THE HI'S AND LO'S OF HYPOGLYCEMIA

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DOM Thurs ECHO meeting
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NO DISCLOSURES

OBJECTIVES

- **Case 1 and 2**
- **Define and diagnose hypoglycemia**
- **Counterregulatory response**
- **Causes: fasting vs postprandial**
- **Fasting hypoglycemia**
- **Critical sample - interpretation**
- **Discussion**

- **Please note: talk is about hypoglycemia in NON-DIABETICS**

CASE 1

CLINICAL VIGNETTE

- 30 year old male. Normal baseline with no chronic illnesses.
- Presented with 1 year history of spells
  - Sweating, "twitching", shakiness, weight gain
  - Realised that if he ate the symptoms would be relieved
  - Google and glucometer = self-diagnosed hypoglycaemia
  - GP referred the patient for assessment

- **On examination**
- Clinically well, BMI=28.
- Normal examination

- **Admitted to ward for assessment**
- Had 3 episodes of unprovoked hypoglycaemia in 1st 24 hours, lowest=1.2 mmol/L
- Bloods were taken at the time of the hypoglycaemia episode

INVESTIGATIONS

Critical Sample		
	Ref ranges	27/07/2021
Glucose (mmol/L)		2.1
Insulin (mIU/L)	2.6 - 24.0	19.8
C-peptide (ug/L)	0.8 - 4.2	3.2
Cortisol (nmol/L)		363
Sulphonylurea		negative

CASE 2

CLINICAL VIGNETTE

- 69 year old male **HIV positive** (CD4=191) virologically suppressed on (DLT/ABC/3TC)
- **Hypertension**: extensive target organ damage
- **Chronic kidney disease:** with proteinuria
- **Dyslipidemia**
- Previous **polysubstance** abuse

- **Presented June 2022**: symptomatic hypoglycemia with predominantly neuroglycopenic symptoms and seizures
- Required IV dextrose initially to prevent recurrent hypoglycemia

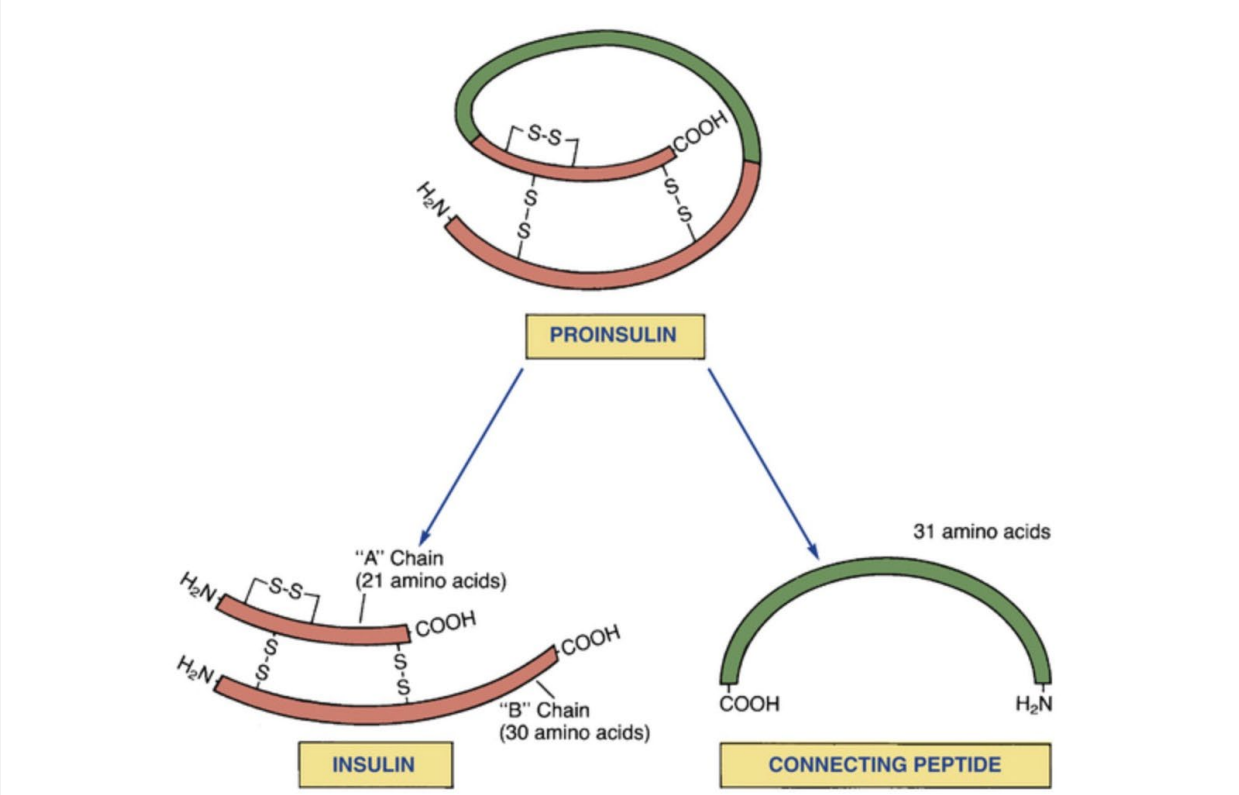
- **On examination**
- Appeared chronically unwell and confused
- Rest of clinical examination essentially normal

INVESTIGATIONS

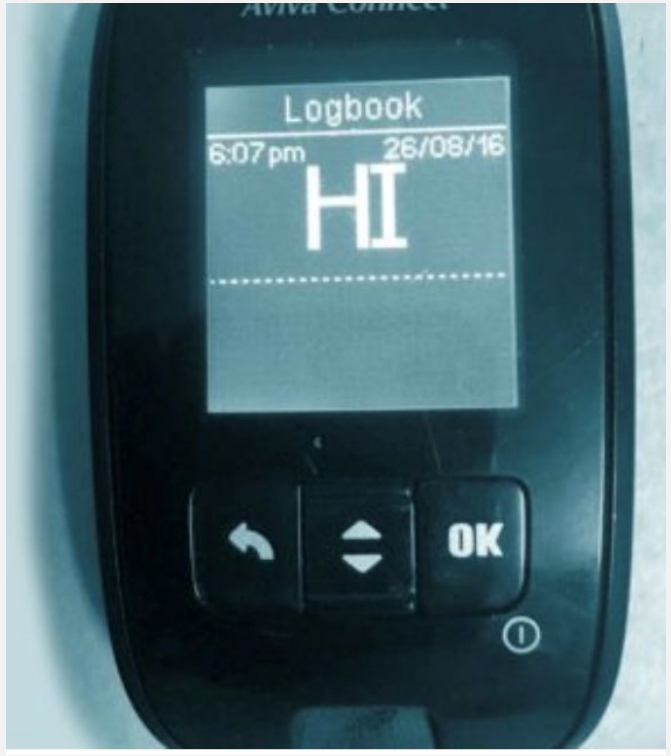
Critical Samples		
	Ref ranges	22/06/2022
Glucose (mmol/L)		2.0
Insulin (mIU/L)	2.6 - 24.0	82.7
C-peptide (ug/L)	0.8 - 4.2	27.1
Cortisol (nmol/L)		747
Sulphonylurea		Not done

SUMMARY

- Hyperinsulinemic hypoglycemia
- Endogenous insulin secretion

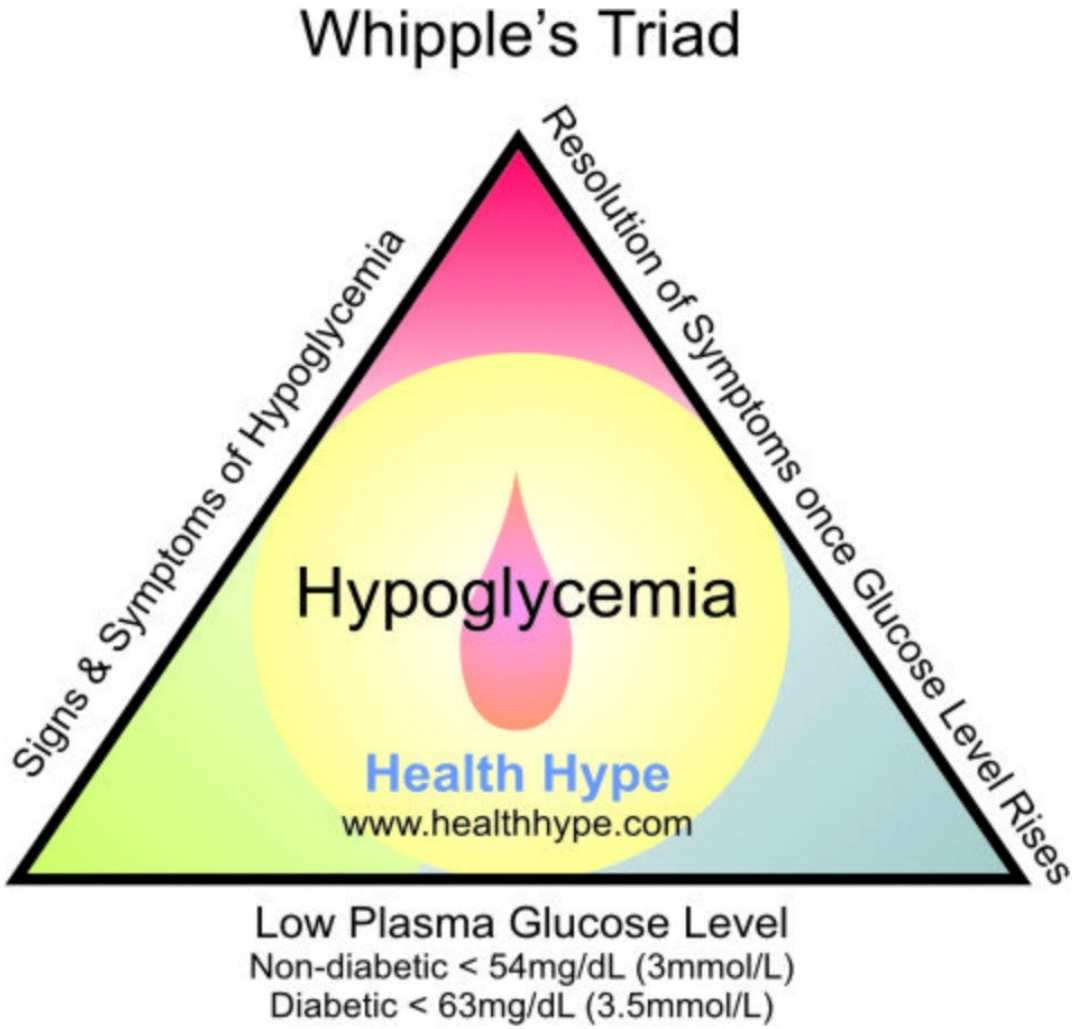


WELL HELLO TO YOU TOO,



BUT I AM REALLY NOT IN THE MOOD FOR SMALL TALK

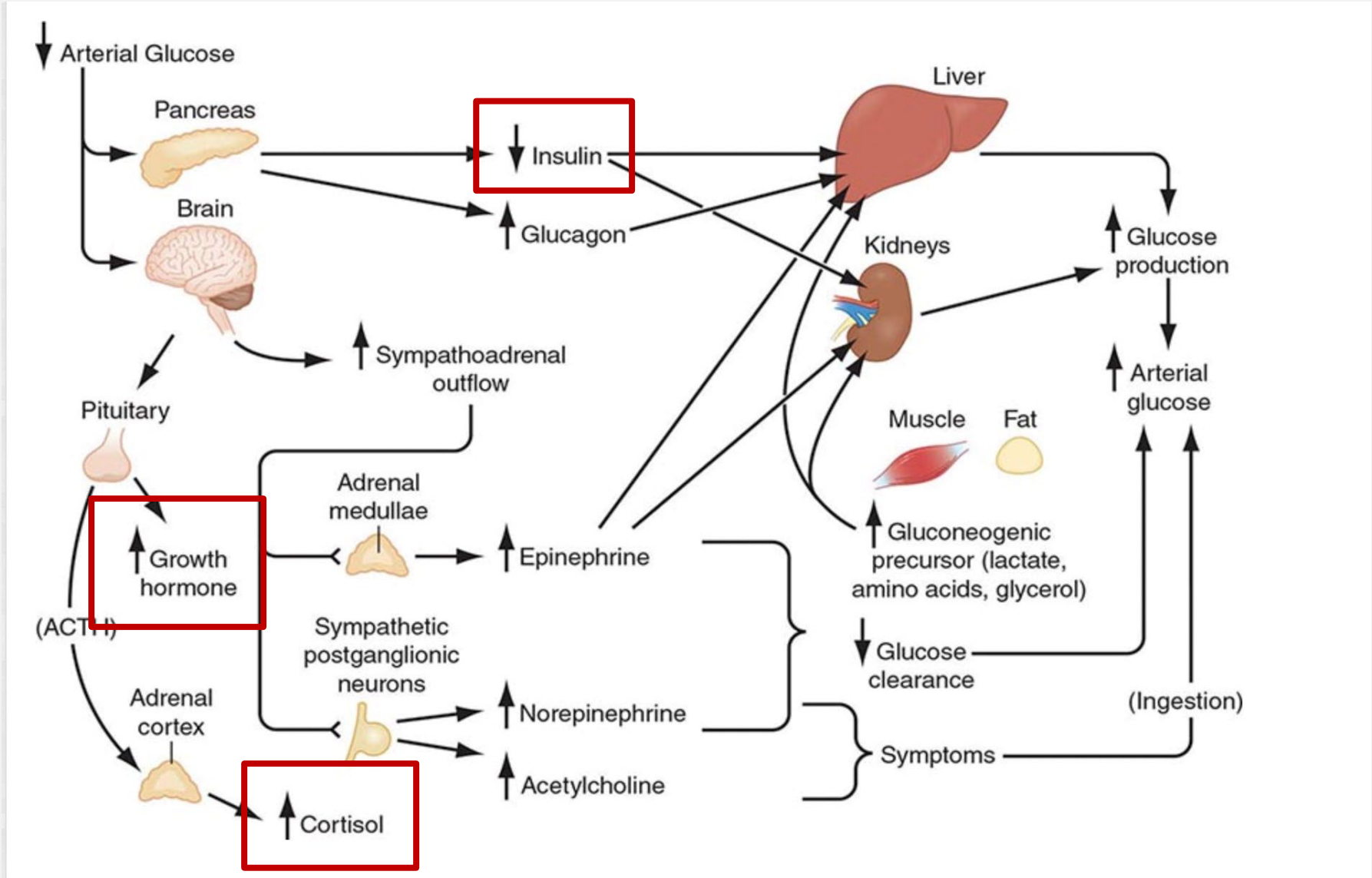
DEFINITION AND DIAGNOSIS



Symptoms of Hypoglycemia

Neurogenic	Neuroglycopenic
Sweating	Behavioral changes
Warmth	Visual changes
Anxiety	Confusion/difficulty speaking
Tremor	Dizziness/lightheadedness
Nausea	Lethargy
Palpitations	Seizure
Tachycardia	Loss of consciousness
Hunger	Coma

COUNTERREGULATORY RESPONSE



APPROACH

Fasting	Reactive (Postprandial)
Occurs after prolonged fast	Follows last meal within 5 hours
Neuroglycopenic symptoms predominate (seizures, coma)	Adrenergic symptoms predominate (sweating, palpitations)
Causes	**Causes**
Insulinoma (↑ c-peptide, proinsulin)	Exuberant insulin response (rapid gastric emptying); early type 2 diabetes (delayed insulin release)
Tumor hypoglycemia (insulin suppressed, ↑IGF 2)	
Exogenous insulin (c-peptide absent)	
Diagnosis	**Diagnosis**
Discordant insulin and glucose levels after fast	Discordant insulin and glucose levels during 5-hour glucose tolerance test

APPROACH

Fasting Hypoglycaemia	
Insulin-dependent	**Non-insulin-dependent**
Endogenous Insulinoma Sulphonylurea use Autoimmune: Insulin Ab Autoimmune: Insulin recep Ab Nesidioblastosis Exogenous	Liver impairment Kidney failure Hypoadrenalism Hypopituitarism Drugs Other

LAB TESTING

- **Artifactual hypoglycemia** → collection tube containing an **inhibitor of glycolysis** (eg. Fluoride).
- Once **Whipple's Triad demonstrated** → goal of testing is to assess the **role of insulin** in the genesis of the hypoglycaemia.

2009 Endocrine Society guidelines for the evaluation and management of hypoglycemic disorders in adults

EVALUATION

- Ideal is to obtain a critical sample at the time of a hypoglycaemic episode

Critical sample required:

- Glucose
- Insulin
- C-peptide
- Beta-hydroxybutyrate (BHOB)
- Sulfonylurea level
- Cortisol, Growth Hormone

If no critical sample or no hypoglycemia → 72 hour fast

72-HR FAST

- Normal individuals → hormonally mediated increase in glucose production and/or lipolysis and ketone body production.
- Gluconeogenesis accounts for approximately 50 percent of glucose production after an overnight fast and for almost all glucose production after 42 hours or more of fasting.
- The prolonged fast will result in hypoglycemia only if there is a defect in the ability to maintain normoglycemia → excess of insulin, which inhibits endogenous glucose production, as well as the transition to alternate sources of fuel and subsequent ketone production. The defect should be identifiable if appropriate testing is performed.

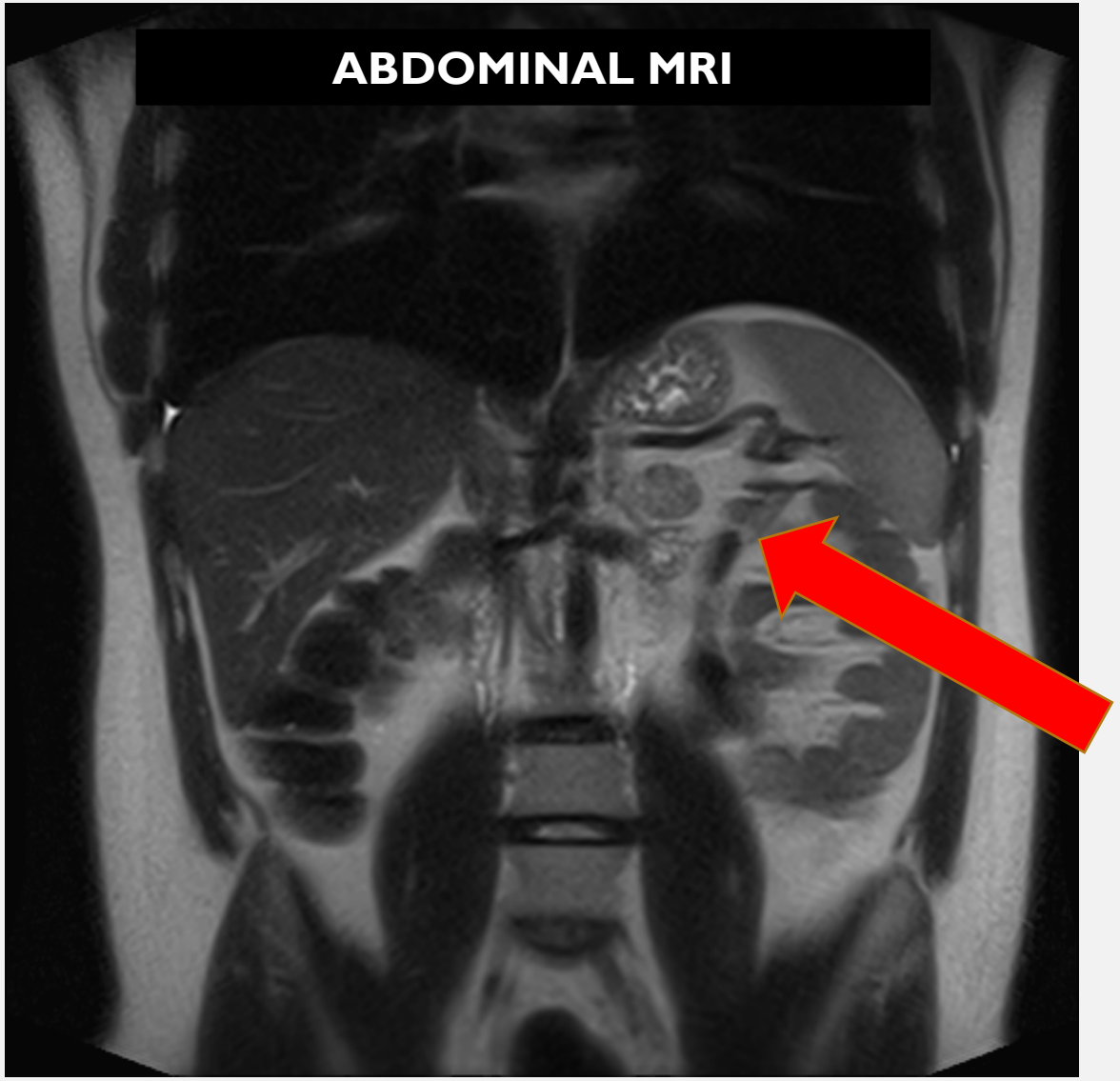
INTERPRETATION OF DATA

- Insulin levels helps distinguish **hyperinsulinemia** (endogenous or exogenous) from other causes of hypoglycemia
- Plasma [Insulin] of >3 mIU/L when the plasma glucose concentration is less than 3.0 mmol/L → excess of insulin and is consistent with hyperinsulinemia
- If the cause of the hypoglycaemia is due to an insulin-dependent mechanism then ketone levels will be absent
- Positive plasma C-peptide distinguishes endogenous from exogenous hyperinsulinemia
- A normal cortisol level at the time of hypoglycaemia can be due to hypoadrenailism, but can also be due to desensitization due to recurrent hypoglycaemia

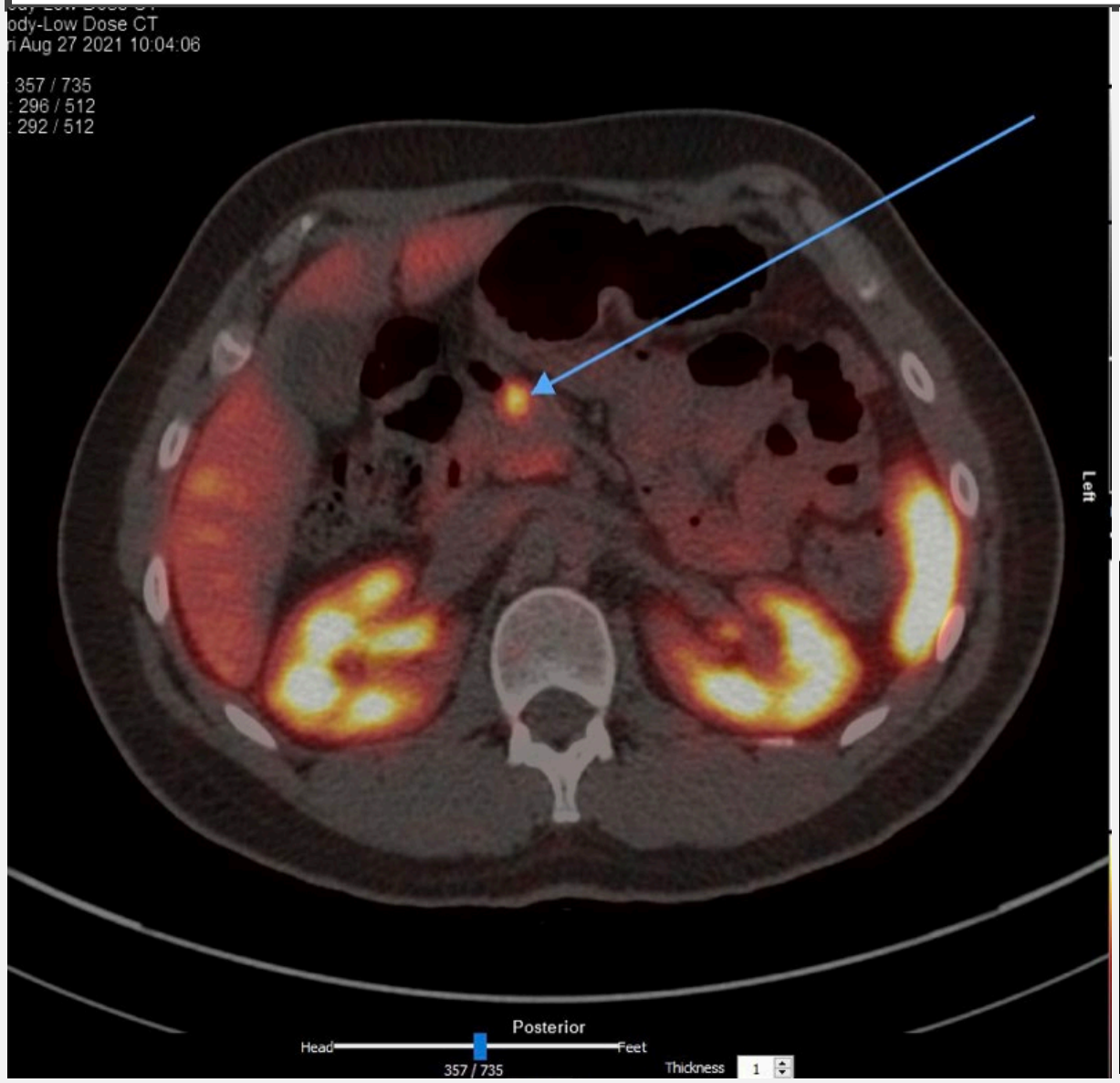
IMAGING

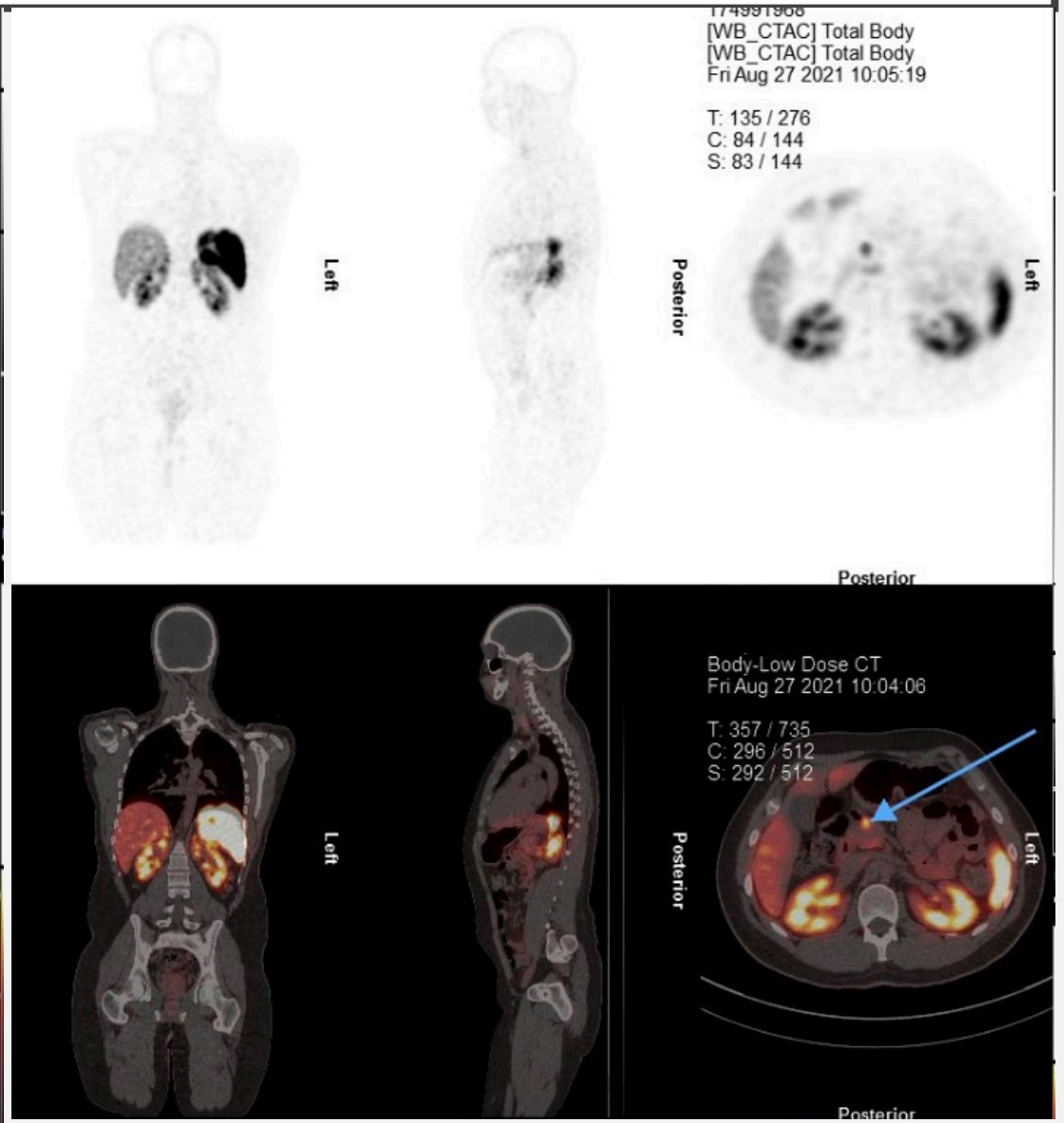
- **Radiological**
- MR and CT and transabdominal U/S can detect most insulinomas
- **Endoscopic ultrasonography**
- With FNA biopsy of the lesion or selective arterial calcium stimulation.
- **Selective arterial calcium stimulation**: distinguishes focal abn (insulinoma) and diffuse process (islet-cell hypertrophy/nesidioblastosis
- **Nuclear medicine**
- Fluorine-18-L-dihydroxyphenylalanine (18-F-DOPA PET)
- Gallium Ga-68 DOTATATE PET/CT (Somatostatin receptor-based imaging modality)
- **PITFALLS:** choosing correct imaging, can be very small, does not always take up the nuclear medicine tracer

CASE 1 IMAGING



CASE 1 IMAGING





CASE 2 IMAGING

Normal CT abdomen
Normal MRI scan
Normal PET CT Scan
Normal endoscopic ultrasound
Normal F-18 DOPA

INSULINOMA

GOING LOW

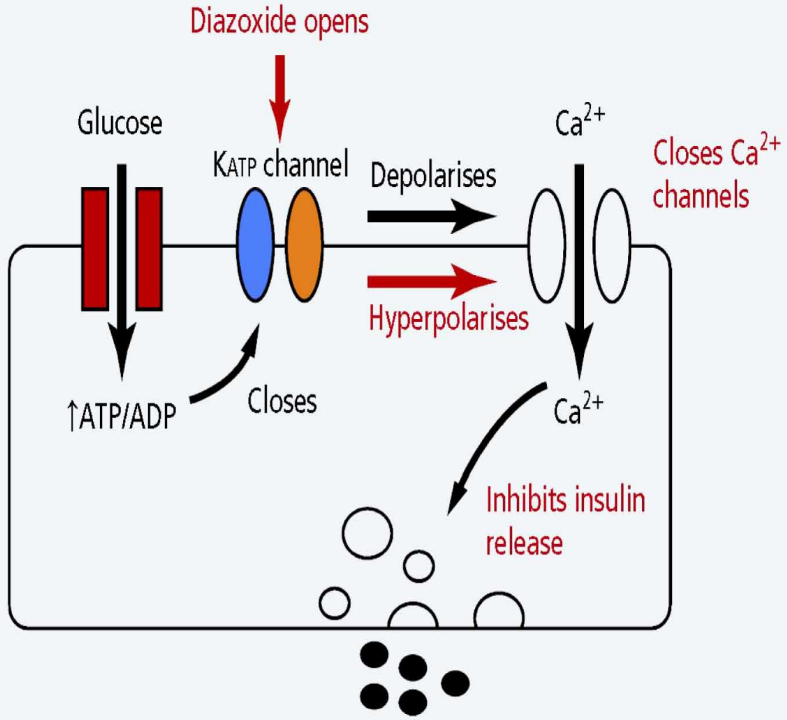
Expectation:

Reality:

PHARMAGOLOGICAL

- **DIAZOXIDE:** diminishes insulin secretion, given in divided doses (1200mg/day)

- **OCTROTIDE:** somatostatin analog, in large doses inhibits insulin and glucagon – highly effective in glucagonomas, VIPomas and carcinoid tumours, but less predictable for symptomatic insulinoma.



NOTES. Above is a representation of the beta cell in the pancreas. Glucose enters the cell via the GLUT-2 glucose transporter and is subsequently metabolised, producing ATP. The increase in the ATP/ADP ratio closes the KATP channel. This depolarises the beta cell membrane and leads to opening of voltage dependent calcium channels. The rise in the intracellular calcium triggers insulin granule exocytosis. In contrast, follow red text for diazoxide action. (ATP = adenosine-5'-triphosphate; ADP = adenosine diphosphate; KATP = ATP-sensitive potassium.)

SURGICAL

- **Resection of primary tumour**
- Treatment of choice
- Procedures performed in Mayo Clinic cohort:
- 1. Enucleation of insulinoma
- 2. Partial distal pancreatectomy
- 3. Combination of the above 2
- 4. Whipple's procedure
- 5. Total pancreatectomy

TAKE HOME MESSAGE

- Suspect hypoglycemia in anyone presenting with ”spells”
- Key points on history: Whipples triad, fasting vs postprandial
- Critical sample at the time of the hypoglycemia and BEFORE any glucose is given
- Imaging only if biochemical evidence suggestive of endogenous insulin production BEWARE of the incidentiloma!!

REFERENCES

1. 2009 Endocrine Society guidelines for the evaluation and management of hypoglycemic disorders in adults
2. Harrison's Endocrinology 4th edition
3. Up-To-Date
4. Endotext