Diabetes and Endocrinology

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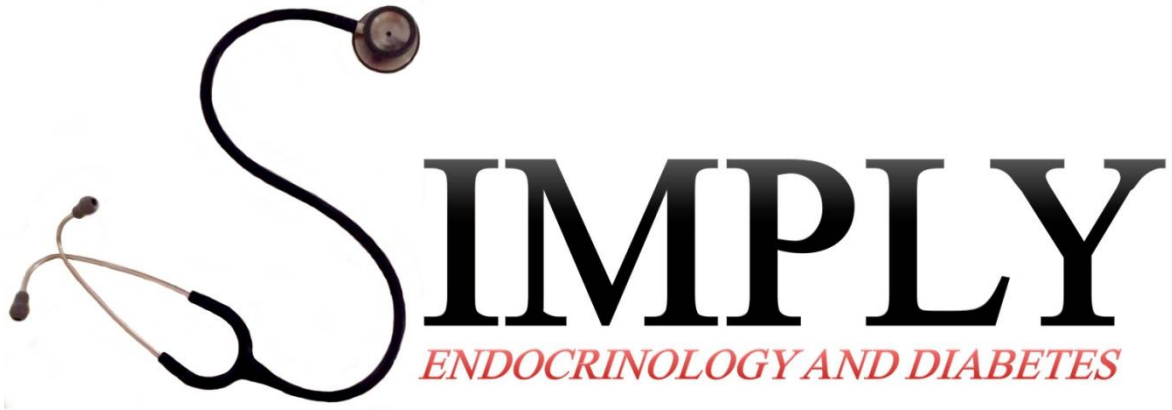

Acute Scenarios + Therapeutics

- Diabetes
  - DKA
  - HHS
- Endocrinology
  - Hypercalcaemia
  - Hypocortisolaemia
  - Thyrotoxic storm
  - Myoedema coma
  - Dynamic testing

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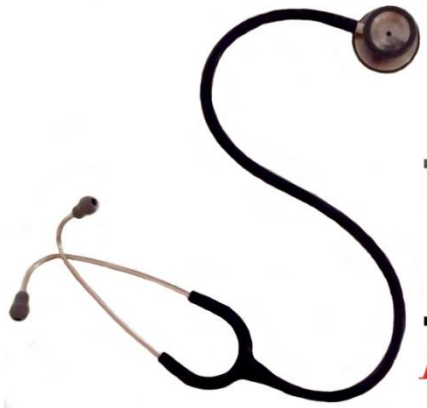
DIABETES MELLITUS



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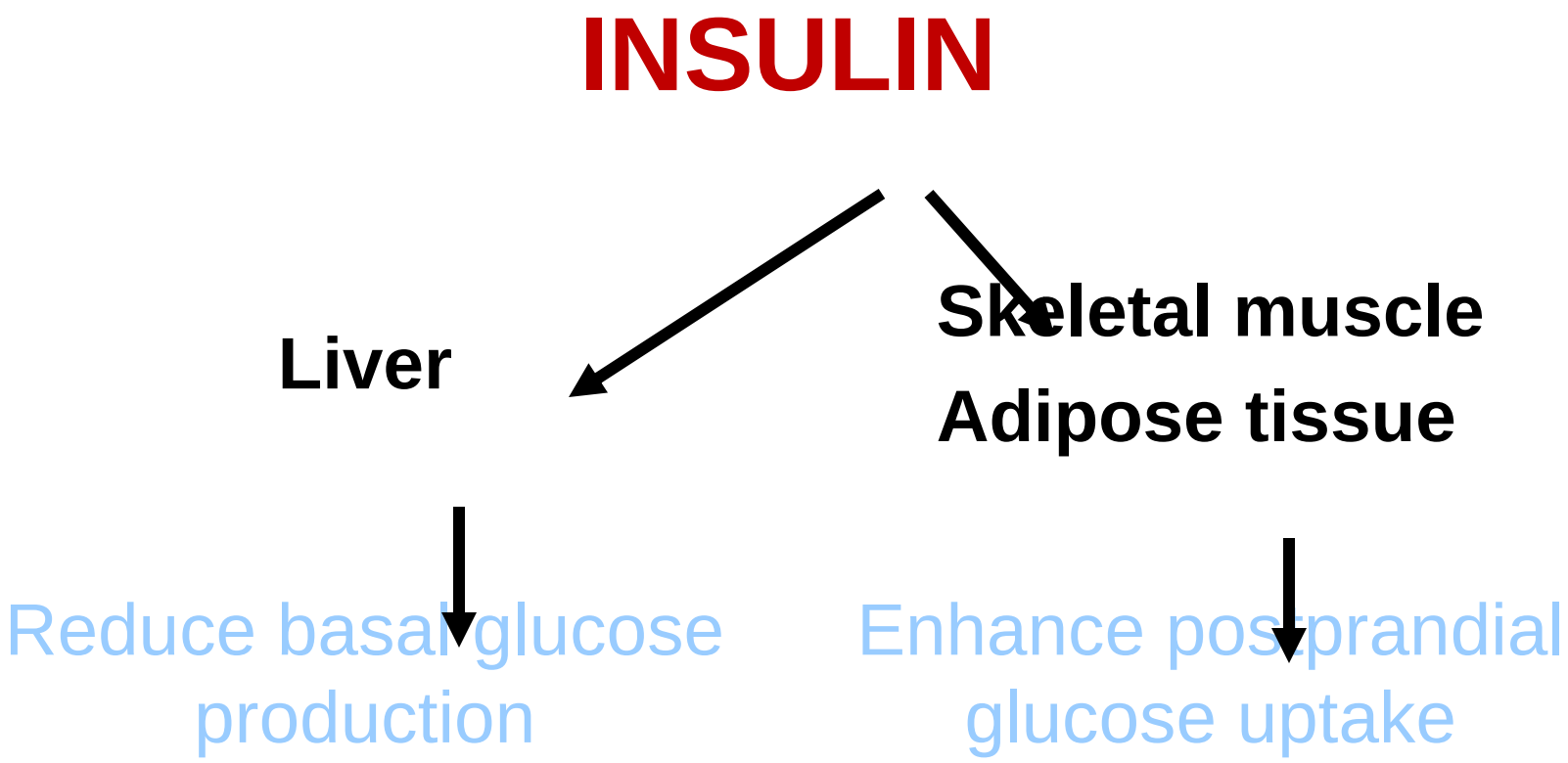
The control of blood sugar



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Degrees of insulin deficiency...

…Absolute insulin deficit

eg. T1DM, pancreatic failure

LOW LEVELS ENDOGENOUS INSULIN

…Relative insulin deficit (insulin resistance)

eg. T2DM, steroid use, intercurrent illness

HIGH LEVELS ENDOGENOUS INSULIN

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What are the features of insulin deficiency?

What are the features of insulin deficiency?

- Ketosis
- Salt, water, potassium loss

What are the features of insulin insufficiency?

What are the features of insulin insufficiency?

- Hyperglycaemia +/- salt water loss

Patient 1

- 22 year old Caucasian male
- 3 week history of polyuria / polydipsia
- Weight loss 8kg

- No other PMH
- Family history: Hypertension

Investigations:

Na	132	FBC	14.2
K	5.4	WCC	11.3
Urea	8.6		
Cr	125		
Glucose	22		

What other immediate tests do you want?

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Further investigations

Urine Dip:	Glucose 3+, Ketones 3+	
POC ketone testing:	5mmol/L	
ABG:	pH	7.20
	CO_2	3.0
	HCO_3	12
	Anion Gap	HIGH

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Diagnosis?

Diagnosis?

DKA

Diagnositc criteria - DKA

- Acidosis: pH < 7.3,
  HCO_3 < 15mmol/L,
  BE < -10

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

- Known diabetes OR plasma glucose >11mmol/L

What are Ketones?

- Ketones are produced as a byproduct of fatty acid synthesis reflecting low effective levels of insulin (starvation, pancreatic failure, extreme insulin resistance)
- 3 types
  - Acetone
  - Acetoacetate (acetoacetic acid)
  - β hydroxybutyrate (β hydroxybutyric acid)

What is ketoacidosis?

Effective insulin deficiency

↓

Failure of glucose metabolism

↓	↓
Breakdown of FFAs for fuel	Hyperglycaemia
↓	↓
Generation of Ketone bodies (acidic)	**Salt + K + water loss**

What is ketoacidosis?

ADIPOSE TISSUE

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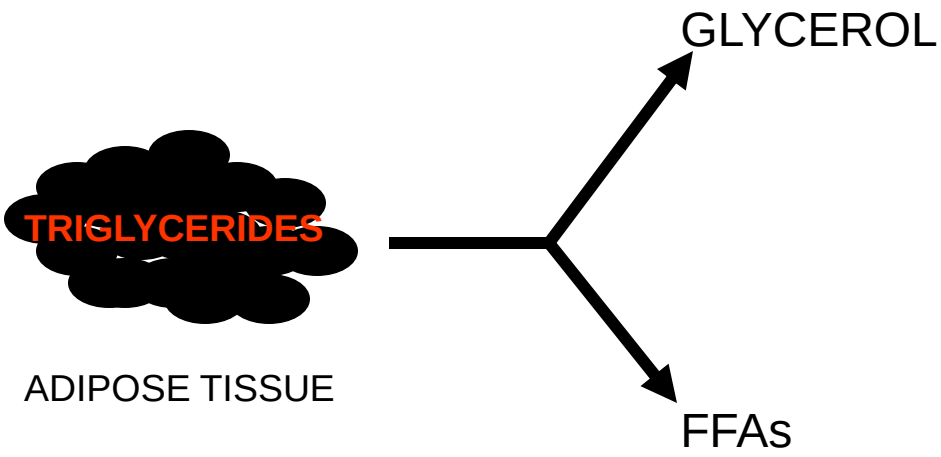
What is ketoacidosis?



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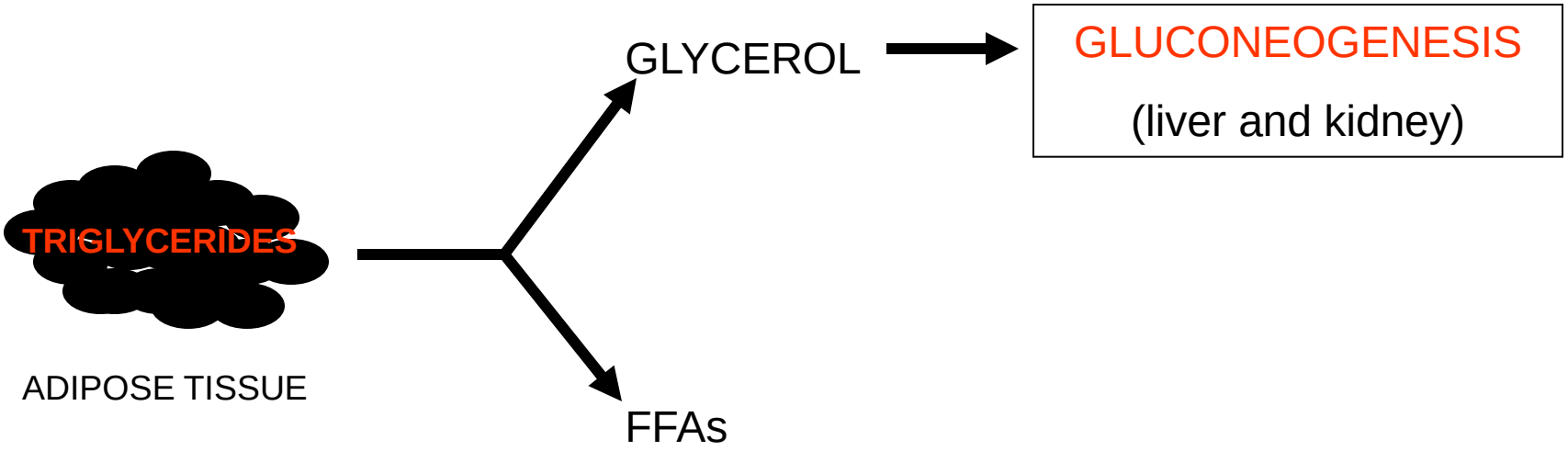
What is ketoacidosis?



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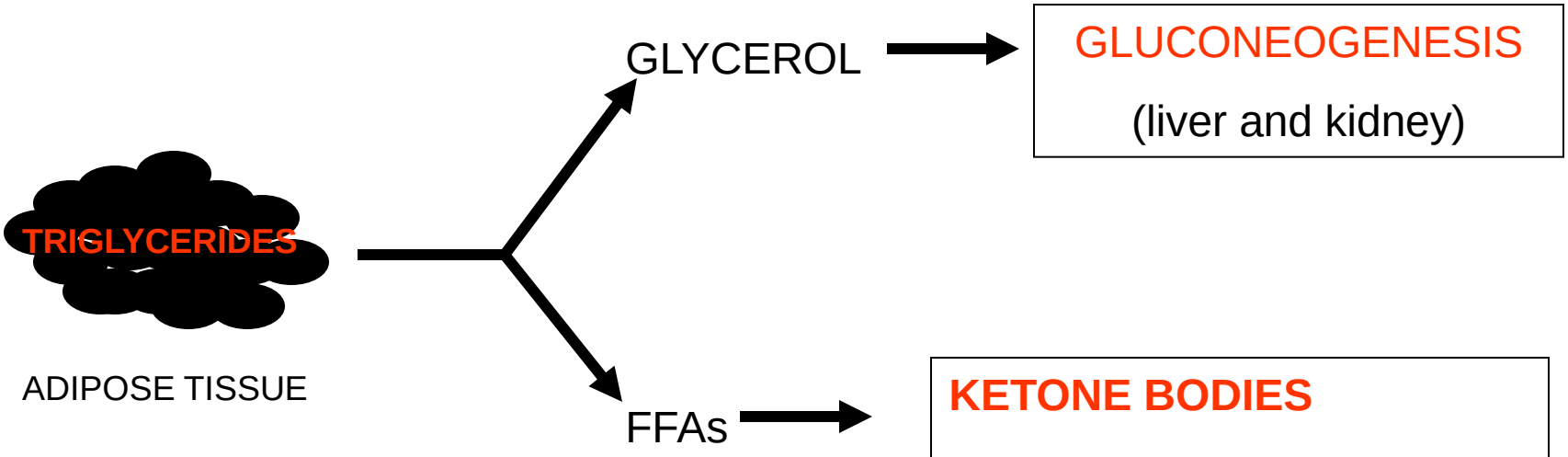

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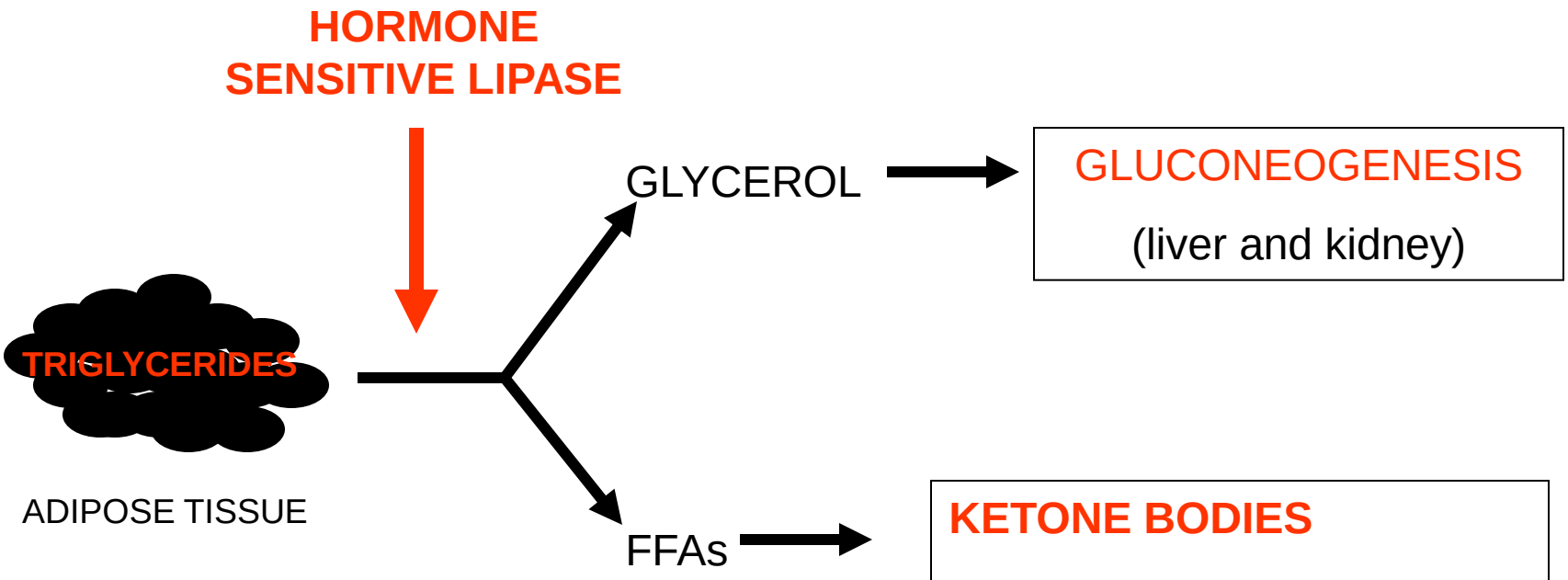

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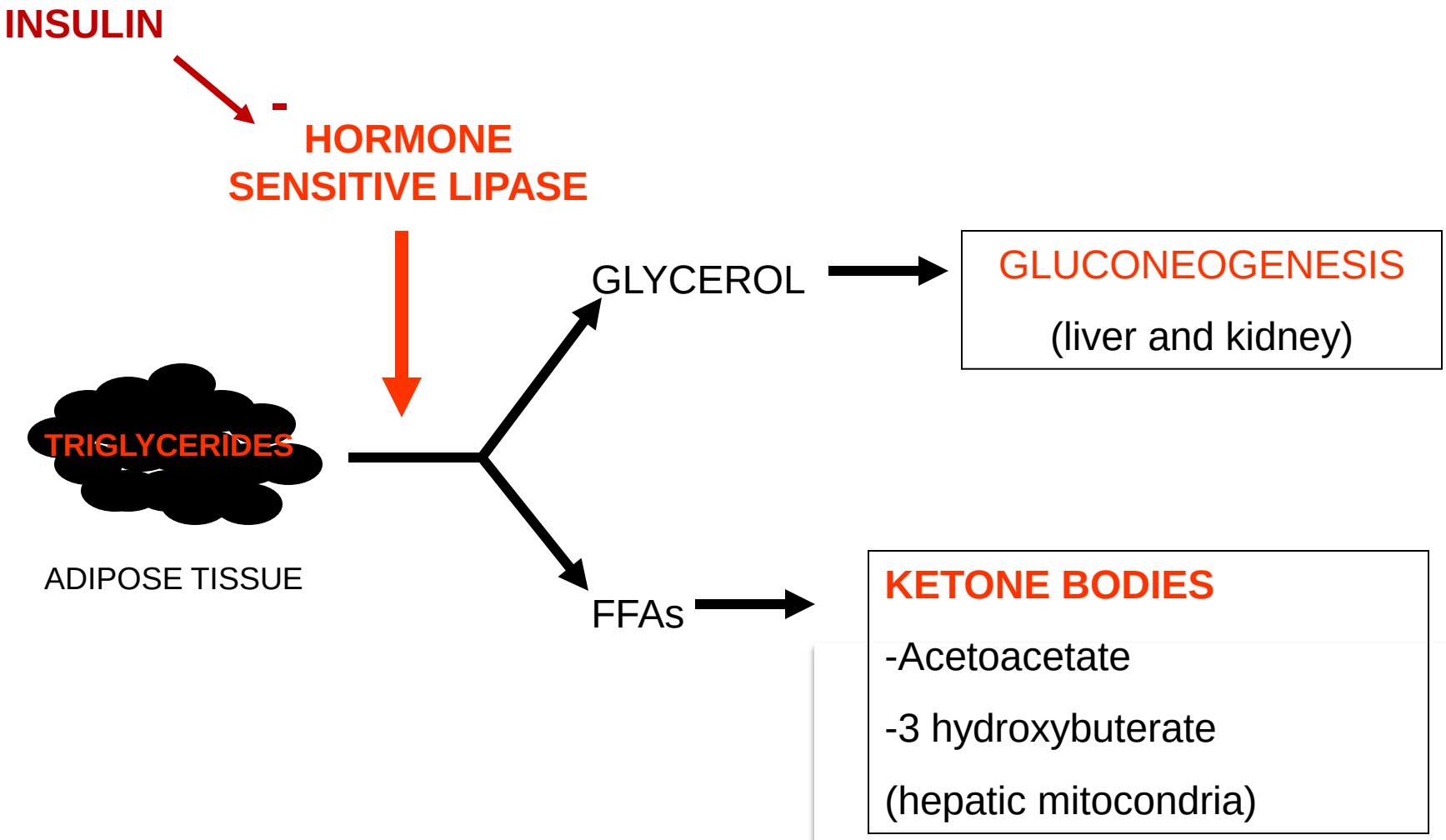

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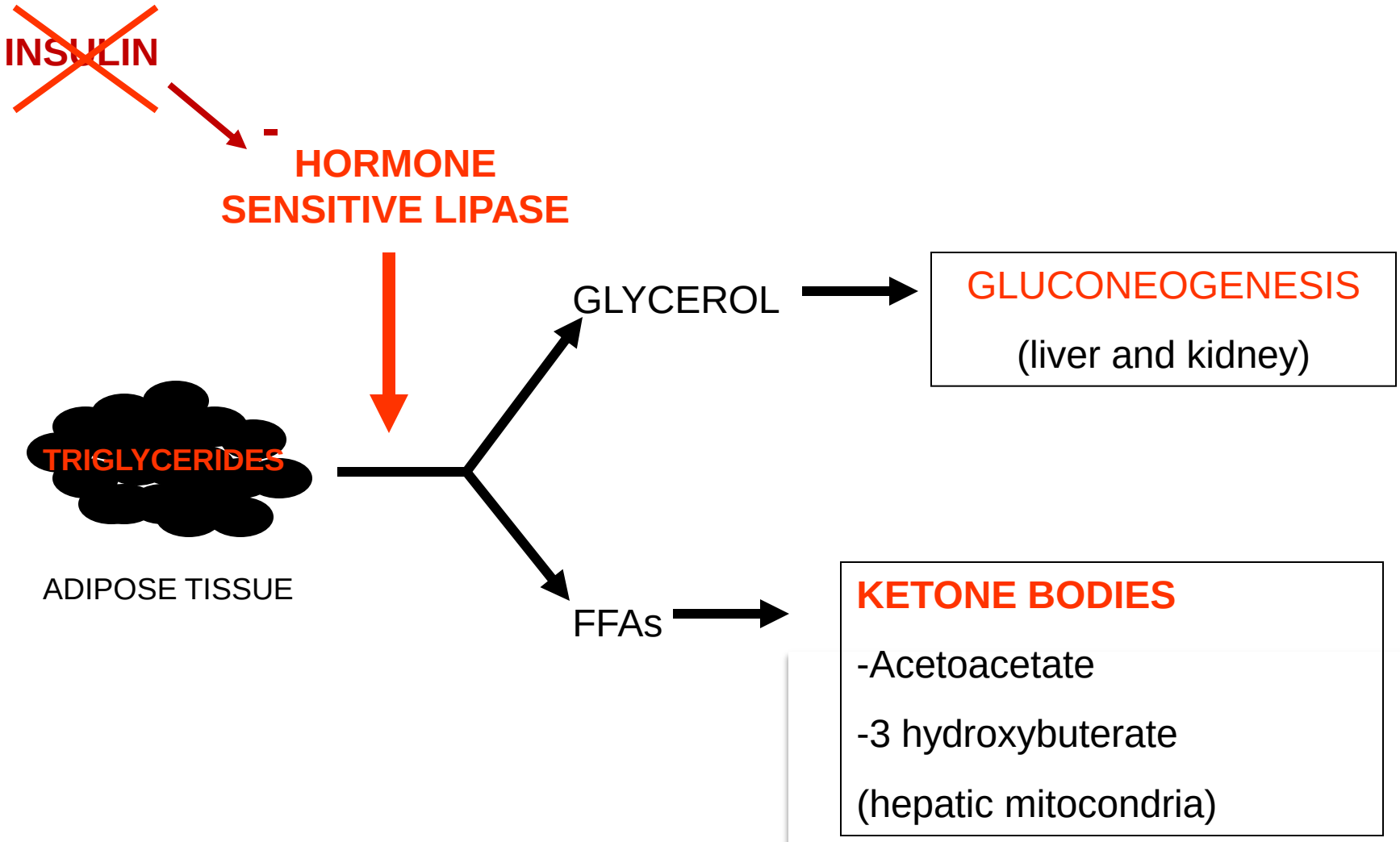

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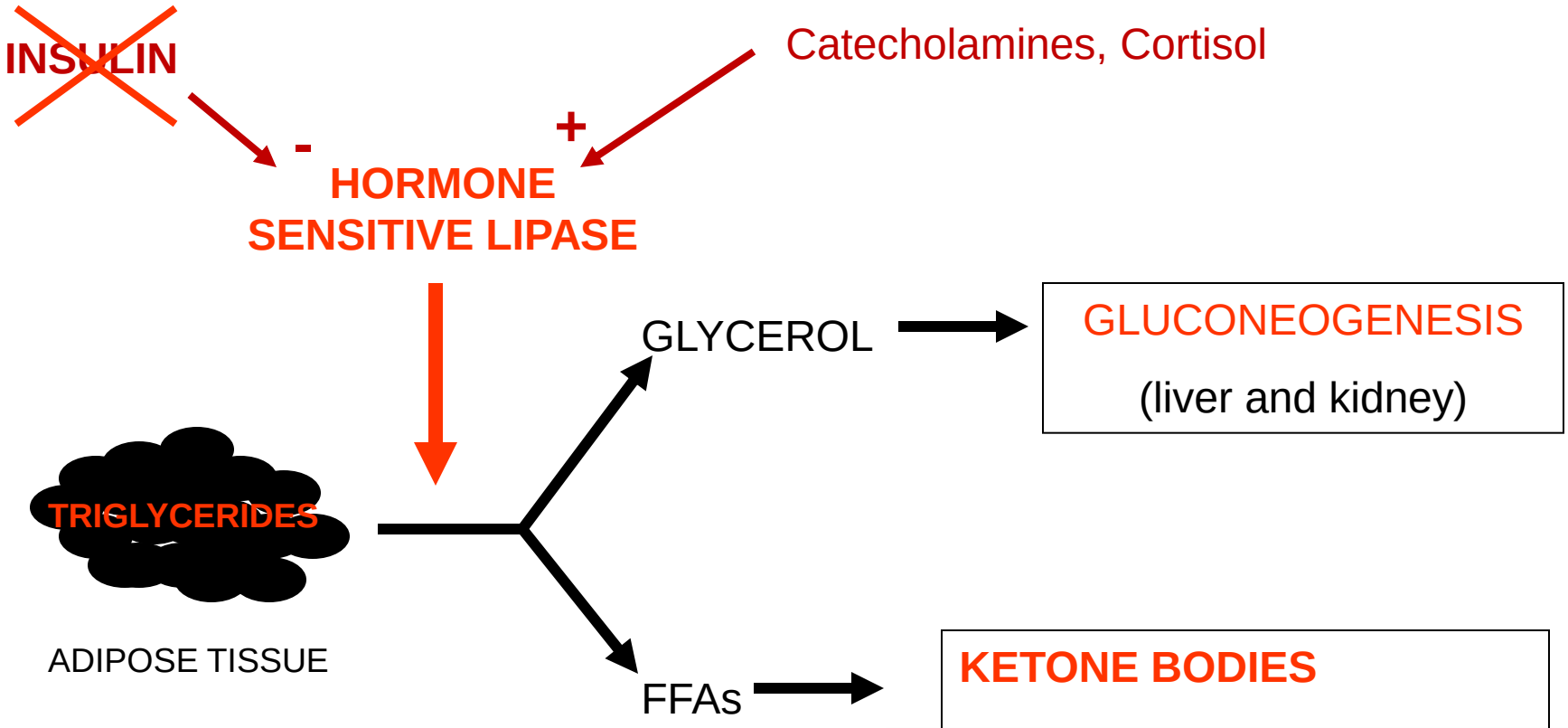
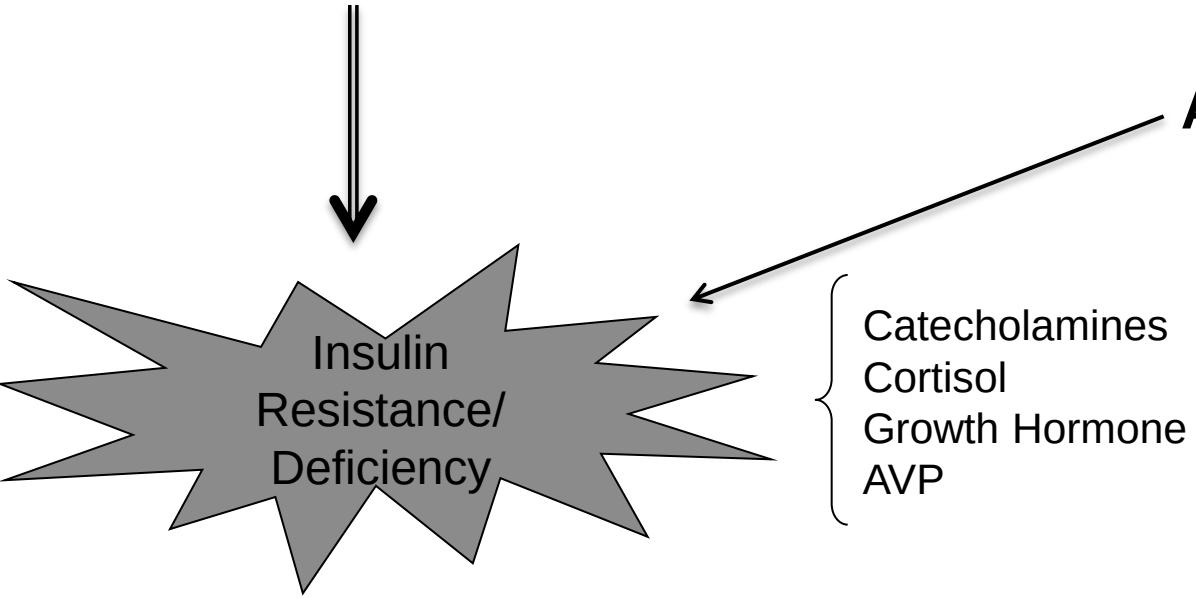


What are Ketones?

- Acetone – cannot be used by the body as fuel and is excreted
- Acetoacetate – can be used by the heart and brain as a source of energy
- β hydroxybutyrate – can be used by the heart and brain as a source of energy
- Both acetoacetate and β hydroxybutyrate are essential during times of fasting

Development of DKA

Poor compliance with insulin therapy



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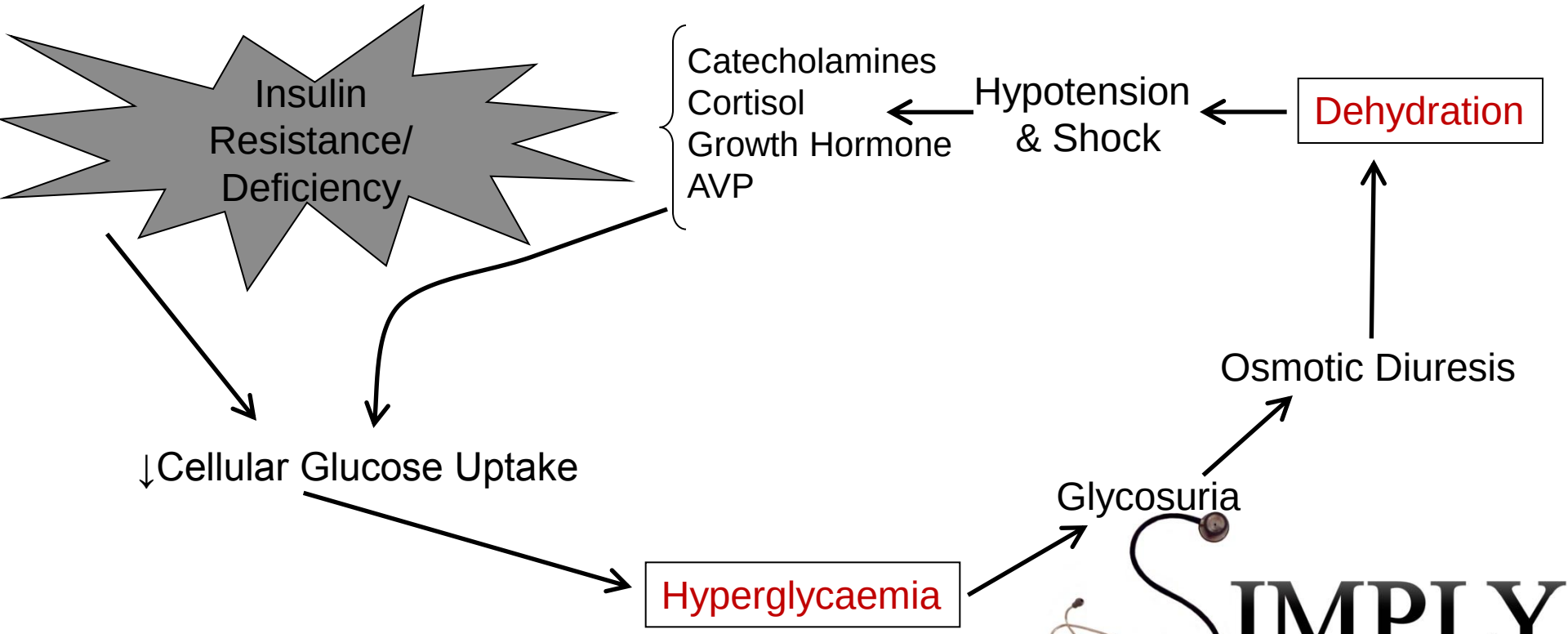
Development of DKA



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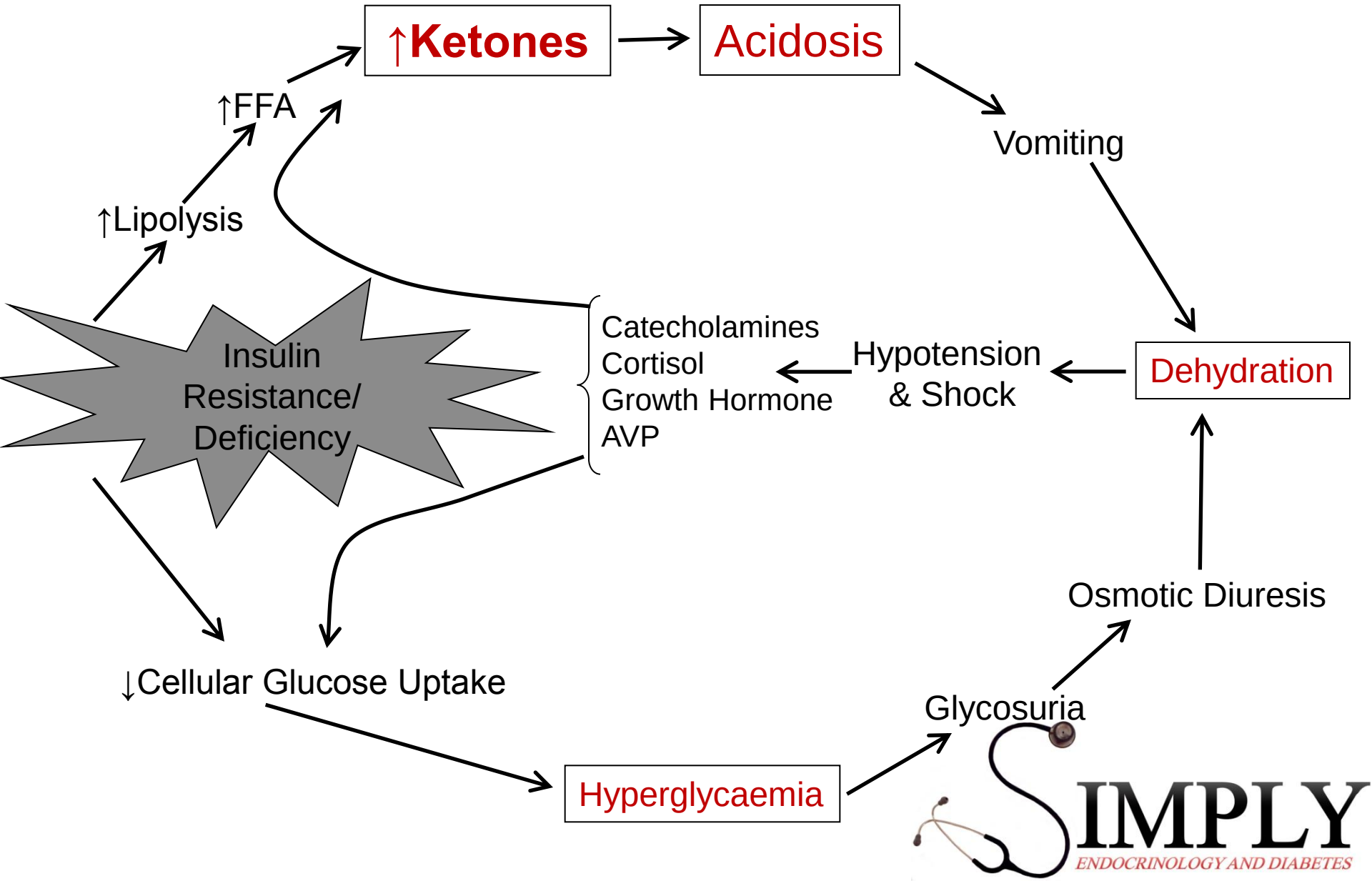
↑Ketones
Acidosis
↑FFA
Vomiting
↑Lipolysis
Insulin Resistance/ Deficiency
Catecholamines
Cortisol
Growth Hormone
AVP
Hypotension & Shock
Dehydration
Osmotic Diuresis
↓Cellular Glucose Uptake
Glycosuria
Hyperglycaemia
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Management – what are the priorities?

- Restore salt and water
- Replace insulin to terminate ketogenesis

AVOID HYPOKALAEMIA
AVOID HYPOGLYCAEMIA

Management

- RESTORE CIRCULATING VOLUME
  0.9% saline infusion until volume replete.
- TERMINATE KETOGENESIS
  Maintain on continuous insulin infusion (may need additional dextrose infusion to permit this, if BG < 14mmol/L).
- AVOID HYPOKALAEMIA
  Monitor serum potassium levels every 2 hours.

When can the fixed rate infusion stop?

As soon as ketogenesis is terminated

- Capillary ketone measurement <0.6mmol/l

- Surrogates:
  - Plasma 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

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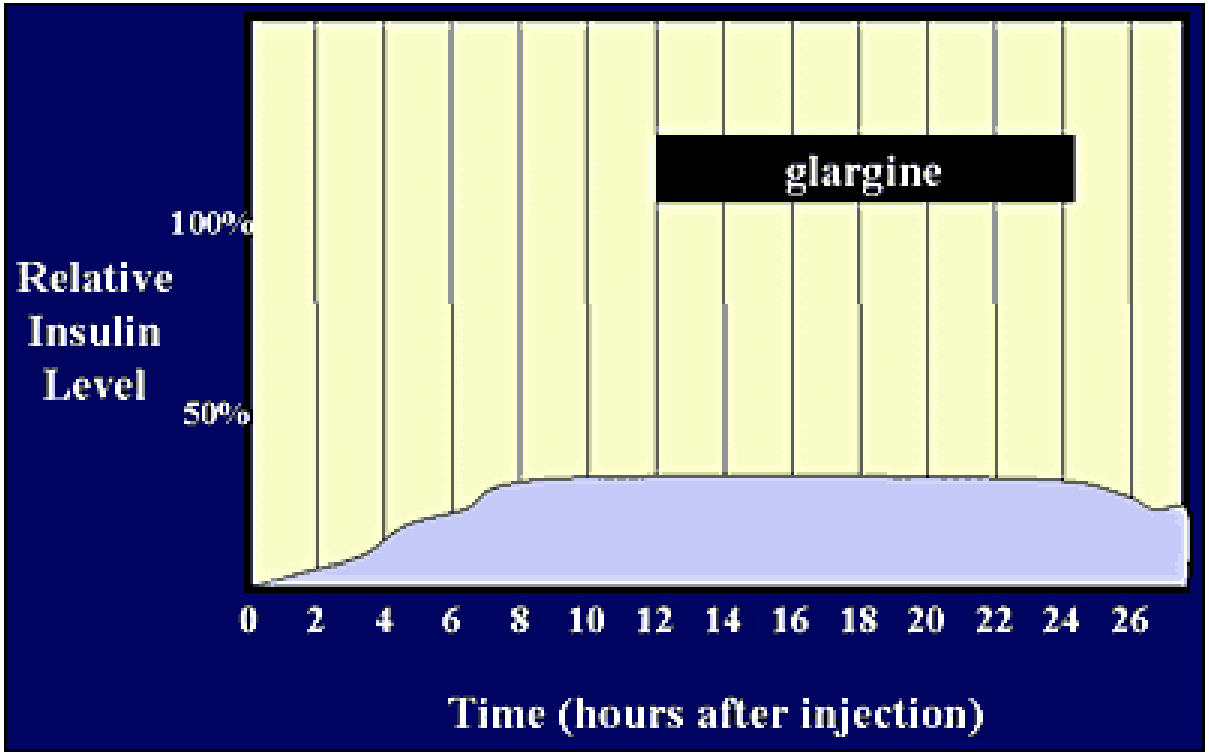
Know your insulins……

- Intermediate (Long) acting
- Basal bolus
- Mixture

Long acting insulin (glargine/detemir)



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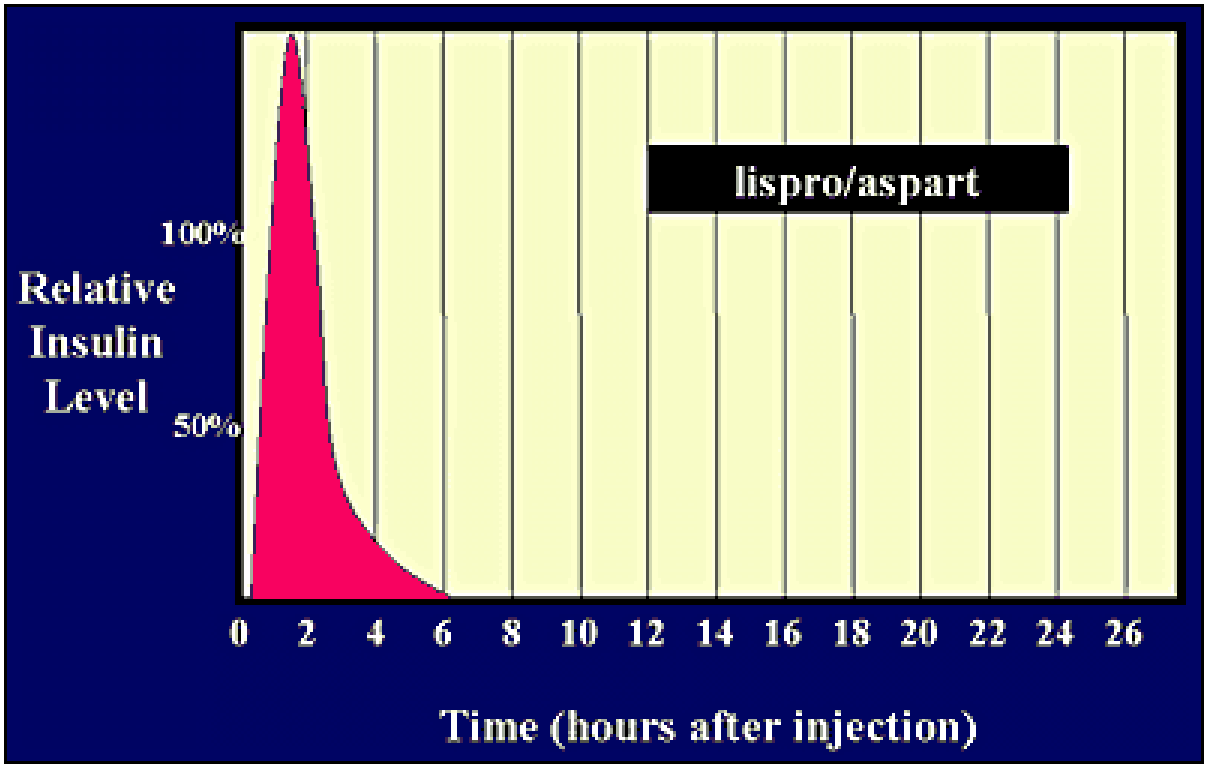
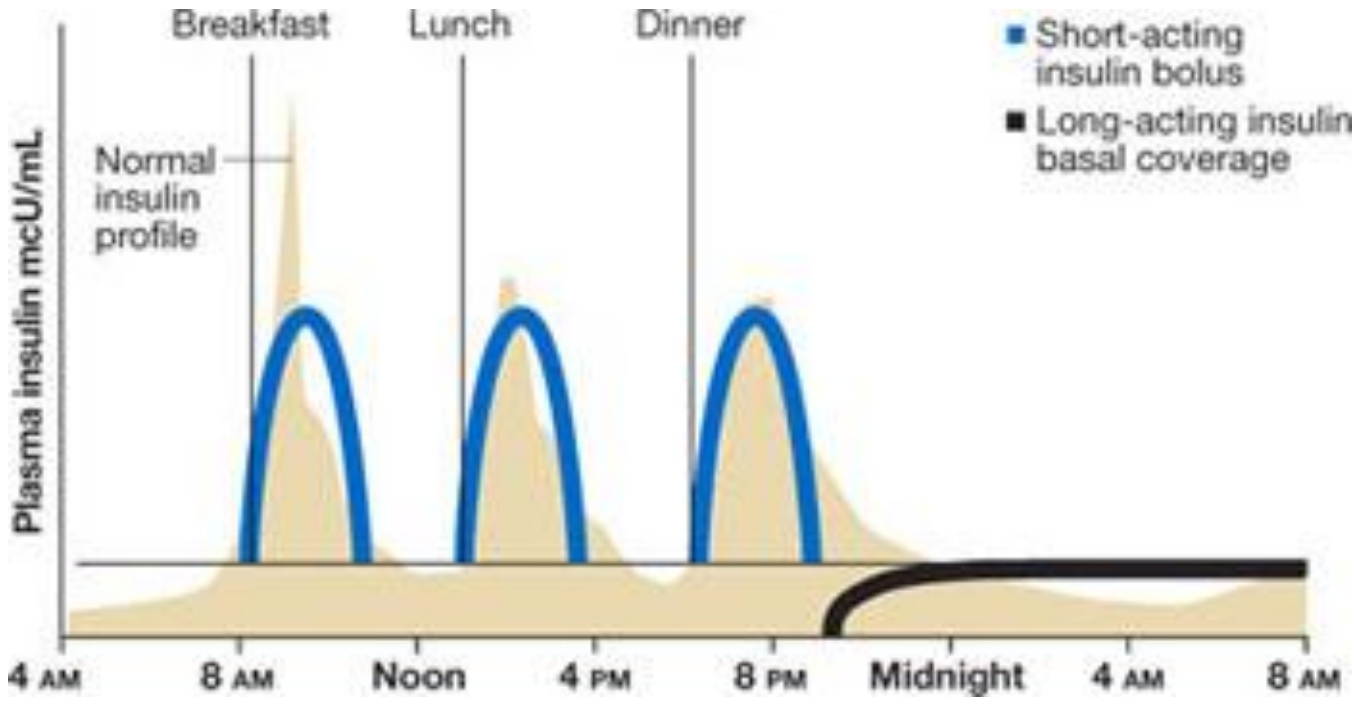
Rapid acting insulins



Basal bolus



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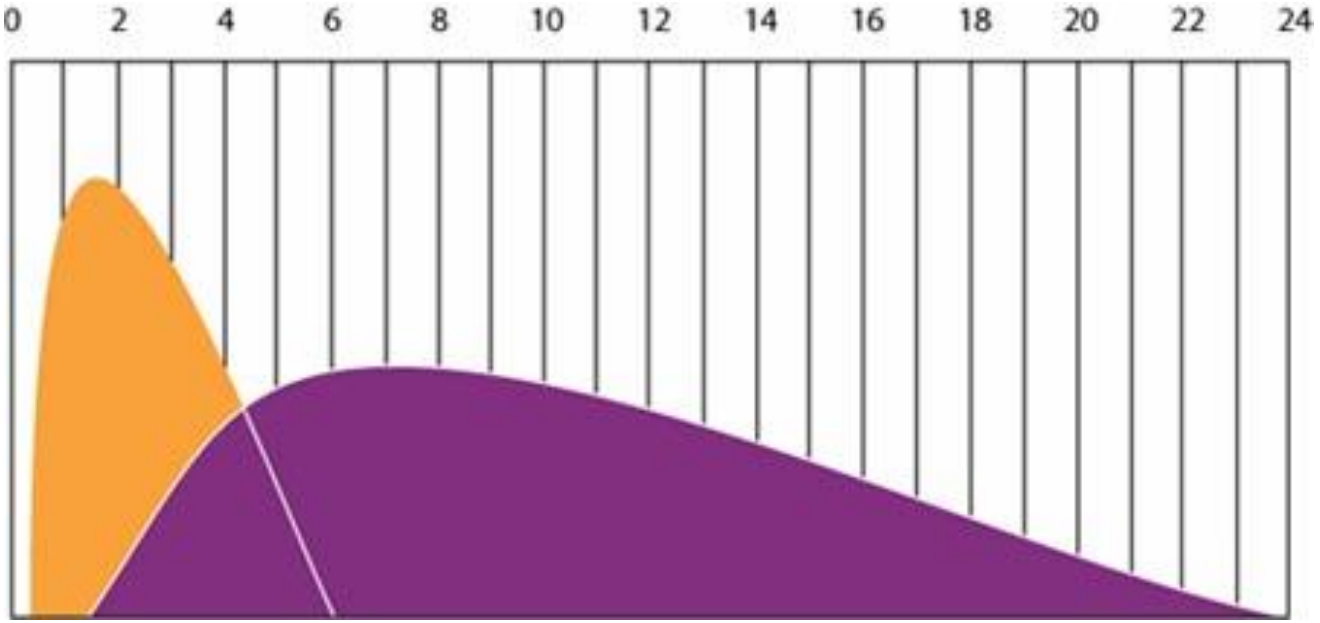
Premixed insulin



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Measure CBG 4x per day

- Fasting
  - Reflects long acting insulin component
- Postprandial
  - Reflects short acting component

+/- 3am blood glucose if on “old style” insulatard.

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Insulin infusions

- Fixed rate (DKA)
- Variable rate (Other)

Keep continuous acting basal insulin alongside

Variable rate insulin infusions

Capillary blood sugar	Insulin infusion (units/hr)
0-4	0.5
4-8	1
8-12	2
12-16	4
16-20	6
20-24	8
24-28	12

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Hyperglycaemic Hyperosmolar State (Type 2 diabetes)

Insulin resistance

vs

Failing β cell function

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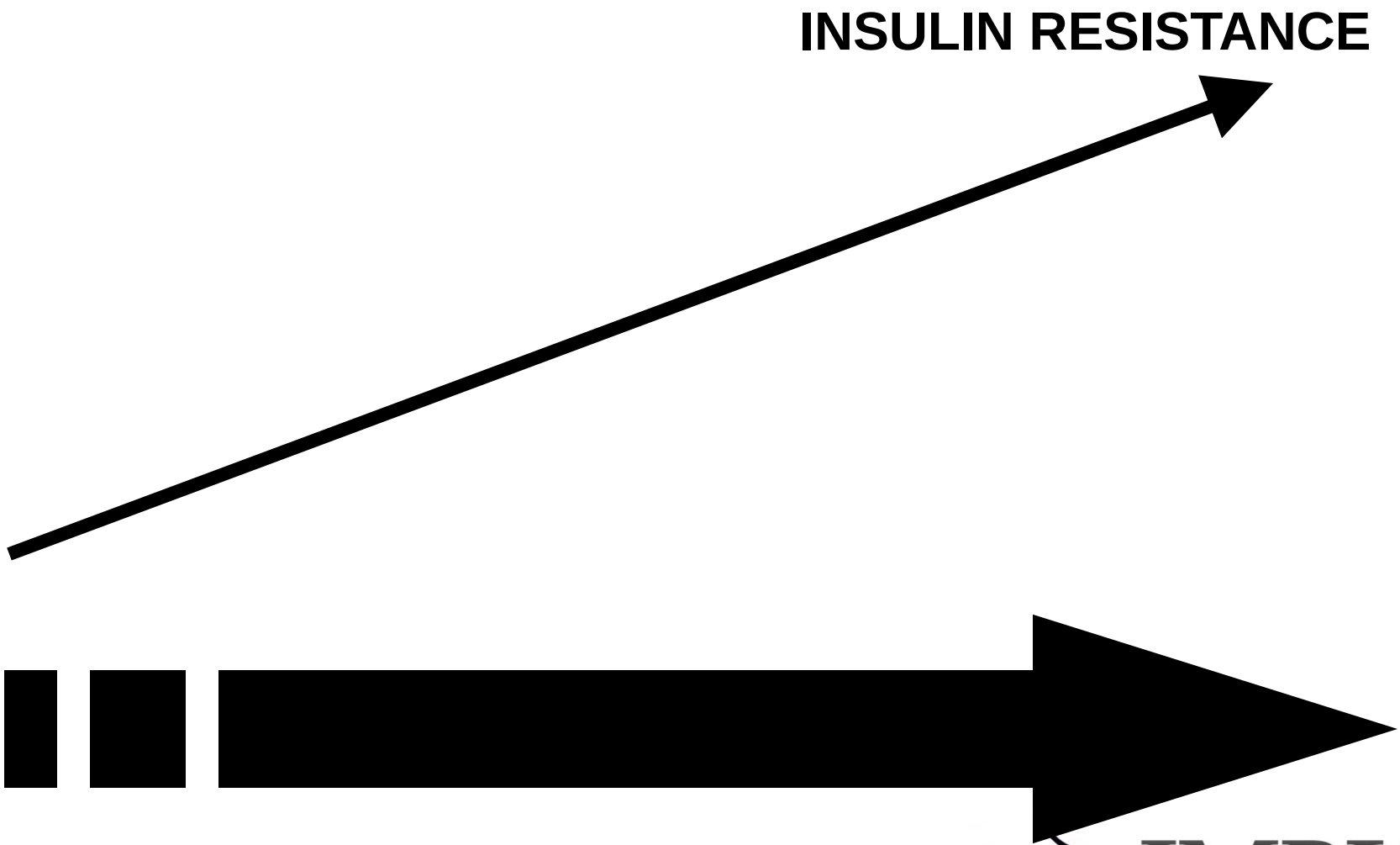

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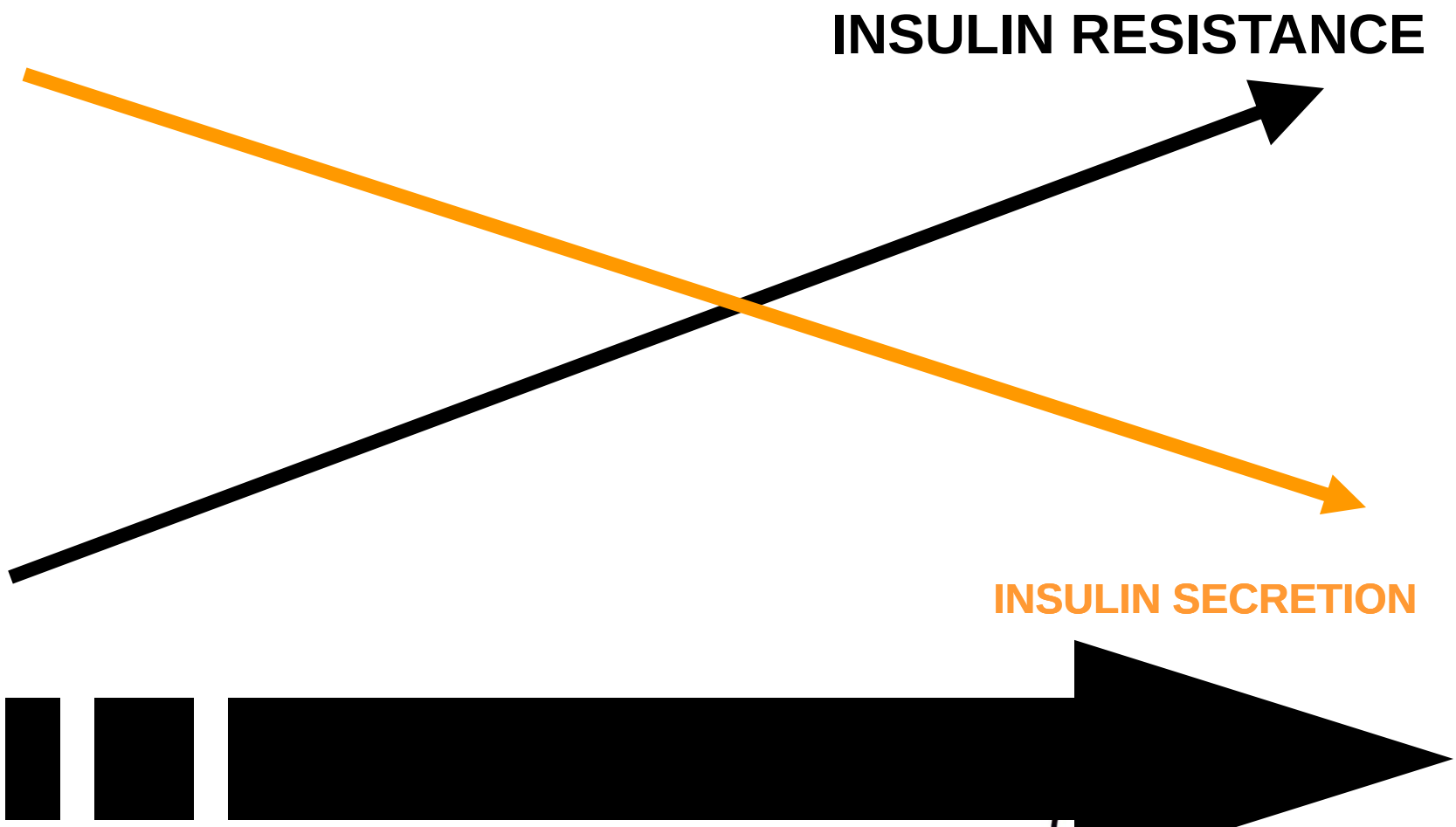

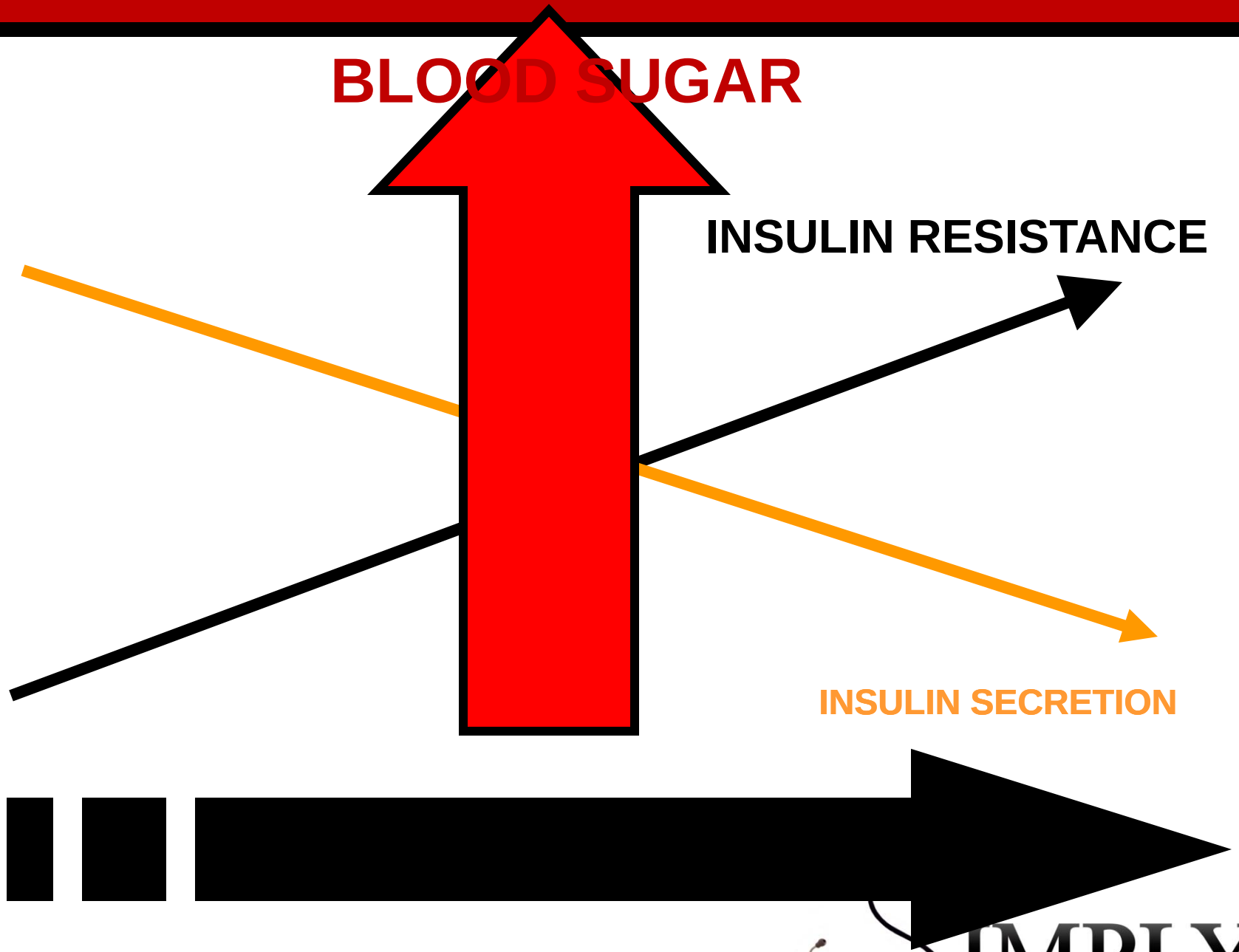

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Patient 4

86 year old man

Brought in from nursing home – reduced conscious level

PMH: bed bound/Stroke/Aphasia and L hemiparesis, Hypertension etc

Clinically DRY

Investigations

Na	165	FBC	14.2
K	5.6	WCC	18.3
Cr	200	Glucose	55

Urine Dip: Glucose 3+, Ketones 1+

pH 7.30, HCO_3 20, CO_2 6.0, Anion Gap Normal

Serum osmolality: (165 x 2) + 55 = ***385***

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Diagnosis?

Diagnosis?

HHS

(Hyperglycaemic Hyperosmolar State)

= HONK

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Management….?

Management

- Restore circulating volume, gradually and safely …
  N Saline

4 hours later

- Serum sodium = 175
- Glucose = 15

- Management…..

Osmolality = (175 x 2) + 15 = 365

ie fall of 20 over 4 hours

= PERFECT, continue N saline

Aim to keep BG around 14

Hyperglycaemic Hyperosmolar State (HHS)

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

Average fluid deficit 10-20L for 100kg man

Diagnosis

Hyperglycaemia
- typically blood glucose >30mmol/L

- Hyperosmolar
  - typically >340mOsm/kg
- Ketones
  - typically <+

Aim of treatment

Aim for a gentle but consistent fall in osmolality

Avoid tight control for 72 hours

Why don’t we give insulin?

T2DM

Therapeutics

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Therapeutic strategies

- Diet and exercise
- Insulin sensitizer
- 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

Thiazolidinediones

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

Side effects

- Oedema, weight gain

Suphonylureas

- Insulin secretagogues
- Will reduce blood glucose levels by 3 -4mmol/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

Incretins

Gut hormones enhance insulin release to a glucose load

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

….and increase satiety?

GLP1

- Enhances postprandial insulin secretion
- Slows gastric emptying
- Suppresses appetite and food intake

Extremely short half life of 2 minutes due to degradation by DPP IV

GLP1 receptor agonists

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DPP IV inhibitors

- “Gliptins”
- Increase endogenous GLP1 levels
- Moderate effect on glycaemic levels, particularly early in the disease

Side effects

- Headache, URTI

SGLT2 inhibitors

- Dipagliflozin
- Cause glycosuria (!)
- No long term efficacy data known

……..

Bariatric surgery

Restrictive procedures:

- Gastric band

Restrictive and malabsorptive procedures

- Gastric bypass

Significant weight loss can reverse diabetes

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Long term complications of diabetes

Microvascular

- Retinopathy
- Nephropathy
- Autonomic neuropathy
- Peripheral neuropathy

Macrovascular

- Atheromatous disease

Management

- Blood pressure control (ACEI)
- Management of dyslipidaemia
- Screening (eyes, feet, microalbuminuria)
- Proactive support (chiropody, psychological, motivation)

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

Background retinopathy

- Microaneurysms
- Dot Blot Haemorrhages
- Hard exudates

Preproliferative retinopathy

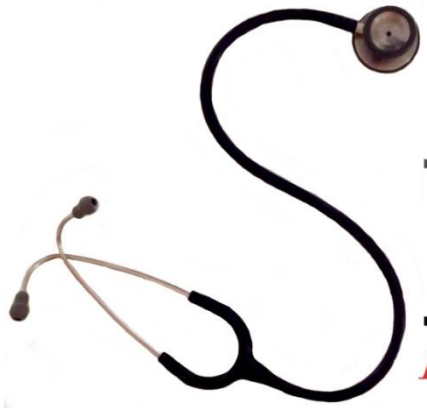
+ cotton wool spots (local infarction)

Venous beading and looping

Proliferative retinopathy

- Growth of new vessels, risk of haemorrhage

ENDOCRINOLOGY



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All you need in an emergency…..

- Salt water (normal saline)
- Hydrocortisone
- Dextrose (rarely)

GOOD CLINICAL ASSESSMENT
AND BEFORE YOU DO ANYTHING
TAKE SAMPLES FOR STORAGE

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Case 1

- 64yo lady
- 4 month hx of polyuria and polydipsia
- Unintentional weight loss 2 stone over 2 months
- Admitted with a fall and #NOF

- O/E BP86/54 Pulse 94 CBG 4.4
  CXR NAD ECG sinus tachycardia

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cCa 3.2mmol.L

- Urea 13.2, Creat 600
- Hb 9.2 MVC 92 WCC 6.0

Issues

1. Acute management of hypercalcaemia
2. Immediate investigations in hypercalcaemia
3. Longer term management

Acute effects of Hypercalcaemia

Dehydration
- ***Renal loss of salt/water**
- Nausea / Vomiting

Neurological Manifestations
- Proximal myopathy
- Poor concentration / drowsiness
- Depression
- Coma

Cardiovascular system
- Shortened QT interval
- 1st Degree AV Block
- Bradycardia
- Asystole

Symptoms of Hypercalcaemia

Severity dependant on speed of change

Fatigue	Constipation
Polydipsia	Proximal Myopathy
Confusion	Nephrolithiasis
Anorexia	Pancreatitis
Depression	Peptic Ulcer disease
Dehydration	Nausea

Management

- N Saline ++++
- Cardiac monitor

Investigation (acute)

- U+E
- Bone profile (Calcium / phosphate)
- Albumin
- Vitamin D
- Urine calcium secretion
- PTH (but must be taken onto ice)

- ECG

ONCE VOLUME REPLETE

- Furosemide
- Bisphosphonates
- Dialysis/haemofiltration

- Consider steroids in haematological malignancy / granulomatous disease

Hypercalcaemia

Causes:

- Hyperparathyroidism
- Malignancy (PTH – RP / Osteolytic bone metastases / haematological malignancy)
- Chronic granulomatous disorders
- Drugs
- Misc (Immobilisation etc)

Case 2

- 76yo man
- Admitted with 2/7 hx of N+V following extensive dental treatment under GA
- PMH COPD
- Tx Blue inhalers / Brown inhalers, prn abx and steroids for COPD exacerbations

- BP 95/56 Pulse 93
- Dehydrated, otherwise unremarkable
- CBG 2.8

- Na 124 K 3.8 Urea 7.8 Creat 160

- ECG Normal
- CXR Changes consistent with COPD no consolidation

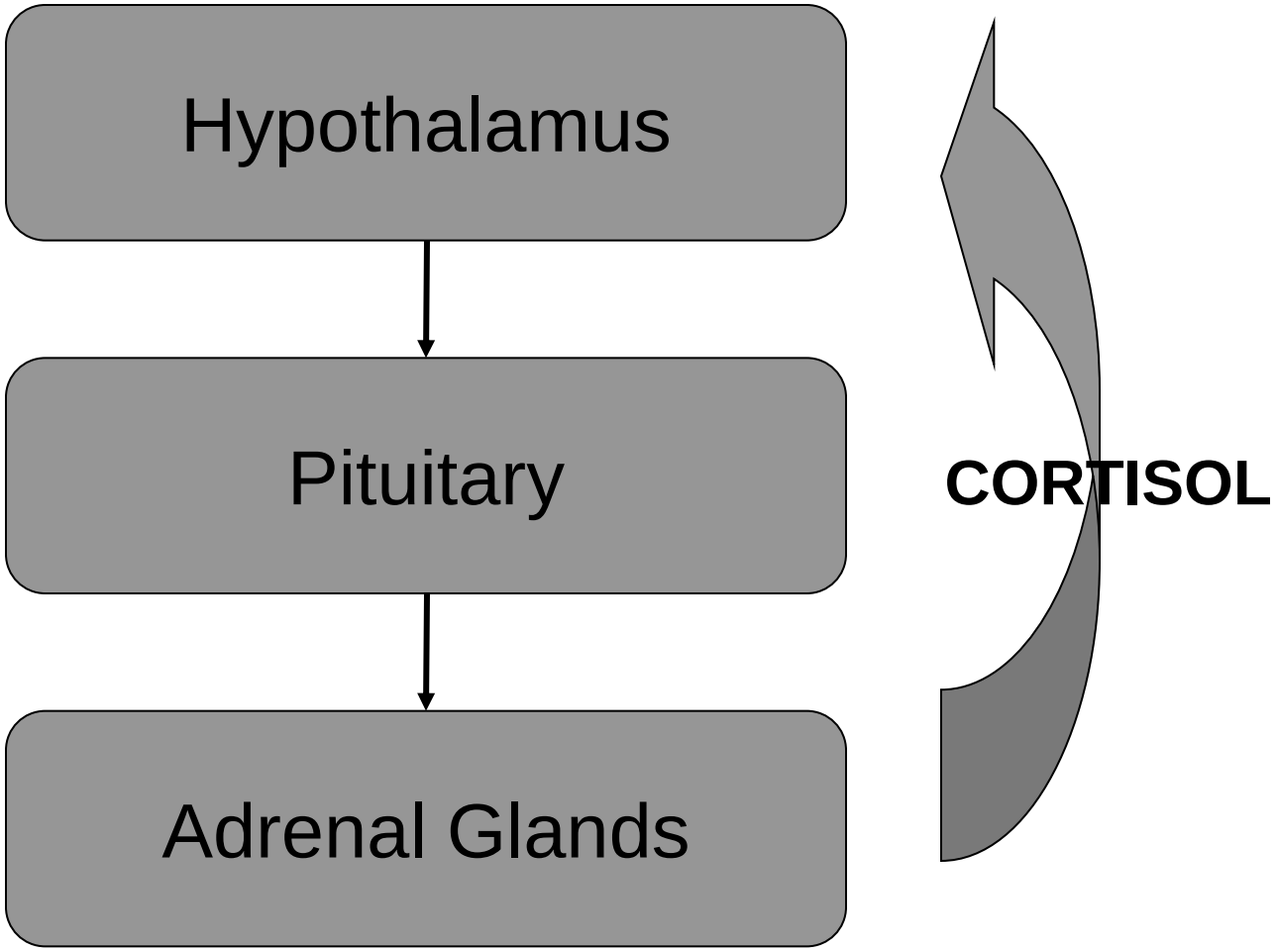
Hypoadrenalism

Adrenal gland produces:

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*



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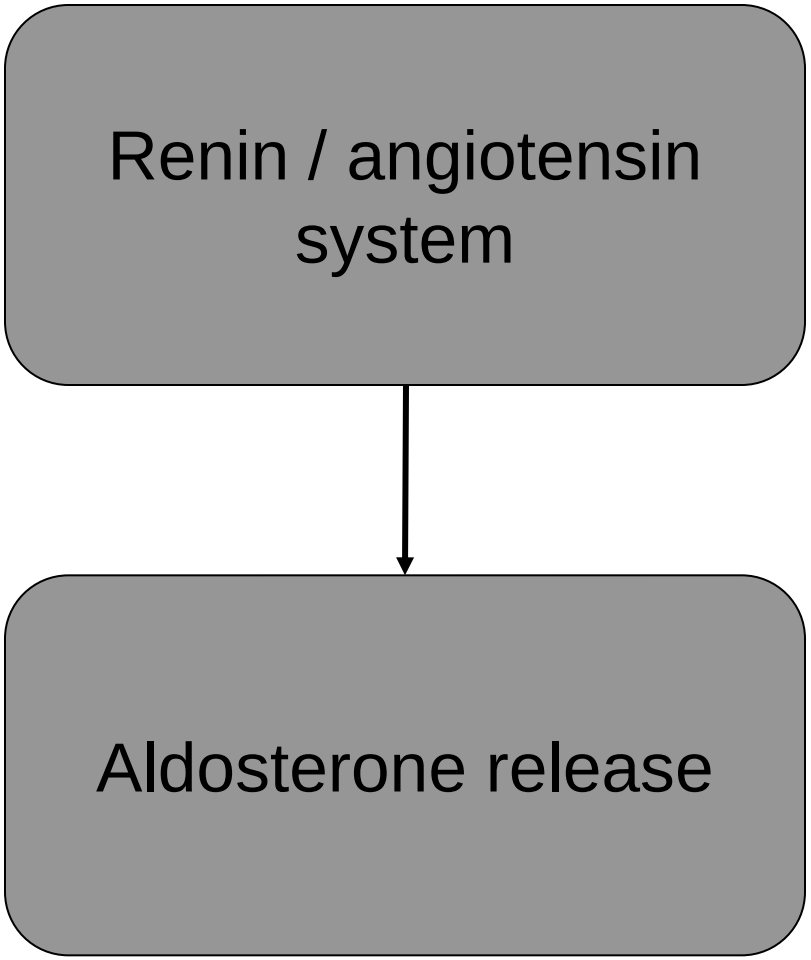

Hypoadrenalism

Causes:

- Primary
  - Adrenal cortex not working
- Secondary / Tertiary
  - “Failure of higher control”

Hypoadrenalism

- Primary
  - TB
  - Autoimmune destruction
  - Malignant infiltration
  - Adrenal infarction/haemorrhage
- Secondary / Tertiary = loss of ACTH stimulation
  - **Cessation of longterm steroid tx (eg Prednisolone)
  - Pituitary/hypothalamic disease

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

Hyperkalaemia

Metabolic acidosis

Primary Adrenal Insufficiency

↓

Loss of Aldosterone

↓

Failure of salt / water retention

↓

HYPOTENSION

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)

Secondary Adrenal Insufficiency

↓

Loss of Cortisol

↓

Hyponatraemia

Hypoglycaemia

Secondary Adrenal Insufficiency

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

↓

Loss of Cortisol

↓

Hyponatraemia

Hypoglycaemia

Investigation

****sample for storage***

- Serum sodium and potassium
- ABG
- Blood glucose
- ACTH / Cortisol
- TFT

Acute management

Circulatory support – 0.9% (Normal) Saline
SAMPLES FOR STORAGE

- im hydrocortisone 100mg qds **or** ivi 1-2mg/hr
- Correct hypoglycaemia
- Avoid hypothermia

Longer term management

- Confirm hypocortisolaemia (admission stored sample)
- Exclude global pituitary failure
- Commence po hydrocortisone
- Unlikely to require fludrocortisone (mineralocorticoid function intact)
- Maintain longer term review of steroid dependence

Case 3

- 46yo woman
- Brought to hospital by police for disturbing the peace
- Acutely confused, aggressive, trying to escape from the hospital
- No PMH
- O/E cachectic, temp 39c, pulse 160 SR, globally hyper-reflexic

Thyroid storm

- Fever
- Tachycardia/arrhythmias
- Anxiety / restlessness / psychosis
- Dehydration

Complications: cardiac failure, liver failure, renal failure

Apathetic storm: Weakness, apathy, confusion, absent fever

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Treatment

- Bed rest (sedation)
- *PTU 150-250mg qds
- *Dexamethasone 2mg qds
- Propranolol – 20-200mg qds
- Cooling
- Nutritional support / vitamins

*reduce T4 to T3 conversion

Aetiology

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

- Homology with HCG (Hyperemesis Gravidarum)

Longer term management

- Antithyroid medications
  - Carbimazole
  - Propylthiouricil
- BBlockers (sympathetic stimulation)
- Radioactive iodine
- Surgery

Case 4

- 64 yo woman
- Found on floor by neighbour
- PMH not known
- GCS 11, core temp 34c, BP 113/96, globally sluggish reflexes

- ECG ST elevation inferior leads

Myxoedema Coma

- Reduced conscious level
- Hypothermia / absence of fever

Mortality 20%

Adaptations include peripheral vasoconstriction to reduce circulating blood volume and maintain core temperature. This results in diastolic hypertension.

Decompensating events: Infection, heart failure, cold exposure, GI bleed, diuretics, sedatives

Treatment

Hypothyroidism	300-500mcg T4 +/- 25mcgT3 iv
Hypocortisolaemia	iv hydrocortisone infusion
Hypoventilation	Intubation
Hypothermia	Central warming / passive
Hyponatraemia	Mild water restriction
Hypotension	Crystalloid / whole blood
Hypoglycaemia	Glucose
Precipitating event	Prophylactic abx

Aetiology

- Autoimmune
- Pituitary failure
- Malignant infiltration (malignancy)

Longer term management

- Thyroxine

NB exclude adrenal failure prior to replacement

Endocrine tests

- 9am pituitary hormone profile
- Midnight cortisol
- Dexamethasone suppression tests
- Insulin tolerance test / glucagon test
- Short synacthen test
- Oral glucose tolerance tests

The Diurnal Rhythm

- 0900 Cortisol, Testosterone
- 0000 Cortisol

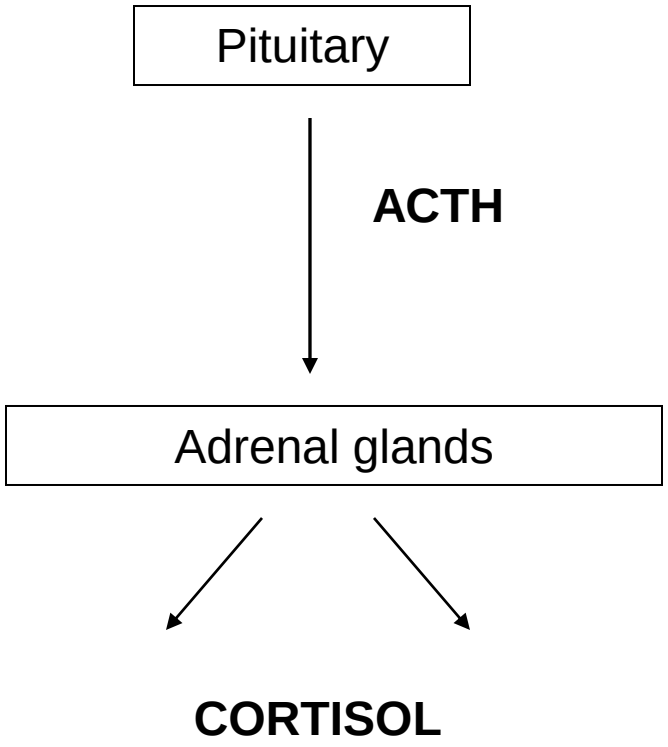
Dexamethasone suppression test

- Low dose: 0.5mg every 6 hours for 48 hours
  - (or 1mg overnight test)
- High dose: 2mg every 6 hours for 48 hours

What does it mean?

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



SIMPLY
ENDOCRINOLOGY AND DIABETES

Insulin tolerance test

- Test full HPA axis, GH axis
- Iatrogenic hypoglycaemia (<2.2)

CI: heart disease, epilepsy

Alternative: Glucagon test

Synacthen test

- Injection of SYNthetic ACTH
- Tests adrenal reserve ONLY

OGTT

- Diagnosis of diabetes mellitus
- Diagnosis of acromegaly (failure of GH suppression)

The End