrhage/infarction – bilateral in meningococcal sepsis/ addisons disease + superimposed infection
  + Chronic: autoimmune adrenalitis (adrenal auto-antibodies), TB, HIV, adrenoleukodystrophy, metastatic tumour, amyloid, haemochromatosis, drugs = ketoconazole
* Dx:
  + Morning serum cortisol and ACTH. If acutely unwell cort <100 early AM diagnostic, esp if ACTH high
  + Secondary 🡪 normal/ low ACTH with pigmentation, normal aldosterone therefore no hyperK
  + Synacthen test, high rise excludes primary hypoadrenalism, does not exclude secondary
* Associations with polyglandular syndromes
  + Polyglandular autoimmune syndrome type 1 🡪 A/R, mucocutaneous candidiasis, hypoparathyroidism, addisons disease, hypogonadism, hypothyroidism, sjogrens, APECED mutation
  + Type 2 🡪 hypothyroidism, vitiligo, type 1 DM, coeliacs disease
* Rx
  + **Acute**
    - Saline resuscitation
    - Hydrocortisone: 100-250mg bolus IV then 100mg infusion per 6-8h initially, aim IMI not IV because rapid clearance
    - Bicarbonate for severe hyperkalaemia – not insulin/glucose or resonium
    - If hypothyroid don’t replace until after cortisol crisis finishes as thyroid increases clearance of cortiol
  + **Chronic** 
    - Glucocorticoid replacement: cortisone acetate or hydrocortisone
    - Mineralocorticoid replacement: fludrocotisone
* Secondary 🡪 most common cause is exogenous, pit tumours + other causes of hypopit, can be opioid induced, ipilumimab can cause hypophysitis
  + Electrolytes usually normal, hypoglycaemia tends to be more marked
  + Recovery from steroid withdrawal 🡪 can happen for up to 1 yr!, vulnerable to lack of stress response in this time
  + If needing to decrease steroid abruptly after more than 3 weeks, can make an assessment based on synacthen test

**Glucocorticoid preparations and stress management**

* Comes in 5 preparations: hydrocortisone, cortisone, prednisolone, dexamethasone, fludrocortisone
* Highest potency = dexamethasone, fludrocortisone has highest mineralocorticoid potency
* Prednisone has 4x potency of hydrocortisone, therefore 5mg pred = 20mg hydrocort, dexa has 30 – 40x potency of hydrocort, 30mg of hydrocort = 0.75mg dex
* Minor Sx 🡪 usual AM dose, major Sx 🡪 usual AM dose + 100mg prior to Sx + 50 TDS for 24hrs + taper 50% each day
* Double HC dose if unwell [tell patient 3 x 3 rule, triple dose for three days], if v unwell, increase 3-4x, parental treatment if N + V + D

**Hyperaldosteronism:**

* Suspicion: hypertension +/- hypokalaemia (40% normokalaemic), 12% of HTN, mild alkalaemia
* Causes of hyperaldosteronism
* Adenoma, idiopathic hyperplasia, carcinoma
* Dx:
* Renin assay: if suppressed/low renin or high aldosterone-renin ratio then proceed to aldosterone suppression test OR 24hr urinary aldosterone (RPA says this, proff Twigg)
* Aldosterone suppression test 🡪 2L N/S over 4h, look for aldosterone suppression <140mM
* Fludrocortisone suppression test over several days
* Once confirmed then imaging. If unilateral 🡪 adrenalectomy, if no tumour then Adrenal vein sampling
  + If lateralization cut adrenal gland out, if no lateralization 🡪 spironolactone

**CAH/ liddles syndrome**

* A/R, mostly due to defect in 21OHase
* Wide ranging presentation 🡪 virilisation, salt wasting form, accumulation of 17OH progesterone, Rx = adrenal steroid replacement
* Liddle syndrome
  + Early onset hypertension, A/D, hypokalaemia, mutation in ENaC
  + Low renin and aldosterone

**Phaeochromocytoma**

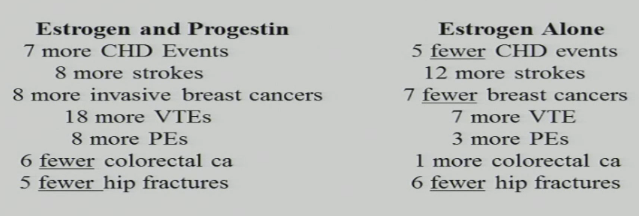
* Catecholamine producing tumor, 0.1% of causes of HTN, suspect if triad severe headache, diaphoresis, palpitations [absence of 3 reliably excludes pheo], can have orthostatic hypotension
* Adrenal medulla, 90% adrenal, 10% extra-adrenal, 10% familial, 10% malignant, 10% bilateral
* Genetically assoc with RET 🡪 MEN2A/2B, NF-1, VHL, SDHB, SDHD
* Dx
  + Plasma metanephrines/ normetanephrines to screen, urinary metanephranies/ normetanephrines to confirm
  + Anatomical : CT or MRI, MIBG scan
  + Mx 🡪 Sx, alpha blockade first then beta blockade

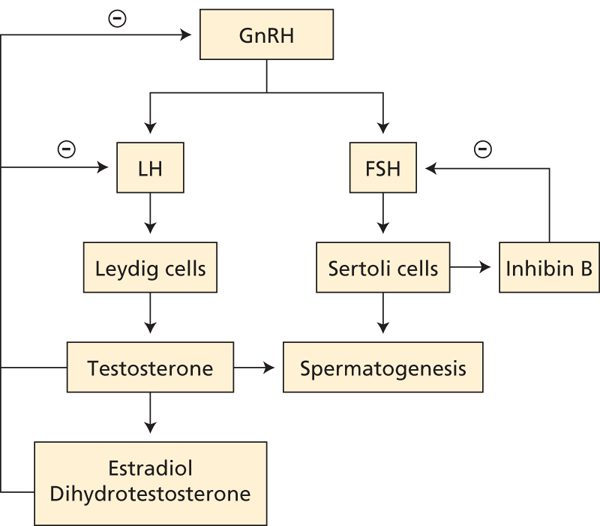
**Adrenal Incidentaloma**

* Most likely benign non-functioning adenoma
* 30% are functioning, mainly cortisol secretiong > phaeo> carcinomas >mets >aldosterone producing lumps
* adrenal Ca, shit 2y prognosis survival <50%
* If found, then Hx to see if sx of hormone excess + phaeo, Ix for phaeo, mineralocorticoid [HTN + hypokalaemia, renin/ aldosterone ratio], cushings, Image to look for signs of malignancy/ phaeo
* Imaging characteristics:
  + Benign = homogenous, smooth border, <10 HFU, no contrast enhancement, similar density to liver on MRI T2
  + Malignant = large, irregular border, >10 HFU, enhance with contrast, microcalcification, hyperintense on liver MRI T2
* Note: FNA cannot differentiate benign from malignant, use FNA Bx only if mets suspected
* Indications for Sx: (1) Tumour >4cm, if phaeo after blockade, if functioning adenoma
  + If not for Sx, THEN 🡪 repeat scans 4 – 6 monthly and growing remove, stable observe

# Reproductive Endocrinology

* Sex steroid biochemistry
  + Females 2 cell model: LH to Thecal cells [cholesterol 🡪 androstenedione] 🡪 FSH to granulosa cell [andronstenedione --> estrone 🡪 estradiol]
  + Males 1 cell: LH on Leydig cells [Cholesterol 🡪 DHEA or androstenedione 🡪 testosterone], FSH on Sertoli cells [spermatogenesis]
* Hirsutism
  + Androgen production in women occurs 50% in theca cells [LH action, if no FSH then don’t get granulosa cells making estradiol from androstenedione, rather shunted to testosterone]
  + Definition 🡪 excess facial and body hair in females in male distribution
  + Causes: Ovarian [PCOS], Adrenal [Cushings syndrome, Late onset CAH as metabolites of 17OH progesterone gets shunted to testosterone]
  + Investigations:
    - SHBG and free androgen index, note SHBG decreases in obesity 🡪 increase free androgens + hirsuitism, OCP increases SHBG 🡪 decreases free androgen
    - DHEAs 🡪 adrenal androgen
* PCOS
  + Diagnostic criterion 🡪 [2/3 of (1) hyperandrogenism (2) oligo or amenorrhea (3) polycystic ovaries AND rule out of (1) hyperprolactinemia (2) non-classical CAH (3) cushing’s (4) Androgen secreting neoplasm]
    - Major cause of anovulatory infertility
    - Increased prevalence of cardiovascular risk factors similar to metabolic syndrome, 40% 40’s with PCOS 🡪 type 2 DM
  + Pathophysiology: LH and insulin increases androgen synergistically production by theca cells in ovaries, increases risk of sleep apnoea and endometrial carcinoma and diabetes related complications. Insulin inhibits hepatic synthesis of SHBG thus increasing free testosterone
  + Investigations 🡪 EXCLUSION OF OTHER CAUSES, LH > FSH, high anti-müllerian hormone, androgen profile, pelvic US [>12 cysts with sufficient volume]
  + Mx (1) Hirsuitism and acne 🡪 cosmetic, ovarian suppression, OCP, anti-androgens [spironolactone] (2) Menstrual disturbances 🡪 weight loss most important, metformin + clomiphene [BMI >30, if <30, then metformin] combination increased live birth rate considerably
* Amenorrhea
  + Primary 🡪 never had menstrual period
  + Secondary 🡪 had a menstrual period
  + Hypergonadotropic hypogonadism
    - PCOS [LH high, FSH Normal], oestrogen [normal]
    - Premature ovarian failure 🡪 oestrogen [low], gonadotrophin [FSH/ LH high]
    - Turner’s syndrome 🡪 Karyotype [45 X,O], oestrogen [low], gonadotrophins [FSH/ LH high], similar for XY gonadal dysgenesis
  + Hypogonadotropic hypogonadism [all low]
    - Hypothalamic [stress, exercise, weight loss, tumour, autoimmune hypophysitis]. Note hyperthyroidism 🡪 low oestrogen, inappropriately low/ normal FSH/LH
    - Structural 🡪 ashermans syndrome [adhesions]
  + Hyperprolactinaemic
    - Check thyroid [hypo 🡪 increased TRH 🡪 incr prolactin], MRI for tumour
* Turner’s
  + Complete or partial absence of X chromosome in phenotypic female
  + 1:2500 live births
  + Clinical features:
    - Short stature, ovarian dysgenesis [primary or secondary], infertility, web neck, wide carrying angle, coarctation + aortic dissection + bicuspid aortic valve, horseshoe kidney



**Primary Hypogonadism**

Primary hypogonadism is due to testicular failure and is defined as a low testosterone level with elevated LH and FSH levels. Primary hypogonadism can have congenital or acquired causes. The most common congenital cause is Klinefelter syndrome (XXY karyotype). Acquired causes include exposure to certain chemotherapy agents, pelvic irradiation, mumps orchitis, trauma, and testicular torsion

**Secondary Hypogonadism**

Caused by a hypothalamic or pituitary defect, secondary hypogonadism is defined as a low testosterone level with simultaneously low or inappropriately normal LH and FSH levels. Secondary hypogonadism also can be due to congenital or acquired causes. Idiopathic hypogonadotropic hypogonadism, with anosmia (Kallmann syndrome) or without anosmia, is an example of congenital secondary hypogonadism. Acquired causes include hyperprolactinemia, functioning or nonfunctioning pituitary adenomas or other sellar masses, chronic opiate use, corticosteroids (exogenous use or excessive endogenous), and infiltrative diseases (such as hemochromatosis).

# Thyroid

**Thyroid autoimmunity**

* Very common, 20% of women
* Graves disease (TRABs), hashimoto’s, idiopathic hypothyroidism, neonatal hypothyroidism (TRABS)
* Antibodies
  + Thyroglobulin antibodies, an epiphenomenon
  + Thyroglobulin reactive T cells – major driver of T cell infiltration
  + TPO antibodies
  + TSH receptor Abs
    - May be blocking, stimulating or neutral

**Graves disease**

* Features include hyperthyroidism, goiter, graves opthalmopathy and thyroid acropatchy
* Susceptibility generalizes to all autoimmune throid disease and patients may move from one disease to the other over the years, eg from graves to hashimotos
* Epidemiology – women >>> men, natural history = relapsing and remitting, untreated 25% will remit, untreated mortality 11 – 50%
* AF related to hyperthyroidism has high embolism risk (10%)
* Graves opthalmopathy
  + Exophthalmos, proptosis, lid lag, chemosis, corneal ulcers due to exposure keratitis, decreased visual acuity
* Mx
  + Antithyroid drugs
    - Benefits – avoids permanent ablation, favoured in pregnancy, < 40, small goiters, low titre TRABS
      * After euthyroidism, and in the young patient, can monitor to see if remission has occured
    - If high Tire TRABS, large goiters and M sex 🡪 ablative Rx more appropriate
    - Drugs include carbimazole and propylthiouracil, carbimazole favoured over PTU except for the following: first trimester pregnancy + unwanted S/E of carbimazole.
      * Carbimazole causes aplasia cutis and choanal syndrome
    - Reason is that PTU risk of severe hepatitis requiring Liver Tx
    - PTU has the added benefit that it decreases peripheral conversion of T4 🡪 T3
    - S/E include agranulocytocis, fever, infection. PTU can have risk of severe hepatitis
  + I-131
    - Safe, only modest reduction in goiter
    - Can exacerbate opthalmopathy
    - Indication: Adults > 40 and those who faile antithyroid rugs
    - Contraindication; pregnancy, try avoid in those of reproductive age
    - Generally start with anti-thyroid drugs to make euthyroid then give I-131
  + Sx
    - Indication: obstructive goiter, uncontrolled thyrotoxicosis 2nd trimester

**Causes of thyrotoxicosis**

* TSHr or Gs mutation mediated
  + MNG/ toxic adenoma
    - MNG – caused by TSHr or Gx mutations 🡪 constitutive ligand independent activation of second messengers
    - Rx – similar to graves disease
    - Toxic adenoma – I-131 particularly suited
    - However: antithyroid drugs less favoured because of lack of remission
* bHCG mediated
  + gestational thyrotoxicosis
  + trophoblastic
* TSH dependent
  + TSHoma
  + TH resistance
* Strua ovarii
* Lingual thyroid
* Amiodarone
  + Two types, Type 1 or type 2
  + Type 1 🡪 due to iodine load from amiodarone
  + Type 2 🡪 thyrocyte cytotoxicity
  + Distinction is difficult
  + Low uptake scan
  + In iodine deplete areas thyrotoxicosis is more common, in iodine replete areas hypothyroidism is more common
  + T4 high, T3 low
  + Rx: carbimazole, prednisolone. Monitor T4 decline to determine when to stop CMZ, stop amiodarone if drug not necessary for non-life threatening indication
* Thyroid destruction
  + Infection/ ischaemia/ infiltration
  + Thyroiditis
    - Subacute (de-quervans)
    - Lymphocytic
  + Radiation induced

**Subclinical hyperthyroidism**

* Subnormal TSH in spite of normal T4/ T3
* Consequences only if TSH <0.1
  + Progression to overt disease, osteoporosis, atrial fibrillation, heart failure
  + Generally Rx if >65 or <65 and MNG, osteoporosis and heart disease
* Rx:
  + Antithyroid drugs for young patients, radioactive ablation for older patients

**Thyroid storm**

* Life threatening emergency
* Fever (>40), sweating, tachy, AF, proximal myopathy, nausea, abdo pain, jaundice, dehydration, shock, coma, seizure, delirium
* Precipitated by:
  + Infection, trauma, surgery – esp antithyroid, radioiodine, iodine load
* Managed by
  + HDU
  + Beta blocker – propanalol, esmolol to maintain P <100, non selective beta blockers help reduce peripheral conversion T4 🡪 T3
  + Rehydration
  + PTU > CBMZ because of its ability to reduce T3 (blocks T4 🡪 T3)
  + Hydrocortisone 🡪 central suppression + decrease peripheral conversion
  + Lugos iodine: Wolf-chaitkoff effect, only used in prep for emergency Sx
  + Cholestyramine 🡪 increase T4 clearance

**Hypothyroidism**

* Dx, raised TSH >10, but unreliable if pituitary disease, here need to rely on T4
* Causes:
  + Iodine deficiency
  + Destruction
  + TSH deficiency
  + Thyroid hormone resistance
* Clinical features: manifestation in every organ: weakness, lassitude, thinning of hair, dry skin, coarse skin, slow speech, thickened tongue, constipation, edema of eye lids, cold intolerance, cognitive decline, memory loss, depression, coma, generalized oedema, weight gain, menorrhagia, brady, slow relaxation of ankle reflexes
* Can cause hypoNa, raised CK, elevated LDL
* Rx
  + L-thyroxine, dose adjustment to maintain TSH ~1, need to increase by 50% in pregnancy

**Subclinical hypothyroidism**

* Raised TSH, normal T4, T3
* Progression to hypothyroidism 2.6%/yr, higher if autoantibody present (40 – 60% of all patients)
* Rx
  + More evidence if SC hyperthyroid
  + Guidelines: TSH >10 Rx, no evidence if TSH <10 unless there is co-existent CVD
  + In pregnancy TSH >2.5 = cut-off

**Myxoedmea coma**

* Dry coase skin, yellow from caroteine staining, hoarse voice, swollen tongue, thin hair, delayed reflexes, pericardial effusion, pleural effusion ascites, myopathy, cardiomyopathy
* Central hypothermia, bradycardia, reduced conscious level, hypotension, fits
* TSH >50, if normal/ low consider pituitary disease
* hypoNa, raised creatinine, CO2 retention
* Mx:
  + ICU
  + Rewarming
  + Respiratory support
  + Fluid resus +/- inotropes
  + Hydrocortisone until hypoadrenalism excluded
  + Thyroid replacement: loading dose, may require parenteral T3
  + Anticipitate reduced renal clearance of many drugs

**Thyroiditis**

* DeQuervans (giant cells FNA, pain in neck, raised ESR)
* Autoimmune
  + Lymphocytic
  + Post-partum
* Riedels
* Subacute
  + Spontaneous and remitting inflammation of thyroid
  + Features of thyrotoxicosis then hypothyroidism then recovery
  + ESR/ CRP and leuks increased, Tg elevated
  + Rx
    - NSAIDS for mild, otherwise 40mg prednisolone + tapering
    - No role for anti-thyroid drugs
    - Thyroxine replacement in hypothyroid phase

**Lymphocytic and post‐partum**

* thyroiditis
* Thyrotoxicosis associated with a painless enlargement of the
* thyroid
* • High thyroglobulin
* • aTPO and a TG antibodies
* • Bx would reveal lymphocytic infiltration
* • Common presentation post‐partum (5‐9%)
* • Thyrotoxicosis is limited , followed by hypothyroidism and 20‐
* 30% have persisting hypothyroidism
* • Those that recover have increased incidence of eventual
* hypothyroidism

**Thyroid nodules**

* Clinically evident up to 5%
* US detectable up to 60%
* Half are solitary and half are part of MNG
* 5‐ 15% clinically apparent nodules are cancer
* 90% are Differentiated TC
* 5% are hot and suppress TSH
* these harbour TSHR or GS protein
* mutations and are rarely malignant(<1%)

Thyroid cancer

• Classification

– Papillary (classic, follicular variant, diffuse sclerosing, tall

cell, oxyphillic, microcarcinoma)

– Follicular (minimally invasive, widely invasive)

– Hurthle cell carcinoma

– Poorly differentiated

– Anaplastic

– Medullary

Others

Selection for FNA

• TSH – if suppressed (<0.01 mIU/l) lesion may be

“hot” and isotope (Tc99m) uptake scan should be

performed. If hot – no FNAC

• Lesion > 2cm and not a cyst or spongioform lesion

then FNA

• Lesions 1‐2 cm selected on the basis of high risk US

features

• Lesions < 1 cm repeat evaluation in 6‐12 months

• Lesions that increase by 30% volume or 10% in diam

should be biopsied

Papillary thyroid carcinoma (PTC)

• 80% of differentiated thyroid tumours

• Commonly multifocal

• Spread to LN very common (80%)

• Spread beyond the neck in <10%

• Lung, bone, brain , liver and adrenals

• Variants

– Follicular variant

– Tall cells

– Diffuse sclerosing (and others)

• 15‐ 30% autopsy subjects have PTC so many PTC are indolent and do not

cause death

• Prognostic features include age > 40, tumour size >4 cm and local

extension or distant metastases.

|  |  |  |  |
| --- | --- | --- | --- |
|  | ↑TSH | TSH normal | ↓TSH |
| fT4↑ | -Poor compliance to thyroxine with recent ↑ ingestion  -Thyroid hormone resistance (rare)  -TSH-secreting adenoma (SHBG) | -measurement error?  -timing of T4 ingestion relative to blood taking  -TSH-secreting adenoma | -10 hyperthyroidism |
| fT4 normal | -subclinical 10 hypothyroidism (different cut offs for age and in pregnancy)  -TSH interference (heterophile Ab)  -ageing  -elevated BMI | -euthyroid | -subclinical hyperthyroidism  -↑thyroxine or on antithyroid Rx  -drug effect (e.g. GCs)  -non-thyroidal illness (+ ↓fT3 – often fT4 nromal until very late) |
| fT4↓ | -10 hypothyroidism | 20 hypothyroidism  -T4 assay (e.g. effect from ↑TBG)  -nn-thyroidal illness (+ ↓fT3) | 20 hypothyroidism  -drug effect (e.g. GCs)  Non-thyroidal illness (+ ↓fT3)  -starvation |

TSH can be misleading in pituitary disease, non-thyroidal illness, early Rx of hyperthyroidism, TSH-secreting adenoma and thyroid hormone resistance.

**Thyroid physiology**

|  |  |
| --- | --- |
| Factors that alter thyroxine and triiodothyronine binding in serum | ↑TBG – pregnancy, oestrogen - ↓fT4  ↓TBG – androgens, GCs - ↑fT4  Binding inhibitors – e.g. heparin - ↑fT4 |
| Factors that affect thyroid gland hormone production and secretion | Iodine uptake   * Iodine e.g. amiodarone, iodinated contrast   Hormone production   * Iodine, amiodarone (effect on TPO), thionamides (carbimazole, PTU)   Secretion   * Iodine, amiodarone   Thyroiditis   * TKIs (sunitinib, sorafenib), IFNα, amiodarone, Li, ipilimumab (also associated with pituitary hypophysitis), pembroluzimab   Development of Graves’   * IFNα |
| Jod-Basedow | Iodine induced hyperthyroidism |
| Wolff-Chaikoff | Give huge amount of iodine (Lugol’s iodine) 🡪 thyroid hormone suppression |
| Direct and indirect effects on the HPA | ↓TSH secretion – GCs, opiates (work at hypothalamic and pit level), starvation/weight reduction |
| Peripheral metabolism (↓T4🡪 T3 conversion) | GCs, amiodarone, PTU, BB (tends to be non-selective BB like propranolol) |
| Interference with absorption of thyroxine | PPI, Fe tablets, calcium tablets, malabsorption syndromes (e.g. coeliac disease) |

**10 hyperthyroidism and subclinical hyperthyroidism**

|  |  |
| --- | --- |
| work-up | ↓TSH  check fT4, fT3, TRAb (look for Graves), if not clinically Graves do thyroid uptake scan  Causes if normal or ↑uptake   * Graves, MNG, toxic adenoma, trophoblastic disease, TSH-producing pituitary adenoma   Causes if near-absent uptake   * Painless thyroiditis, amiodarone-induced thyroiditis, subacute (granulomatous, de Quervain’s) thyroiditis, iatrogenic thyrotoxicosis, factitious ingestion of thyroid hormone, struma ovarii, acute thyroiditis, extensive mets from follicular thyroid cancer |
| Mx | Medical   * Almost always use carbimazole > PTU (except in 1st ∆) * 12-18/12, withdraw Rx once TSH normal on low dose and TRAb neg * Agranulocytosis and liver toxicity (carbimazole – cholestatic, PTU – hepatitis) rare * 50% relapse rate * Smoking cessation (smoking associated with high risk of eye dx) * High TRAb in 2nd/3rd ∆ ↑ risk of fetal hyperthyroidism   I131   * Lower dose than what’s used in thyroid cancer * 15-20% need 2nd dose * No pregnancy for 6-12/12 after * Used if medication intolerance or relapse * Avoid if thyroid-associated orbitopathy (RF for TAO – smoker, high TRAb)   Total thyroidectomy   * Used for large glands, uncontrolled hyperthyroidism, high TRAb, desire for pregnancy, relapse |
| Causes of thyroiditis | subacute (painful), drug-induced/hashitoxicosis/ postpartum (painless) |
| Rx thyroiditis | Hyperthyroid - Symptoms – BB  Hypothyroid – symptoms – thyroxine  NSAID/aspirin or prednisone for painful thyroiditis (↑ESR) |
| Drug-associated thyrotoxicosis | Amiodarone – type 1 (iodine induced), type 2 (thyroiditis)  Li – painless thyroiditis  IFNα – painless thyroiditis, GD  IL-2 – painless thyroiditis, GD  Iodinated contrast – often there might be underlying thyroid autonomy, could present weeks to months after the contrast  Radioactive iodine – can cause early (<1/12) or late (3-6/12) thyrotoxicosis |
| Rx amiodarone induced thyrotoxicosis | Type 1 – usually have preexisting thyroid nodular disease, iodine deficient area – ATD  Type 2 – usually normal thyroid, iodine sufficient area – use prednisone  Usually overlap  In severe cases and unstable cardiac status – consider thyroidectomy |
| Mx thyroid storm | PTU  Propranolol  Lugol’s iodine  hydrocortisone |
| Subclinical hyperthyroidism | Generally Rx if > 65yo  Also if <65 with comorbidities e.g. heart disease, OP, symptomatic  If <65, asymptomatic, consider Rx |

**Hypothyroidism**

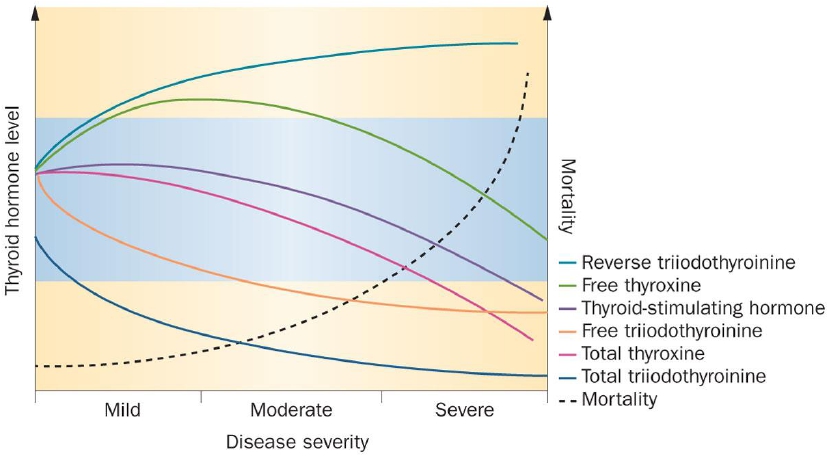
|  |  |
| --- | --- |
| Work-up | ↑TSH  Check fT4, TPO Ab, TGB Ab (esp useful if have thyroid cancer) |
| Rx | Thyroxine – aim TSH in reference range  In early pregnancy, aim TSH < 3.5  In 20 hypothyroidism, keep fT4 in mid-normal range |
| Rx subclinical hypothyroidism | TSH > 10 - ↑risk cardiac failure and CV mortality  Symptomatic with +ve ATA  Nodules (b/c TSH might have a trophic effect on the nodule)  Subfertility and pregnancy with +ve ATA - ↓miscarriage rate and preterm delivery |

**Sick euthyroid**

↑rT3, ↓fT3

fT4 stays normal until the very end and then it drops off

in sick phase – everything goes down except rT3



**Thyroid and pregnancy**

|  |  |
| --- | --- |
| Normal physiology |  |
| Hypothyroid | TSH < 2.5 in 1st ∆ and < 3 in 2nd and 3rd ∆  Often need dose ↑ in thyroxine in pregnancy (30-50%) |
| Hyperthyroid | GD > hCG effect  PTU 1st ∆ then carbimazole in 2nd and 3rd ∆  Check TRAb in 3rd ∆ to assess risk for fetal hyperthyroidism  Check post-partum |

**Thyroid nodules**

|  |  |
| --- | --- |
| ↓TSH | Do thyroid scan, if autonomously fxning nodule ablate (20% need 2nd dose), BB if PHx of CVD, age > 54 or mod/severe hyperthyroidism |
| TSH N or ↑ | Consider FNABx if   * FHx of thyroid cancer, PHx of neck irradiation, nodule > 1cm, suspicious sonographic features * If multiple nodules, thyroid scan and FNABx   Bethesda I and II – repeat FNABx in 3-6/12  For Bethesda III/IV, consider BRAF testing (+ve = cancer, -ve does not exclude cancer) |

