Diabetes and Endocrinology

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Diabetes

Failure of glucose homeostasis resulting from either:

- Lack of insulin secretion
- Failure of insulin effect
Insulin – Carbohydrate metabolism

**INSULIN**

- **Liver**: Reduce basal glucose production
- **Skeletal muscle, Adipose tissue**: Enhance postprandial glucose uptake
Insulin – other effects

- **Fat metabolism**
  - PROMOTES Tg synthesis
  - INHIBITS Tg breakdown (FFA and KETONE BODIES)

- **Protein metabolism**
  - INHIBITS protein breakdown to AA (precursors for hepatic gluconeogenesis)
Classification of Diabetes

- **Type 1 Diabetes**
  - B cell destruction
  - Immune mediated / Idiopathic

- **Type 2 Diabetes**
  - Insulin resistance
  - Relative insulin deficiency

- **Gestational Diabetes**

- **Other**
  - Diseases of the exocrine pancreatic disease
  - Genetic disease (B cell function, insulin action)
  - Endocrinopathies
  - Drugs
Type 1 Diabetes

Which of the following statements regarding Type 1 Diabetes is / are true

• T1DM results from the autoimmune destruction of α cells in the pancreas
• Patients typically need to reduce their insulin doses by 1/3 when ill
• Ketosis heralds insulin deficiency in the context of hyperglycaemia
• A variable rate insulin infusion is indicated in the acute management of diabetic ketoacidosis
Type 1 Diabetes

**ABSOLUTE INSULIN DEFICIENCY**

- Pancreatic β cell destruction
- Failure of insulin secretion

**Cardinal features:**
- Hyperglycaemia
- Salt / water loss
- Ketogenesis (uncontrolled breakdown of fat and muscle)
Therapeutic options in T1DM

.....Insulin
Therapeutic options in T1DM

.....Insulin

.....Or they die
Types of insulin

- Long acting
- Short acting
- Mixtures of the above
Insulin - Profiles of action

Aspart, lispro, glulisine

Plasma Insulin Levels

Hours

0 2 4 6 8 10 12 14 16 18 20 22 24

Regular

NPH

Detemir

Glargine
Continuous insulin infusion ("pumps")
What are the features of insulin deficiency?
What are the features of insulin deficiency?

- **Ketosis**
- Salt, water, potassium loss (hyperglycaemic diuresis)
- Hyperglycaemia
What is ketoacidosis?

Effective insulin deficiency

Failure of glucose metabolism

Breakdown of FFAs for fuel

Generation of Ketone bodies (acidic)

Hyperglycaemia

Salt + K + water loss
Diagnostic criteria - DKA

- Acidosis: pH < 7.3,
  \[ \text{HCO}_3^- < 15\text{mmol/L}, \]
  \[ \text{BE} < -10 \]

- Ketonuria ++ OR plasma ketones >3mmol/L

- Known diabetes OR plasma glucose >11mmol/L
Management – what are the priorities?
Management – what are the priorities?

- **Restore salt and water**
  - N Saline +/- K

- **Replace insulin to terminate ketogenesis**
  - Fixed rate insulin +/- 10% Dextrose

**AVOID HYPOKALAEMIA**
**AVOID HYPOGLYCAEMIA**
When can the fixed rate infusion stop?

As soon as ketogenesis is terminated
- Capillary ketone measurement $<0.6 \text{mmol/l}$

Surrogates:
- Plasma $\text{HCO}_3^-$ (caution after 6hrs saline resuscitation)
- Urine ketones - may remain positive for up to 24hrs following resolution of DKA
- pH $> 7.3$

If E+D return to basal bolus. If NBM covert to standard variable rate insulin infusion
Type 2 Diabetes

INSULIN RESISTANCE vs Failing β cell function

= Relative insulin deficiency
INSULIN RESISTANCE

TIME
A 65 year old man describes symptoms of polyuria and polydipsia for 4 months. He has a family history of Type 2 Diabetes. His BMI is 32. Which of the following statements is true?

- An HbA1c measurement of 82mmol/mmol would confirm the diagnosis
- An HbA1c of 46mmol/mmol would exclude the diagnosis
- An OGTT is the only conclusive test for T2DM as recommended by the WHO
- Presence of Acanthosis Nigricans would support a diagnosis of Type 1 Diabetes
- Acromegaly is a recognised cause of insulin resistance
Diagnosis of Type 2 Diabetes

- **HbA1c**
  - Reflects glycaemia over 100 days
  - >48mmol/mmol
  - May be reduced by rapid RBC turnover eg anaemia
  - May be increased in certain ethnic groups

- **OGTT**
  - Fasting 7.1mmol/L
  - Two hr 11.1mmol/L
  - Not reliably reproducible

The different methods will detect slightly different populations
Secondary causes of Type 2 Diabetes

- **Endocrinopathies**
  - Cushing’s Disease
  - Acromegaly
  - Phaeochromocytoma
  - Thyrotoxicosis
  - Glucagonoma
  - Somatostatinoma

- **Drugs**
  - Corticosteroids
  - Psychotropic drugs

 ....... Pregnancy (Gestational Diabetes)
Therapeutic options
A 65 year old man attends his GP surgery with a history of T2DM diagnosed 6 months previously. He has managed to lose 5kg in weight with lifestyle changes and his HbA1c is 62mmol/mmol. His BMI is 30. Which of the following is true?

- His target HbA1c is 60mmol/mmol
- A good first line treatment for him would be a GLP1 inhibitor to help him lose more weight
- He should monitor his blood sugar levels to confirm fasting hyperglycaemia before commencing metformin
- A history of pancreatic cancer would be an absolute contraindication for offering him an SGLT2 inhibitor
- Presence of urinary ketones would be an indication for insulin therapy
Therapeutic options in T2DM

- Diet and exercise
- Insulin sensitisier
- Insulin secretagogue
- Reduce food absorption
- Increase glucose loss
- Insulin
Metformin

- Reduces hepatic glucose output
- Stimulates skeletal muscle glucose uptake

Side effects
- GI (Diarrhoea, bloating etc)

Contraindications
- Renal failure, heart failure, hepatic failure

FIRST LINE THERAPY
Thiazolidinediones

- “Glitazones”
- Reduce insulin resistance
- Work at the level of gene transcription – between 4 - 12 weeks for clinical effectiveness

Side effects
- Oedema, weight gain, osteoporosis
Suphonylureas

- Insulin secretagogues
- Will reduce blood glucose levels by 3 - 4 mmol/l
- Will reduce HbA$_{1c}$ by 1.5 – 2%

Side effects
- Weight gain, risk of hypoglycaemia, particular caution in renal failure
Meglitinides

- Insulin secretagogues
- Glucose sensitive
- Short onset and duration of action

Side effects
- hypoglycaemia, URTI, headache
α Glucosidase inhibitors

- Acarbose
- Block the breakdown of complex carbohydrates in the small intestine

- Side effects
  - Flatulence, bloating
SGLT2 inhibitors

“Subtype 2 Sodium Glucose Transport protein inhibitors”
- Canagliflozin
- Dapagliflozin

- Lower the renal threshold for glycosuria

Side effects:
- Vulvovaginal candidiasis
- Postural hypotension (diuretic effect)
- ?UTI
- ?bladder cancer

- Beware of glycosuria
- Limited risk of hypoglycaemia
The Incretin effect

![Graph showing plasma insulin levels over time for oral glucose and intravenous glucose](image)
Incretins

Enhance insulin release in response to a glucose load

- GIP: Glucose dependent insulinotropic peptide
- GLP1: Glucagon like peptide 1

....and increase satiety?

Extremely short half life of 2 minutes due to degradation by DPP IV
Therapeutic strategies with GLP1

- Longer acting GLP1 receptor agonists
  - Exenatide, Liraglutide

- DPP-IV inhibitors
  - Sitagliptin, Vildagliptin, Saxagliptin,
GLP1 receptor agonists
GLP1 receptor agonists

- Injectable (twice daily – once / week)
- Common side effects:
  - Nausea
- Limited risk of hypoglycaemia unless used in conjunction with insulin secretagogue
- ? Pancreatitis
- Safety warnings regarding pancreatic cancer / medullary thyroid cancer
DPP IV inhibitors “Gliptins”

- Oral medications
- Common side effects:
  - Headache, URTI
- Low risk of mild hypoglycaemia
- Perceived risk of pancreatitis, but unconfirmed
- Increase endogenous GLP1 levels
- Moderate effect on glycaemic levels, particularly early in the disease
Bariatric surgery

Restrictive procedures:
- Gastric band

Restrictive and malabsorptive procedures
- Gastric bypass

Significant weight loss can reverse diabetes
Therapeutic targets

Individually defined

- Aim to achieve HbA1c <48mmol/mmol if diet / lifestyle controlled +/- metformin
- Aim to achieve HbA1c < 53mmol/mmol if taking medications with risk of hypoglycaemia
- Intensify therapy where HbA1c <58mmol/mmol if individually appropriate
The GP notices that his blood pressure is 165/90mmHg despite adherence to lifestyle changes, Which of the following is correct?

- The optimal blood pressure would be 130/80mmHg
- A calcium channel blocker is a good first line agent
- In people of African / Caribbean origin dual therapy would be indicated as first line therapy combining an ACEI +/- Diuretic or Calcium Channel blocker
- Combining an ACEI and Angiotensin II receptor antagonist achieves optimal renal protection
- Antiplatelet therapy should be offered to all men aged >45 years
Primary Prevention

Blood pressure

- First line agent ACEI
  - African / Caribbean population ACEI + Diuretic or Calcium channel blocker
- Second / third line therapies
  - Diuretic / Calcium channel blocker

Antiplatelet therapy

- Not indicated as primary prevention
Hyperglycaemic Hyperosmolar State

HHS

(HONK)
Diagnosis

Hyperglycaemia
- typically blood glucose >30mmol/L

Hyperosmolar
- typically >340mOsm/kg

Ketones
- typically <+
Hyperglycaemic Hyperosmolar State (HHS)

- Hyperglycaemia
- Renal salt / water loss (dehydration)
  - Potassium wasting

Average fluid deficit 10-20L for 100kg man
Management....?
Management

- Restore circulating volume, gradually and safely ... N Saline
Aim of treatment

Aim for a gentle but consistent fall in osmolality
Avoid tight control for 72 hours

\((2 \times Na + \text{Glucose})\)
Why don’t we give insulin?
Long term complications of diabetes
Long term complications of diabetes

Microvascular
- Retinopathy
- Nephropathy
- Autonomic neuropathy
- Peripheral neuropathy

Macrovascular
- Atheromatous disease
The eye in diabetes

- Cataracts
- Reduced visual acuity due to osmotic changes
- Ocular nerve palsy
- Diabetic retinopathy
  - Thickening of the basement membrane
  - Increased vascular permeability
  - Aneurysm formation
  - Vascular occlusion
    - Ischaemia and growth of superficial fragile blood vessels
Nonproliferative retinopathy

- **Microaneurysms**
  - Weak points in the capillary wall leading to bulges
- **Dot Blot Haemorrhages**
  - Rupture of deeper microaneurysms
- **Hard exudates**
  - Leakage of serum proteins and lipids from weakened vessels
- **Cotton wool spots**
  - Nerve fibre infarction
- **Venous beading and looping**
  - Herald onset of neovascularisation
Proliferative retinopathy

- Growth of new vessels
- Haemorrhage
- Macular oedema
Endocrinology
...all you need to know about Endocrinology

- Pituitary disorders
- Thyroid disorders
- Parathyroid disorders
- Adrenal disorders
- Calcium homeostasis
- Endocrine emergencies
The Pituitary

Which of the following statements regarding pituitary macroadenomas is correct?

- May frequently be associated with low prolactin levels
- Typically associated with a homonymous hemianopia
- Larger size usually indicates malignancy
- May produce Growth Hormone, Gonadotrophins, Oxytocin
- May lead to CN III, IV and VI nerve palsy
Normal pituitary function

- **Anterior pituitary hormones**
  - ACTH
  - TSH
  - GH
  - Gonadotrophs (LH/FSH)
  - Prolactin (under inhibitory control)

- **Posterior Pituitary Hormones**
  - ADH (Vasopressin)
  - Oxytocin

NB Hypothalamic factors released via the posterior pituitary
Disorders of the Pituitary

- Pituitary adenomas
  - Micro, Meso, Macroadenomas
  - Functioning / Non functioning
- Craniopharyngiomas
- Rathke’s Cleft Cyst
- Inflammatory masses
- Infections
- Metastases
- (Primary malignancy)
- Empty Sella syndrome
- Trauma
Anterior Pituitary Tumours

- **Local Compression**
  - Failure of normal pituitary function
  - Bitemporal hemianopia
  - III, IV and VI palsy (V1, V2)
  - Loss of dopaminergic control and hyperprolactinaemia
  - Posterior pituitary function rarely affected

- **Uncontrolled hormone release**
  - ACTH – Cushing’s Disease
  - GH – Acromegaly
  - LH / FSH – typically NFPA
  - Prolactin
  - TSH – (rare)
Anterior Pituitary tumours
A 58 year old man is found to have a large pituitary adenoma after his optician detected a bitemporal hemianopia. Which of the following investigations would be appropriate in the *initial assessment* of pituitary function

- Midnight cortisol
- OGTT to stimulate Growth Hormone response
- TRH test
- Short synacthen test
- Water deprivation test
Pituitary function tests

- Pituitary - adrenal axis
- Pituitary – thyroid axis
- Pituitary - gonadal axis
- Growth Hormone
- Prolactin

- Posterior pituitary function
Key points

- Most patterns of endocrine hormone secretion are diurnal / pulsatile
- Tests should be appropriately timed to assess for hypo / hyperfunction
- If it is too low – STIMULATE it
- If it is too high SUPPRESS it
Pituitary – Adrenal axis

Pituitary

ACTH

Adrenal Glands

CORTISOL
Pituitary – Adrenal axis (tests)

ACTH / Cortisol deficiency:

ACTH / Cortisol excess:
Pituitary – Adrenal axis (tests)

ACTH / Cortisol deficiency:
- 0900 cortisol – Secretory peak (NB Shift workers)
- Insulin Tolerance Test / Glucagon test
- (Short SynthACTHen Test)

ACTH / Cortisol excess:
- MN cortisol – Secretory trough (NB Shift workers)
- LDDST
- HDDST
Insulin Tolerance Test (ITT)

Gold Standard test of pituitary - adrenal axis
- Iatrogenic induction of hypoglycaemia (<2.2mmol/l)
- Stimulates stress response
  - ACTH
  - GH

Glucagon test
- Causes transient rise then fall in blood glucose

Short synACTHEN Test
- Many studies have shown good correlation with ITT in assessing both pituitary and adrenal function (Cortisol only)
Cushing’s Syndrome

Which of the following statements is false, in the context of Cushing’s Syndrome:

- Dexamethasone cross reacts with the biochemical assay for measuring serum cortisol
- Prednisolone cross reacts with the biochemical assay for measuring serum cortisol
- Abnormal cortisol dynamics can be associated with alcohol use
- A raised ACTH is diagnostic of pituitary dependent Cushing’s Disease
Investigations in Cushing’s Syndrome

- MN cortisol
- ACTH (Cushing’s Disease, Ectopic ACTH)
- LDDST
  - 0.5mg dexamethasone every 6 hours for 48 hours
  - 1mg dexamethasone overnight
- HDDST
  - 2mg dexamethasone every 6 hours for 48 hours
What does it mean?

- Suppression on low dose = NORMAL
- Suppression on high dose = Pituitary driven cortisol excess through ACTH
- No suppression = Adrenal autonomy / ectopic ACTH
A 36 year old man attends the clinic complaining of erectile dysfunction for one year. He completed normal puberty and has one child. His BMI is 42 and he was diagnosed with Type 2 Diabetes 5 years ago. Which of the following are true.

- Measured testosterone levels closely reflect biologically active “free testosterone”
- SHBG levels fall in chronic liver disease
- A diagnosis of Hypogonadotrophic Hypogonadism would be best treated with testosterone supplements
- Testosterone levels are highest at 4pm in the afternoon
- Testosterone therapy would help support spermatogenesis
A 36 year old lady complains of secondary amenorrhoea and galactorrhoea. Her prolactin levels are high. She is taking Risperidone. Which of the following statements is true?

- The presence of galactorrhoea excludes Risperidone as a cause for her symptoms
- Macroprolactinomas require urgent surgical reduction since they can grow unexpectedly
- Macroprolactin is a more severe form of hyperprolactinaemia seen when the levels are so high it starts to precipitate
- Prolactin levels can increase in response to phlebotomy
- Hyperprolactinaemia in men is usually associated with gynaecomastia
Hyperprolactinaemia

Aetiology:

• Failure of Dopaminergic suppression of prolactin release
  ○ Hypothalamic disorders
  ○ Drugs
  ○ Compression of pituitary stalk

• Lactotroph cell adenomas (Prolactinomas)
  ○ Micro / macro

Amenorrhea, galactorrhoea, local pressure effects
Hypopituitarism

Key immediate investigations

- Pituitary – adrenal axis
  - 0900 cortisol
- Pituitary – thyroid axis
  - TFT
- Prolactin
- Posterior pituitary function
  - Serum sodium, fluid balance (input/output), serum / urine osmolalities
Diabetes Insipidus

Which of the following options is NOT correct with regards to suspected Diabetes Insipidus

- Aggressive rehydration should be given with Normal Saline if hypotensive
- Lithium may be associated with nephrogenic diabetes insipidus
- Hypokalaemia is associated with tubular resistance to AVP
- In cranial diabetes insipidus the posterior pituitary bright spot may be lost
Diabetes Insipidus

Posterior pituitary
- Not typically associated with benign pituitary adenomas
- Uncontrolled inability to retain free water
- Polyuria with consequent polydipsia

Investigations (ensure normal glucose / calcium levels)
- Serum sodium
- Paired serum / urine osmolality
- Urine output
- (Water deprivation test +/- DDAVP)
Hypoadrenalism

Adrenal cortex produces:

- **Glucocorticoids (Cortisol)**
  - Supports gluconeogenesis
  - Enhances vascular response to catecholamines
  - Varied other effects (anti-inflammatory etc)

- **Mineralocorticoids (Aldosterone)**
  - Sodium (+ water retention)
  - Maintenance of blood pressure

- **Androgens / Oestrogens**
Cholesterol

\[
\begin{align*}
Pregnenolone \quad & \xrightarrow{17 \text{ alpha}} \quad 17 \text{ OH Pregnenolone} \\
& \xrightarrow{3 \text{ beta}} \quad Progesterone \\
& \xrightarrow{17 \text{ alpha}} \quad 17 \text{ OH Progesterone} \\
& \xrightarrow{3 \text{ beta}} \quad Deoxycortocosterone \\
& \xrightarrow{11 \text{ beta}} \quad Corticosterone \\
& \xrightarrow{18 \text{ OH}} \quad Aldosterone \\
DHEA \quad & \xrightarrow{17,20} \quad Androstenedione \\
& \xrightarrow{3 \text{ beta}} \quad Testosterone \\
& \xrightarrow{11 \text{ beta}} \quad Deoxycortisol \\
& \xrightarrow{11 \text{ beta}} \quad Cortisol \\
& \xrightarrow{17,20} \quad Dihydrotestosterone \\
& \xrightarrow{} \quad Estrone \\
& \xrightarrow{} \quad Estradiol
\end{align*}
\]
Renin / angiotensin system

Aldosterone release
Hypoadrenalism

**Primary**

- Adrenal cortex not working (Loss of Cortisol and Aldosterone)
  - TB
  - Autoimmune destruction
  - Malignant infiltration
  - Adrenal infarction/haemorrhage
  - CAH

**Secondary / Tertiary**

- “Failure of higher control” (Loss of ACTH only)
  - **Cessation of longterm steroid tx (eg Prednisolone)**
  - Pituitary/hypothalamic disease
Hypoadrenalism

True or False?

- In isolated ACTH deficiency there is relative protection from hyperkalaemia
- In isolated ACTH hypotension overpowers the clinical presentation
- Normal saline is the rehydration fluid of choice
- It is important to wait for confirmation of low cortisol levels before replacing hydrocortisone in case the diagnosis is adrenal or pituitary TB
Primary adrenal failure

Loss of mineralocorticoid (aldosterone) and glucocorticoid (cortisol) effect

Effects of mineralocorticoid (aldosterone) deficiency overwhelm clinical presentation
Primary Adrenal Insufficiency

Loss of Aldosterone

- Failure of salt / water retention

**HYPOTENSION**
- Hyponatraemia
- Hyperkalaemia
- Metabolic acidosis

Presentation may be of insidious onset with abrupt decompensation due to intercurrent illness

Hyperpigmentation may be present reflecting high ACTH levels driving residual adrenal function
Secondary (tertiary) adrenal failure

Loss of glucocorticoid effect predominates (absence of ACTH drive to release cortisol)

- Loss of Cortisol reduces vascular responsiveness to vasoconstrictive mechanisms
- Reduced gluconeogenesis
- Preserved AVP drives free water retention in the face of hypotension

NB patients on long term steroid tx
Secondary Adrenal Insufficiency

There may be evidence of previous steroid excess (exogenous), pituitary failure or pituitary tumour (visual field defect, cranial nerve deficit)

Loss of Cortisol

- Hyponatraemia
- Hypoglycaemia
Which of the following are features of late onset CAH

- Late onset CAH is an important differential in the diagnosis of PCOS in girls
- Late onset CAH in men is associated with early puberty
- Late onset CAH in men is associated with tall stature
- Late onset CAH in men may be associated with increased testicular size and high sperm count
- Late onset CAH is best diagnosed using a LDDST
Which of the following is pathognomonic of Grave’s Disease

- Lid lag
- Exophthalmos
- Tacchycardia
- Pretibial myoedema
- Diplopia
Aetiology

- Autoimmune thyrotoxicosis
- Toxic multinodular goitre
- Acute thyroiditis
- Amiodarone

- Homology with HCG (Hyperemesis Gravidarum)
Thyrotoxicosis

- Look for features of thyrotoxicosis (many mediated by the sympathetic nervous system)
- Consider specific features of autoimmune thyrotoxicosis (Grave’s)
- Management:
  - Carbimazole, *Propylthiouricil
  - Propranolol
  - (*Steroids)
  - Radioactive Iodine
  - Surgery

*Reduce T4 to T3 conversion
Hypothyroidism (myxoedema coma)

Which of the following statements regarding hypothyroidism is / are true

- A low TSH and low Free T4 are diagnostic
- In suspected myxoedema coma it is important to replace thyroid function with sc T3 as an immediate priority
- Diastolic hypertension may be a feature and rewarming risks hypotension
- Mortality may be predicted in 20% cases
A lady is referred to the Endocrinology clinic with a PTH of 12.2 pmol/L (NR 1.2-6.8). Which of the following statements may be true?

- A low vitamin D level may be associated with a high PTH
- Patients with confirmed hyperparathyroidism should not be offered vitamin D supplements incase this increases their serum calcium levels to dangerous levels
- Vitamin D deficiency results in reduced urinary calcium loss and may confound investigations for hypocalciuric hypercalcaemia
- Emergency management of hypercalcaemia includes intravenous Pamidronate with the patient on a monitored bed
- Bed rest is a recognised cause of hypercalcaemia
The End

THANK YOU AND

GOOD LUCK