The Endocrinology Block

DKA, type 2 diabetes and its chronic complications, HHS, thyrotoxicosis, hypercalcaemia, pituitary and adrenal disorders, and lipids.

Cases 19–27 · 12,505 words

This block covers the endocrine teaching of both internal medicine courses. The **first course** supplies cases 19, 20 and 23; the **second course** supplies cases 24 and 27, adding pituitary and adrenal disease, the chronic complications of diabetes, and the lipid disorders.

Case	Lecture it serves
System opener: the endocrine history and examination	History taking in endocrinology; physical examination of the endocrine system
Case 19 — Diabetic ketoacidosis	Acute complications of diabetes
Case 20 — Newly diagnosed type 2 diabetes mellitus	Diabetes mellitus; diabetes mellitus part 2 (management)
Case 21 — Hyperosmolar hyperglycaemic state, with hypoglycaemia	Acute complications of diabetes; diabetic emergencies
Case 22 — Thyrotoxicosis, with hypothyroidism	Disorders of the thyroid gland
Case 23 — Hypercalcaemia and primary hyperparathyroidism	Disorders of the parathyroid and calcium metabolism
Case 24 — Pituitary disorders	Pituitary disorders: acromegaly and hypopituitarism
Case 25 — The chronic complications of diabetes	Chronic complications of diabetes mellitus
Case 26 — Cushing syndrome and adrenal insufficiency	Cushing and Addison diseases
Case 27 — Lipid and lipoprotein disorders	Lipid and lipoprotein disorders

System Opener · The Endocrine History and Examination

Endocrine disease is harder to recognise than cardiac or respiratory disease because its symptoms are systemic, non-specific and slow. Fatigue, weight change and mood disturbance describe half of general practice. The discipline that makes the history work is to stop thinking in symptoms and start thinking in **axes**, asking of each: is there too much hormone, or too little?

The history

The combinations that discriminate

Symptom pattern	What it points to
Weight loss with a good or increased appetite	Thyrotoxicosis, or uncontrolled diabetes mellitus — calories are being lost or burned, not refused
Weight loss with a poor appetite	Adrenal insufficiency, malignancy, chronic infection
Weight gain with fatigue, cold intolerance and constipation	Hypothyroidism
Weight gain with thin skin, bruising, proximal weakness and striae	Cushing syndrome — the distinguishing features are catabolic, not the weight itself
Thirst and polyuria	Diabetes mellitus, hypercalcaemia, diabetes insipidus, chronic kidney disease
Proximal muscle weakness	Thyroid disease in either direction, Cushing syndrome, osteomalacia, hypokalaemia of aldosteronism

Then screen the other axes briefly

- **Reproductive:** menstrual pattern, galactorrhoea, hirsutism, libido, erectile function, infertility, gynaecomastia. Menstrual history is one of the most sensitive indicators of endocrine disturbance and is regularly omitted.
- **Pituitary mass effect:** headache and visual field loss.
- **Change in appearance over time:** ring, shoe or hat size, coarsening features, skin darkening. **Ask to see old photographs** — the patient and family adapt to a change that occurs over years and cannot see it.
- **Autoimmune clustering:** personal and family history of thyroid disease, type 1 diabetes, coeliac disease, vitiligo, pernicious anaemia, adrenal insufficiency. Also multiple endocrine neoplasia syndromes and consanguinity.
- **Drugs:** corticosteroids in any form including inhaled, injected and topical; amiodarone; lithium; immune checkpoint inhibitors; and **weight-loss, energy or thyroid-containing preparations bought without prescription** — ask directly, because patients rarely consider them medicines.
- Previous neck surgery, radioiodine or radiotherapy.

The examination

- **General:** body habitus and fat distribution, hydration, voice, and the skin — pigmentation, vitiligo, thinning and bruising, striae, acanthosis nigricans, hair distribution and loss.
- **Hands:** tremor, warm sweaty or cold dry palms, onycholysis, palmar erythema, acromegalic soft-tissue changes, carpal tunnel signs.
- **Pulse and blood pressure, including a standing reading** — a postural drop is one of the few bedside clues to adrenal insufficiency.

- **Eyes:** lid retraction and lid lag, proptosis assessed from above and behind the patient, ophthalmoplegia, chemosis, and **visual fields by confrontation** for the bitemporal defect of a pituitary lesion.
- **Neck — the sequence:** inspect from the front, then ask the patient to **swallow** (a thyroid swelling rises) and then to **protrude the tongue** (a thyroglossal cyst rises). Palpate from behind: size, symmetry, consistency, nodules, tenderness, mobility. Then percuss for retrosternal extension, listen for a bruit, examine the cervical nodes, and check the tracheal position.
- **Neuromuscular:** ask the patient to stand from a chair with arms folded to demonstrate proximal myopathy; test reflexes for the **slow-relaxing ankle jerk** of hypothyroidism; examine for peripheral neuropathy.
- **Legs:** pretibial myxoedema, oedema, and in every diabetic patient a full foot examination — inspection between the toes, pulses, monofilament and vibration sensation.
- **Bedside tests:** capillary glucose, urinalysis, weight, body mass index, waist circumference.

Case 19 · Diabetic Ketoacidosis

CLINICAL VIGNETTE

A **22-year-old woman** with type 1 diabetes mellitus of eight years is brought in by her sister. For two days she has vomited repeatedly and been unable to keep food down. She has diffuse abdominal pain, has been passing large volumes of urine and drinking constantly. She has had a sore throat and fever since the weekend and, because she was not eating, **stopped taking her insulin**.

Her sister reports she has become drowsy since this morning and is breathing strangely.

On arrival: temperature 37.6 °C, heart rate 124/min, blood pressure 98/60 mmHg, respiratory rate 30/min and deep, oxygen saturation 99% on air, Glasgow Coma Scale 14. Mucous membranes are dry. Capillary glucose 28 mmol/L (504 mg/dL); capillary ketones 5.8 mmol/L.

1. Focused History

The diagnosis here is already almost certain from the bedside tests. **The history has a different job: to find the precipitant.** Diabetic ketoacidosis is always provoked by something, and the provocation kills more often than the acidosis does.

Hunt the precipitant systematically

Category	What to ask
Infection	Fever, dysuria, cough, sore throat, diarrhoea, foot ulcer or cellulitis, dental pain. Infection accounts for a third of episodes.
Insulin omission or failure	Exactly which insulins, what doses, when was the last dose. Pump users: site problems, occlusion alarms, cannula age. Cost or supply problems. Deliberate omission to lose weight.
Infarction and other vascular events	Chest pain, breathlessness, focal neurological symptoms. Silent myocardial infarction occurs in long-standing diabetes.
Intercurrent illness	Pancreatitis, cholecystitis, trauma, surgery, pregnancy.
Iatrogenic and drugs	Corticosteroids, thiazides, atypical antipsychotics, and sodium–glucose co-transporter 2 (SGLT2) inhibitors, which cause ketoacidosis at near-normal glucose.
Intoxication	Alcohol binge, cocaine or other stimulant use.

Also establish

- Whether this is **new-onset diabetes** — weeks of thirst, polyuria and weight loss in a previously well person.
- Number of previous admissions with ketoacidosis. Recurrent episodes in a young woman should raise the question of insulin omission for weight control, and of psychological distress; ask about it gently but ask.
- Whether she knows the **sick-day rules** — that insulin is never stopped during illness, and that requirements usually rise.
- Last menstrual period, and a pregnancy test in any woman of childbearing age.

Red flags

- Falling conscious level, headache with bradycardia and rising blood pressure (cerebral oedema), chest pain, and abdominal pain that persists or localises after the acidosis has been corrected, which points to a surgical cause rather than to ketoacidosis itself.

2. Physical Examination

General and neurological

- **Level of consciousness**, formally scored and repeated. Deterioration during treatment is the warning sign of cerebral oedema.
- **Kussmaul respiration** — deep, sighing, unlaboured hyperventilation. It is the respiratory compensation for metabolic acidosis, and its disappearance in a still-acidotic patient means exhaustion, not improvement.
- **Ketotic breath** — the sweet acetone smell. Roughly a third of people cannot detect it genetically, so its absence proves nothing.

Volume status — the assessment that guides the first two hours

- Dry mucous membranes, reduced skin turgor, sunken eyes, delayed capillary refill, tachycardia, postural or frank hypotension, low jugular venous pressure, reduced urine output. The typical adult deficit is around 100 mL/kg — six litres in a 60 kg woman.

Search for the source of infection

- Examine the chest, throat, ears, abdomen, skin, perineum and **especially the feet, between the toes**; inspect cannula and insulin injection sites. **Ketoacidosis itself does not cause fever** — a temperature means infection until proved otherwise, and a normal or low temperature does not exclude it.

Abdomen

- Diffuse tenderness with guarding is common in ketoacidosis itself and typically resolves within hours of treatment. Tenderness that persists, localises, or is accompanied by rebound after correction requires a surgical opinion and imaging.

3. Diagnosis and Differential

The diagnostic triad — all three must be present:

- **Hyperglycaemia:** glucose above 11 mmol/L (200 mg/dL), *or* known diabetes mellitus.
- **Ketonaemia:** capillary beta-hydroxybutyrate 3.0 mmol/L or more, or ketonuria of 2+ or greater.
- **Acidosis:** venous pH below 7.30 *or* bicarbonate below 15 mmol/L.

Condition	Glucose	Ketones	Acidosis	The discriminator
Diabetic ketoacidosis	High	High	Yes, high anion gap	All three present together
Hyperosmolar hyperglycaemic state	Very high, often >33 mmol/L	Minimal	No	Osmolality >320 mosmol/kg; older patient; days to weeks of onset
Euglycaemic ketoacidosis	Normal or mildly raised	High	Yes	On an SGLT2 inhibitor, or pregnant, or starved
Alcoholic ketoacidosis	Normal or low	High	Yes	Binge then vomiting and starvation; glucose not raised
Starvation ketosis	Normal	Mild, <3	Minimal	Bicarbonate largely preserved
Lactic acidosis	Variable	Normal	Yes	Raised lactate; shock, sepsis or metformin accumulation
Salicylate or toxic alcohol	Variable	Normal	Yes	Raised osmolar gap or the drug history

Anion gap = sodium − (chloride + bicarbonate); normal is 8–16 mmol/L. **Corrected sodium** = measured sodium + 2.4 mmol/L for every 5.5 mmol/L (100 mg/dL) that glucose exceeds 5.5. **Effective osmolality** = 2 × sodium + glucose.

4. Investigations

At the bedside — within minutes

- **Capillary glucose** and **capillary beta-hydroxybutyrate**. Blood ketones are preferred over urine dipstick: the dipstick measures acetoacetate, which paradoxically *rises* early in successful treatment and lags behind recovery.
- **Venous blood gas** for pH, bicarbonate and potassium. A venous sample is sufficient — arterial puncture adds pain and little information unless there is respiratory failure.
- **Electrocardiogram** for the peaked T waves of hyperkalaemia and for silent ischaemia.
- **Urinalysis** for ketones and infection, and a **pregnancy test**.

Laboratory

Test	Interpretation
Potassium	The most important number in the chart. Total body potassium is always depleted, yet the serum level is often normal or high on arrival because acidosis and insulin deficiency drive potassium out of cells. It falls fast once insulin is started.
Sodium	Often low on arrival because glucose draws water into the vascular space. Use the corrected value. A rising sodium during treatment is expected and reassuring, not a complication.
Urea and creatinine	Raised from volume depletion. Some assays are interfered with by ketones.
Complete blood count	A leucocytosis up to 25 × 10^9/L occurs in ketoacidosis without infection. A left shift, or a count above that, is more suggestive of sepsis.
C-reactive protein, blood and urine cultures	Directed at the precipitant.
Amylase and lipase	Amylase is non-specifically raised in ketoacidosis. Only lipase with a compatible picture supports pancreatitis.
Troponin, glycated haemoglobin, lactate, osmolality	Troponin if there is any cardiac risk; glycated haemoglobin to document control before the episode.

Imaging and monitoring

- Chest radiograph for occult infection; further imaging directed by findings. Computed tomography of the head only for unexplained deterioration in conscious level.
- **Monitoring schedule:** hourly capillary glucose and hourly capillary ketones; venous gas with potassium at one, two, four, eight, twelve and twenty-four hours; strict fluid balance with hourly urine output.

5. Management

THE SINGLE MOST IMPORTANT PRINCIPLE

Resolution is defined by the ketones and the pH, not by the glucose: ketones below 0.6 mmol/L, venous pH above 7.30 and bicarbonate above 18 mmol/L. A normal glucose with ketones of 4 is not a treated patient.

Step 1 — Fluid, before insulin

Time from start	Fluid
If systolic blood pressure <90 mmHg	500 mL of 0.9% sodium chloride over 10–15 minutes, repeated as needed, then reassess.
Hour 1	1 litre of 0.9% sodium chloride
Hours 2–3	1 litre over each 2 hours, with potassium
Hours 4–7	1 litre over each 4 hours, with potassium
Hours 8–13	1 litre over 6 hours, with potassium

Give fluid more cautiously — and with senior input — in the young, the elderly, the pregnant, and in heart or kidney failure. Young people are the group at risk of cerebral oedema.

Step 2 — Potassium

Serum potassium (mmol/L)	Action
Above 5.5	No potassium in this litre. Recheck within the hour.
3.5 – 5.5	Add 40 mmol of potassium chloride to each litre.
Below 3.5	Senior review now. Higher-rate replacement through an appropriate line, in a monitored bed. Do not start or continue insulin until potassium is being replaced.

Step 3 — Insulin

- **Fixed-rate intravenous insulin infusion at 0.1 units/kg/hour** of soluble insulin. A bolus is not required.
- **Continue the patient's usual long-acting basal insulin** at the usual dose throughout. Stopping it is a common error and causes rebound ketosis when the infusion ends.
- **Targets per hour:** ketones falling by at least 0.5 mmol/L, bicarbonate rising by at least 3 mmol/L, glucose falling by at least 3 mmol/L. If these are not met, increase the infusion by 1 unit/hour and check the giving set and cannula.
- **When glucose falls below 14 mmol/L (250 mg/dL), add 10% glucose at 125 mL/hour** alongside the saline and **continue the insulin**. Insulin is being given to clear ketones, not to lower glucose.

Step 4 — What not to do

- **Bicarbonate** is not given routinely. It may worsen intracellular acidosis and hypokalaemia. Consider it only at a pH below 6.9 and only with senior involvement.
- **Phosphate** replacement is not routine and has no demonstrated outcome benefit.
- Do not use a sliding scale in place of a fixed rate, and do not stop the infusion because the glucose has normalised.

Step 5 — Supportive care and the precipitant

- Treat the infection or other cause. Give venous thromboembolism prophylaxis. Consider a nasogastric tube if there is vomiting with a reduced conscious level, because of aspiration risk, and a urinary catheter if there is no urine output after four hours.

Step 6 — Transition and discharge

- Move to subcutaneous insulin only when ketones are below 0.6, pH is above 7.3, and the patient is eating and drinking. **Give the short-acting subcutaneous dose 30–60 minutes before stopping the infusion** so that the two overlap.
- Every patient is reviewed by the diabetes specialist team before discharge. Revisit sick-day rules, provide a blood ketone meter, review the insulin regimen and injection technique, and address any psychological or eating-related contributor.

Complications — mostly of treatment

Complication	Prevention
Hypokalaemia	The commonest preventable cause of death in ketoacidosis. Potassium in every litre once it is below 5.5, and hourly measurement early.
Hypoglycaemia	Add 10% glucose once the level falls below 14 mmol/L rather than reducing insulin.
Cerebral oedema	Mainly in children and young adults. Avoid over-rapid fluid and osmolality shifts; monitor conscious level hourly.
Aspiration pneumonia	Nasogastric tube if vomiting with impaired consciousness.
Hyperchloraemic acidosis	A recognised consequence of large-volume saline; self-limiting and not a treatment failure.
Venous thromboembolism	Prophylactic anticoagulation.

6. Teaching Points and Viva Questions

- Patients die of hypokalaemia and cerebral oedema during treatment, not of hyperglycaemia on arrival.
- Fluid comes before insulin. Insulin given to an unresuscitated, potassium-depleted patient is dangerous.
- The basal insulin continues. The intravenous infusion supplements it; it does not replace it.
- A normal glucose does not exclude ketoacidosis — check the ketones in any acidotic patient on an SGLT2 inhibitor.
- A white cell count of 20×10^9/L may be the acidosis alone; a fever is never the acidosis alone.

Questions you should be able to answer:

- Why is the serum potassium normal on arrival when total body potassium is severely depleted?
- Why does the sodium rise during successful treatment, and why is that reassuring?
- Why is capillary beta-hydroxybutyrate better than urine ketone testing for monitoring?
- The abdomen is tender. How do you decide whether to call the surgeons?
- Glucose is now 9 mmol/L but ketones are 3.5. What do you do with the insulin infusion?

Case 20 · Newly Diagnosed Type 2 Diabetes Mellitus

CLINICAL VIGNETTE

A **52-year-old man** attends because of three months of tiredness, passing urine frequently at night, and constant thirst. He has lost about 6 kg without trying, although his appetite is good. His vision has become blurred over the past few weeks and he has already booked an appointment for new glasses. He has had two episodes of itching and soreness of the foreskin.

His father and two brothers have diabetes. He works long hours as a driver, eats most meals outside the home and takes no exercise.

On examination: body mass index 32 kg/m^2 with central adiposity, blood pressure 148/90 mmHg. There is **acanthosis nigricans** at the neck and axillae. Foot pulses are present; monofilament sensation is reduced at both great toes.

Random plasma glucose 16.8 mmol/L (302 mg/dL). Glycated haemoglobin 10.2% (88 mmol/mol). Urine ketones negative.

1. Focused History

Confirm the syndrome

- Osmotic symptoms — thirst, polyuria, nocturia — and their duration. Weight change and its direction relative to appetite.
- Recurrent infections: candidal balanitis or vulvovaginitis, skin sepsis, urinary infection, poor wound healing.
- **Blurred vision.** Explain that this is osmotic swelling of the lens, that it will resolve within weeks of glycaemic control, and that he should **postpone the new glasses for six to eight weeks** — otherwise he will pay for lenses he cannot use.

Decide which type of diabetes this is

Feature	Type 1	Type 2
Onset	Weeks, often abrupt	Months to years, often found on screening
Body habitus	Usually lean, marked weight loss	Usually overweight with central adiposity
Ketosis	Prominent; may present in ketoacidosis	Absent or mild
Associated features	Personal or family autoimmune disease	Hypertension, dyslipidaemia, fatty liver, acanthosis nigricans
Tests when uncertain	Low C-peptide; positive glutamic acid decarboxylase or islet antigen-2 antibodies	Preserved C-peptide; antibodies negative

- Do not assume from age alone. **Latent autoimmune diabetes in adults** presents in a lean middle-aged patient who fails oral therapy quickly, and **monogenic diabetes** should be considered where there is diabetes in three consecutive generations with young onset and no obesity.
- **Screen for secondary causes:** pancreatic disease and pancreatic surgery, corticosteroids and antipsychotics, Cushing syndrome, acromegaly, and haemochromatosis — ask about arthralgia, skin bronzing and family history.

Assume complications are already present, and ask about them

- Numbness, burning or tingling in the feet; foot ulcers; claudication; chest pain or breathlessness; erectile dysfunction — often the earliest reported complication and rarely volunteered; visual symptoms; frothy urine.
- Occupation, driving licence category and shift pattern, which affect the choice of drugs; and a full cardiovascular risk history.

2. Physical Examination

- Weight, body mass index, waist circumference, and blood pressure with a standing reading.
- Acanthosis nigricans, skin and genital candidal infection, injection sites where relevant, lipohypertrophy.
- **The foot examination, performed at diagnosis, not at the first ulcer:** inspect the dorsum, sole and **between the toes**; look for deformity, callus, dry skin and nail disease; palpate dorsalis pedis and posterior tibial pulses; test protective sensation with a 10 g monofilament and vibration with a tuning fork; and inspect the footwear.
- Fundoscopy through dilated pupils, or arrange retinal photography.

3. Diagnosis

Test	Diagnostic threshold
Fasting plasma glucose	7.0 mmol/L (126 mg/dL) or above
Two-hour glucose in an oral glucose tolerance test	11.1 mmol/L (200 mg/dL) or above
Glycated haemoglobin	6.5% (48 mmol/mol) or above
Random plasma glucose with classical symptoms	11.1 mmol/L (200 mg/dL) or above

In an **asymptomatic** patient a single abnormal result must be confirmed on a second occasion. This man has classical symptoms with a random glucose above threshold, so the diagnosis is made today.

> **A CAUTION THAT MATTERS HERE**
>
> Glycated haemoglobin measures the average lifespan of the red cell as much as the average glucose. **It is unreliable, and may be frankly misleading, in:**
>
> **Haemoglobinopathies and thalassaemia trait** · haemolysis of any cause · recent blood transfusion or blood loss · iron and vitamin B12 deficiency and their treatment · advanced chronic kidney disease · pregnancy.
>
> Given how common sickle cell disease, sickle trait and thalassaemia are in this region, this is not an examination footnote. **Where the glycated haemoglobin is unreliable, diagnose and monitor with glucose measurements or fructosamine instead**, and be alert to a result that does not match the clinical picture.

4. Investigations at Diagnosis

Type 2 diabetes has usually been present for several years before it is diagnosed. Complication screening therefore begins today, not after five years — that is the single most important structural difference from type 1.

- **Renal:** urine albumin-to-creatinine ratio on an early morning sample, urea, electrolytes, creatinine and estimated glomerular filtration rate.
- **Eyes:** retinal screening at diagnosis.
- **Feet:** risk stratification from the examination above.
- **Cardiovascular and metabolic:** lipid profile, blood pressure, electrocardiogram, liver function tests for fatty liver disease.
- Thyroid function; C-peptide and autoantibodies only if the type is genuinely uncertain.

5. Management

Education and lifestyle — the foundation, not the preamble

- Structured education and dietetic referral. Explain the diagnosis, the natural history and the purpose of each intervention; adherence follows understanding.
- **Weight reduction of 5–10% improves glycaemia substantially, and substantial sustained weight loss can produce remission** of type 2 diabetes, particularly within the first few years of diagnosis. Say this to the patient — it changes the conversation from managing decline to reversing a condition.
- At least 150 minutes of moderate activity weekly, dietary change appropriate to how he actually eats, and smoking cessation.

Drug therapy

- **Metformin** first line unless contraindicated. Titrate slowly with food to limit gastrointestinal effects; review the dose against renal function; monitor vitamin B12 with long-term use.
- **Choose the second agent by comorbidity, not by glucose alone:** a sodium–glucose co-transporter 2 inhibitor where there is established cardiovascular disease, heart failure or chronic kidney disease; a glucagon-like peptide-1 receptor agonist where obesity or atherosclerotic disease dominates.
- Sulfonylureas are effective and inexpensive but cause hypoglycaemia and weight gain — relevant to a professional driver and during fasting. Dipeptidyl peptidase-4 inhibitors are weight-neutral and well tolerated. Insulin is used where glycaemia is severe, catabolic symptoms are marked, or other agents fail.
- **Glycated haemoglobin target, individualised:** around 7% (53 mmol/mol) for most; tighter in a young, newly diagnosed patient without vascular disease; more relaxed in the frail elderly, in advanced complications, and where hypoglycaemia awareness is impaired.
- **Treat the vascular risk, not only the glucose:** blood pressure control, a statin according to risk assessment, and an angiotensin-converting enzyme inhibitor or receptor blocker where albuminuria is present.

FASTING DURING RAMADAN

Most patients with diabetes intend to fast, and most do not raise it with their doctor. **Ask, and plan before Ramadan, not during it.**

Risk-stratify: recent ketoacidosis or hyperosmolar state, severe or unaware hypoglycaemia, advanced complications, pregnancy or dialysis place a patient at very high risk and fasting is inadvisable.

Adjust the regimen: sulfonylureas and insulin need dose reduction and timing changes — in general the larger dose moves to the sunset meal. Metformin is redistributed. **Sodium–glucose co-transporter 2 inhibitors carry a dehydration and euglycaemic ketoacidosis risk** during a long fast in a hot climate.

Educate: capillary glucose testing does **not** invalidate the fast. The fast must be broken for hypoglycaemia below 3.9 mmol/L, for glucose above 16.7 mmol/L, or for symptoms of dehydration. Encourage generous fluid between sunset and dawn.

Ongoing review

- Annually: retinal screening, foot assessment, urine albumin-to-creatinine ratio, renal function, lipids, blood pressure and weight. Vaccination, sick-day rules, and driving advice where relevant.

6. Teaching Points and Viva Questions

- Type 2 diabetes is diagnosed years after it begins. Screen for complications on the day you diagnose it.
- Blurred vision at presentation is osmotic and reversible — tell the patient to delay new spectacles.
- Glycated haemoglobin lies in haemoglobinopathy, haemolysis and recent transfusion. Know when not to trust it.
- Examine the feet and ask about erectile dysfunction. Neither will be volunteered.
- Choose the second drug for the heart and the kidney, not only for the glucose.

Questions you should be able to answer:

- What features would make you doubt this is type 2 diabetes, and what would you test?
- His glycated haemoglobin is 6.1% but his fasting glucose is 9.4 mmol/L. Explain the discrepancy.
- Which complications must be screened for today, and by what test?
- He drives a lorry for a living. How does that affect your prescribing?
- He intends to fast for Ramadan in two months. What do you do now?

Case 21 · Hyperosmolar Hyperglycaemic State

CLINICAL VIGNETTE

A **74-year-old woman** with type 2 diabetes treated with gliclazide is brought in by her son. Over the past ten days she has become steadily more confused and drowsy. She has been drinking constantly and passing large volumes of urine. She had burning on passing urine a fortnight ago. She lives alone and has mild dementia.

On examination: she is very dry, with reduced skin turgor and sunken eyes. Temperature 37.9 °C, heart rate 118/min, blood pressure 96/58 mmHg, respiratory rate 18/min and **not deep**. Glasgow Coma Scale 11. There is no ketotic breath. There is a mild left-sided facial droop that her son says is new.

Glucose 42 mmol/L (756 mg/dL) · sodium 152 mmol/L · urea 19 mmol/L · calculated osmolality 355 mosmol/kg · pH 7.34 · bicarbonate 20 mmol/L · capillary ketones 0.9 mmol/L.

1. Recognising the Syndrome

	Diabetic ketoacidosis	Hyperosmolar hyperglycaemic state
Typical patient	Younger, type 1	Older, type 2, often with impaired access to fluid
Onset	Hours to a day	Days to weeks
Glucose	Usually 20–40 mmol/L	Usually above 30 mmol/L, often far higher
Ketones	3.0 mmol/L or more	Below 3.0 mmol/L
Acidosis	pH below 7.3, bicarbonate below 15	pH above 7.3, bicarbonate above 15
Osmolality	Variable	320 mosmol/kg or above — the defining feature
Fluid deficit	Around 100 mL/kg	Greater — 100 to 220 mL/kg
Mortality	Low with correct treatment	Substantially higher, reflecting age and comorbidity

Calculated osmolality = (2 × sodium) + glucose + urea, all in mmol/L. Learn it; it is the number that defines the diagnosis and the number that governs the speed of treatment.

2. Focused History

- The slow tempo — days to weeks of thirst, polyuria and declining function — distinguishes this from ketoacidosis and explains the size of the deficit.
- **Hunt the precipitant.** Infection, particularly urinary and respiratory; myocardial infarction and stroke, both of which may be silent; drugs including corticosteroids, thiazides and sodium–glucose co-transporter 2 inhibitors; and, very commonly, **simple inability to obtain enough fluid** because of frailty, dementia, immobility or living alone.
- This may be the **first presentation of diabetes**. Ask about the preceding months.

3. Physical Examination

- **Profound dehydration** — the dominant physical finding, and the one that guides the first 24 hours.
- Conscious level, formally scored and repeated. Depression of consciousness correlates with osmolality rather than with glucose.

- **Focal neurological signs and seizures occur in the hyperosmolar state itself and usually reverse with treatment.** Do not assume a stroke — but do not dismiss one either. Reassess after correction.
- A full search for the precipitant: chest, urine, skin, **feet**, and pressure areas.
- Assess pressure areas and thrombotic risk, both of which are high in an immobile, hyperviscous, dehydrated patient.

4. Investigations

- Capillary and laboratory glucose; **capillary ketones**, to confirm this is not ketoacidosis; venous blood gas for pH, bicarbonate and potassium.
- **Sodium and calculated osmolality**, repeated hourly at first — these, not the glucose, are what you titrate treatment against.
- Urea, creatinine, complete blood count, C-reactive protein, blood and urine cultures, chest radiograph, electrocardiogram and troponin, creatine kinase for rhabdomyolysis, lactate.
- Computed tomography of the head only if focal signs persist after biochemical correction, or if the conscious level deteriorates.

5. Management

THE GOVERNING PRINCIPLE

The instinct carried over from ketoacidosis — fluid fast, insulin early — is wrong here and is dangerous.

Correct slowly. Aim to fall in glucose by no more than **4–6 mmol/L per hour** and in osmolality by no more than **3–8 mosmol/kg per hour**. Replace the fluid deficit over **48 hours**, not over 12. Rapid shifts risk cerebral oedema and osmotic demyelination.

Fluid is the treatment; insulin is secondary. Glucose falls with rehydration alone.

Sequence

- **1. Fluid.** Sodium chloride 0.9% is the fluid of choice. Give 500 mL to 1 litre in the first hour, faster if shocked, then continue at a rate that replaces the deficit over 48 hours while monitoring for overload in an elderly heart.
- **2. Expect the sodium to rise as the glucose falls.** This is predictable and is not by itself a reason to change fluid. Judge progress by the **osmolality**: if it is falling appropriately, continue; if it plateaus or rises despite adequate volume, then consider 0.45% saline.
- **3. Potassium** as in ketoacidosis — none if above 5.5 mmol/L, 40 mmol per litre if 3.5–5.5, and senior review below 3.5.
- **4. Insulin — later and lower.** Do not start it while the glucose is still falling with fluid alone. When it is needed, use a fixed rate of **0.05 units/kg/hour**, half the ketoacidosis rate. If significant ketonaemia is present, treat as a mixed picture at the full ketoacidosis rate.
- **5. Thromboprophylaxis in every patient.** Hyperviscosity, dehydration and immobility together make this one of the most thrombogenic states in medicine.

- **6. Treat the precipitant**, protect the pressure areas and the feet, and involve the diabetes team early.

Expectations and recovery

- **Recovery of consciousness lags behind the biochemistry, often by 24 hours or more.** Do not escalate treatment because the patient is still drowsy when the numbers have normalised.
- Many patients do not need long-term insulin and can return to oral therapy once the acute illness resolves.
- Address the reason it happened: fluid access, care arrangements, medication review, and recognition of sick days.

THE OTHER ACUTE COMPLICATION: HYPOGLYCAEMIA

Definition: glucose below 3.9 mmol/L (70 mg/dL). **Severe** means requiring the help of another person, whatever the number.

Conscious and able to swallow: 15–20 g of rapid-acting carbohydrate; recheck at 15 minutes and repeat if still low; then **give long-acting carbohydrate** to prevent relapse.

Impaired consciousness: intravenous glucose, or intramuscular glucagon if there is no access. **Glucagon fails** where hepatic glycogen is depleted — in alcohol excess, liver disease, starvation and prolonged sulfonylurea hypoglycaemia.

The trap: sulfonylurea hypoglycaemia is prolonged and relapsing. These patients must be admitted and observed, not corrected once and discharged from the emergency department. Refractory cases may require an octreotide infusion. Renal impairment prolongs it further.

Afterwards: identify the cause, review the regimen and targets, and ask about **hypoglycaemia unawareness** — which is an indication to deliberately relax control until awareness returns.

6. Teaching Points and Viva Questions

- Older, slower, drier and without ketones — and the osmolality, not the glucose, makes the diagnosis.
- Fluid first and generous, insulin later and half-rate.
- A rising sodium during treatment is expected. Judge by the osmolality.
- Focal neurological signs may be the hyperosmolar state and may reverse. Reassess rather than committing to a stroke diagnosis at the door.
- Every one of these patients receives thromboprophylaxis.
- Never discharge a sulfonylurea hypoglycaemia after a single correction.

Questions you should be able to answer:

- Calculate her osmolality and explain why it matters more than the glucose.
- Why is the insulin rate half that used in ketoacidosis, and why is it started later?
- Her sodium rises from 152 to 158 in four hours. What do you do?
- Why does this condition carry such a high thrombotic risk?
- A patient on gliclazide has a corrected hypoglycaemia and feels well after an hour. Can she go home?

Case 22 · Thyrotoxicosis

CLINICAL VIGNETTE

A **31-year-old woman** presents with four months of weight loss — 9 kg — despite eating more than usual. She feels her heart racing, cannot tolerate heat, sweats constantly, and describes herself as anxious and short-tempered in a way that is unlike her. Her periods have become light and infrequent. Her bowels open three or four times daily. Her eyes feel gritty and her husband says they look prominent.

She smokes 10 cigarettes a day. Her mother has hypothyroidism.

On examination: pulse 118/min and **irregularly irregular**. Blood pressure 142/62 mmHg. Warm sweaty palms with a fine tremor. There is **lid retraction, lid lag and bilateral proptosis** with conjunctival injection. The thyroid is **diffusely enlarged, smooth and non-tender, with an audible bruit**. She cannot rise from a chair without using her arms.

1. Focused History

- The symptoms of hormone excess: weight loss with preserved appetite, heat intolerance, sweating, palpitations, tremor, anxiety and irritability, insomnia, frequent loose stools, oligomenorrhoea, proximal weakness, and fatigue.
- **Neck symptoms.** A **painful, tender** thyroid points to subacute thyroiditis rather than Graves disease and changes the treatment entirely.
- **Eye symptoms:** grittiness, watering, prominence, **double vision**, retro-orbital pain, and any change in vision or colour perception — the last is sight-threatening and demands same-day referral.
- **Recent pregnancy or delivery**, which raises postpartum thyroiditis.
- **Drugs and preparations:** amiodarone, lithium, iodinated contrast, immune checkpoint inhibitors, and **thyroid hormone taken for weight loss or energy, often in unlabelled preparations**. Ask directly and without judgement.
- **Smoking** — it markedly worsens Graves orbitopathy and reduces the response to its treatment. This is the strongest modifiable factor in the eye disease and must be raised at the first consultation.
- Personal and family autoimmune history; previous radioiodine or thyroid surgery.

2. Physical Examination

- **Hands and pulse:** fine tremor, warm moist palms, onycholysis, thyroid acropachy, palmar erythema; tachycardia and **atrial fibrillation**, which occurs in around one in ten and more often in older patients.
- **Eyes — and the distinction that matters: lid retraction and lid lag occur in thyrotoxicosis of any cause**, being due to sympathetic overactivity. **Proptosis, chemosis, conjunctival injection, periorbital oedema and ophthalmoplegia are specific to Graves orbitopathy**, an autoimmune orbital process. Assess proptosis by looking down over the patient's forehead from behind, and always check **visual acuity, colour vision and eye movements**.
- **Neck:** a diffuse, smooth, non-tender goitre with a bruit is Graves disease; a lumpy multinodular gland suggests toxic multinodular goitre; a single nodule suggests a toxic adenoma; a tender gland suggests thyroiditis.

- **Legs and skin:** pretibial myxoedema — raised, non-pitting, orange-peel plaques over the shins, uncommon but essentially diagnostic of Graves disease.
- Proximal myopathy, brisk reflexes, and signs of high-output cardiac failure.

3. Differential Diagnosis — Which Cause?

Cause	Distinguishing features
Graves disease	Diffuse smooth goitre with bruit, orbitopathy, pretibial myxoedema, positive thyrotropin receptor antibodies, diffusely increased isotope uptake.
Toxic multinodular goitre	Older patient, lumpy gland, no eye signs, patchy uptake. Often presents with atrial fibrillation alone.
Toxic adenoma	Solitary nodule, single area of uptake with suppression of the remaining gland.
Subacute (de Quervain) thyroiditis	Painful tender gland, preceding viral illness, raised inflammatory markers, absent isotope uptake, followed by a hypothyroid phase then recovery.
Postpartum or silent thyroiditis	Painless, within a year of delivery, absent uptake, self-limiting biphasic course.
Iodine-induced, including amiodarone	Recent contrast or amiodarone; two distinct types requiring different treatment.
Factitious thyrotoxicosis	No goitre, absent uptake, and a low thyroglobulin — the test that exposes it.

4. Investigations

- **Thyroid function:** suppressed thyroid-stimulating hormone with raised free thyroxine, or raised triiodothyronine alone in T3 toxicosis. A suppressed hormone with normal free levels is subclinical thyrotoxicosis.
- **Thyrotropin receptor antibodies** — positive in Graves disease, and their presence removes the need for isotope scanning in a typical case.
- **Radionuclide uptake scan** when the cause is not clear from the clinical picture and antibodies: diffusely increased in Graves, patchy in multinodular disease, focal in an adenoma, and **absent in thyroiditis, factitious ingestion and iodine excess**. This single distinction — high uptake versus no uptake — separates conditions treated with antithyroid drugs from those that must not be.
- **Before starting treatment:** complete blood count and liver function tests as a baseline, since the important drug reactions affect both.
- Electrocardiogram, and a pregnancy test before any radioiodine — this is mandatory, not a formality.
- Erythrocyte sedimentation rate if thyroiditis is suspected; thyroglobulin if factitious ingestion is suspected.

5. Management

Symptom control

- **A beta blocker such as propranolol** relieves tremor, palpitations, anxiety and sweating within hours, long before any antithyroid drug works. Start it at the first visit.

Antithyroid drugs

- **Carbimazole** (or methimazole) is first line. **Propylthiouracil** is reserved for the first trimester of pregnancy and for thyroid storm.
- Either a titration regimen or block-and-replace. For Graves disease, continue for 12–18 months and then withdraw; about half remain in remission, and relapse is commonest in the first year.

THE WARNING YOU MUST GIVE

Every patient starting carbimazole or propylthiouracil must be told, and it must be documented:

"If you develop a sore throat, mouth ulcers or a fever, stop the tablet immediately and get an urgent white cell count." Agranulocytosis is rare but abrupt, and it is fatal when missed.

Also warn about **hepatotoxicity** — particularly with propylthiouracil — and about rash. Give the warning in writing.

Definitive treatment

- **Radioiodine** — effective and simple. Contraindicated in pregnancy and breastfeeding, and avoided in **active moderate-to-severe orbitopathy**, which it can worsen. Hypothyroidism is the expected outcome, not a complication, and lifelong thyroxine follows.
- **Surgery** — for a large or compressive goitre, suspected malignancy, patient preference, or failure of medical therapy in pregnancy. Risks are **recurrent laryngeal nerve palsy and hypoparathyroidism**; the patient must be rendered euthyroid before operation.

Graves orbitopathy

- **Stop smoking** — the most effective single intervention. Artificial tears, head elevation at night, and prisms for diplopia in mild disease. Selenium may help mild disease.
- Moderate-to-severe active disease requires intravenous glucocorticoids, and in selected cases orbital radiotherapy, immunomodulatory therapy or surgical decompression.
- **Same-day ophthalmology referral** for reduced acuity, impaired colour vision, corneal exposure or optic nerve compression.

EMERGENCY: THYROID STORM

Recognise it: fever above 38.5 °C, marked tachyarrhythmia or heart failure, agitation, delirium or coma, and vomiting, diarrhoea or jaundice, in a thyrotoxic patient. Usually precipitated by infection, surgery, trauma, labour, an iodine load or ketoacidosis.

Treat in this order, and the order is examinable:

1. Propylthiouracil, to block synthesis and peripheral conversion. **2. Iodine (Lugol solution) at least one hour later** — given first, iodine provides substrate and makes matters worse. **3.** A beta blocker. **4.** Hydrocortisone, which also reduces peripheral conversion. **5.** Active cooling, fluid resuscitation, treatment of the precipitant, and high-dependency care.

6. The Other Direction: Hypothyroidism

	Detail
Symptoms	Fatigue, weight gain, cold intolerance, constipation, dry skin, hair loss, hoarseness, menorrhagia, low mood, cognitive slowing, carpal tunnel syndrome.
Signs	Bradycardia, dry coarse skin, periorbital puffiness, loss of the outer eyebrow, goitre or an absent gland, and the slow-relaxing ankle reflex.
Causes	Autoimmune (Hashimoto) thyroiditis; after radioiodine or surgery; iodine deficiency; drugs including amiodarone and lithium; and central causes with a low or normal stimulating hormone.
Diagnosis	Raised thyroid-stimulating hormone with low free thyroxine. Raised hormone with normal thyroxine is subclinical disease. Thyroid peroxidase antibodies confirm autoimmune cause.
Treatment	Levothyroxine, taken on an empty stomach and separated from iron, calcium and proton pump inhibitors. Start at a low dose in the elderly and in ischaemic heart disease, where rapid replacement can precipitate angina. Recheck at 6–8 weeks and titrate against the stimulating hormone.
Myxoedema coma	Hypothermia, bradycardia, hypoventilation with carbon dioxide retention, hyponatraemia and reduced consciousness. Requires intravenous thyroid hormone and hydrocortisone until adrenal insufficiency is excluded, plus supportive care.

7. Teaching Points and Viva Questions

- Lid lag and lid retraction come with any thyrotoxicosis; proptosis and ophthalmoplegia mean Graves disease.
- A painful thyroid is thyroiditis. Antithyroid drugs will not help, because the gland is leaking hormone rather than making it.
- The isotope scan question is simply: is uptake high, or absent?
- Warn every patient about agranulocytosis, in writing, and document it.
- In thyroid storm, propylthiouracil before iodine — never the reverse.
- Smoking cessation does more for the eyes than anything else you can offer.

Questions you should be able to answer:

- Which of her eye signs indicate Graves disease specifically, and why?
- How would you distinguish Graves disease from subacute thyroiditis without a scan?
- She is planning pregnancy. How does that change your treatment options?
- Explain why iodine must follow rather than precede propylthiouracil in thyroid storm.
- Her atrial fibrillation persists. What do you do about it?

Case 23 · Hypercalcaemia and Primary Hyperparathyroidism

CLINICAL VIGNETTE

A **58-year-old woman** is referred after a routine blood test showed a **calcium of 2.94 mmol/L (11.8 mg/dL)** with an albumin of 41 g/L. She was told she felt well, but on direct questioning she describes months of fatigue, constipation, low mood and difficulty concentrating, and she passes urine several times each night. She passed a renal stone two years ago and thought no more of it.

She takes no regular medication and no supplements. There is no weight loss, cough or bone pain.

Initial results: parathyroid hormone 8.9 pmol/L (upper limit of normal 6.8) · phosphate 0.72 mmol/L · alkaline phosphatase mildly raised · creatinine normal · vitamin D low-normal.

1. Focused History

The old mnemonic is crude but it works: **bones, stones, abdominal groans and psychic moans** — with **thirst and polyuria** added, since hypercalcaemia causes a nephrogenic diabetes insipidus.

- **Bones:** bone pain, fragility fracture, previous osteoporosis diagnosis.
- **Stones:** renal colic, haematuria, recurrent urinary infection.
- **Abdominal:** constipation, nausea, dyspepsia and peptic ulceration, and pancreatitis.
- **Psychic:** fatigue, low mood, poor concentration, and in severe cases confusion and drowsiness. Patients frequently describe themselves as well until questioned, then recognise months of change.
- **Screen for malignancy**, which is the other major cause: weight loss, smoking history, breast symptoms, cough or haemoptysis, bone pain, haematuria, and change in bowel habit.
- **Drugs and supplements:** thiazide diuretics, lithium, calcium and vitamin D preparations, vitamin A, and antacids taken in quantity.
- **Granulomatous disease:** sarcoidosis and tuberculosis raise calcium by unregulated vitamin D activation.
- **Family history and age.** Hypercalcaemia in a young patient, or with a family history, raises **multiple endocrine neoplasia** and **familial hypocalciuric hypercalcaemia**. Ask about pituitary and pancreatic tumours, phaeochromocytoma and medullary thyroid cancer.
- Prolonged immobilisation.

2. Physical Examination

- Hydration and conscious level — hypercalcaemia causes polyuria and therefore volume depletion, which in turn worsens the hypercalcaemia. This cycle is the reason fluid is the mainstay of acute treatment.
- A **deliberate search for malignancy**: breast, lymph nodes, chest, abdomen, prostate and rectum where appropriate, and bone tenderness over the spine, ribs and long bones.
- Neck scars from previous surgery; proximal myopathy; band keratopathy at the corneal margin in longstanding disease, which is rare but memorable.

3. Investigations

THE STEP STUDENTS SKIP

First, correct for albumin. Only about half of plasma calcium is free and active; the rest is protein-bound.

Corrected calcium = measured calcium + 0.02 × (40 − albumin in g/L)

A patient with a low albumin can be genuinely hypercalcaemic with a normal total calcium, and a dehydrated patient with a high albumin can appear hypercalcaemic when they are not. Where available, an ionised calcium settles the question directly.

Then measure parathyroid hormone. It divides the entire differential in two, and no other test does as much work.

Parathyroid hormone raised or inappropriately normal	Parathyroid hormone suppressed
Primary hyperparathyroidism — the commonest cause in an outpatient	Malignancy — the commonest cause in an inpatient: parathyroid hormone-related peptide, bone metastases, myeloma
Tertiary hyperparathyroidism in chronic kidney disease	Granulomatous disease — sarcoidosis, tuberculosis
Familial hypocalciuric hypercalcaemia	Vitamin D or vitamin A toxicity, milk-alkali syndrome
Lithium therapy	Thyrotoxicosis, immobilisation, adrenal insufficiency

A "normal" parathyroid hormone in the face of hypercalcaemia is abnormal. A healthy parathyroid gland should be fully suppressed. This trips up students who compare the number to the reference range instead of to the calcium.

- **Supporting tests:** phosphate (low in primary hyperparathyroidism), alkaline phosphatase, magnesium, renal function, and 25-hydroxyvitamin D.
- **Twenty-four hour urinary calcium, with the calcium-to-creatinine clearance ratio.** A ratio below 0.01 indicates **familial hypocalciuric hypercalcaemia** — a benign lifelong condition that requires **no treatment and must not be operated on**. Failing to check this before referring a patient for parathyroidectomy is a classic and consequential error.
- **If parathyroid hormone is suppressed:** parathyroid hormone-related peptide, myeloma screen with protein electrophoresis and serum free light chains, imaging directed at the likely primary, and angiotensin-converting enzyme with chest imaging for sarcoidosis.
- **Electrocardiogram** — a short QT interval, and arrhythmia in severe hypercalcaemia.
- **Once primary hyperparathyroidism is confirmed biochemically:** bone densitometry, including the **distal radius**, which is affected preferentially; and renal imaging for stones or nephrocalcinosis. **Localisation imaging — ultrasound and sestamibi scanning — is performed to guide the surgeon, not to make the diagnosis.** A negative scan does not exclude the disease.

4. Management

Acute severe hypercalcaemia

Symptomatic, or a corrected calcium above about 3.5 mmol/L, is an emergency.

- **Intravenous sodium chloride 0.9%** — typically 3 to 6 litres over 24 hours, adjusted for age and cardiac function. Rehydration alone lowers calcium substantially and is the first and most important step.
- **Loop diuretics are not given routinely.** They were once standard and are now reserved for managing fluid overload during rehydration, in a patient who is already volume-replete.
- **Intravenous bisphosphonate**, such as zoledronic acid, after rehydration. The effect takes two to four days, so it is not the treatment for the first hour.
- **Calcitonin** produces a rapid but modest and short-lived fall, useful as a bridge in the first 48 hours.
- **Corticosteroids** for granulomatous disease, vitamin D toxicity and some haematological malignancies. **Denosumab** where bisphosphonates are contraindicated by renal impairment or have failed. Dialysis in extremis.
- Stop the contributing drugs — thiazides, lithium, calcium and vitamin D supplements.

Definitive treatment of primary hyperparathyroidism

Parathyroidectomy is the only cure. Operate if the patient is symptomatic. In an asymptomatic patient, operate if **any one** of the following is present:

- Corrected calcium more than 0.25 mmol/L above the upper limit of normal.
- Estimated glomerular filtration rate below 60 mL/min, nephrolithiasis or nephrocalcinosis on imaging, or urinary calcium excretion above 10 mmol per day.
- Osteoporosis on densitometry, or any vertebral or fragility fracture.
- Age below 50 years.
- **If surgery is not undertaken:** maintain hydration, avoid thiazides, **keep vitamin D replete** — which is counterintuitive but correct, since deficiency drives the parathyroid glands harder — and monitor calcium, renal function and bone density. **Cinacalcet** lowers calcium where surgery is not possible, but does not improve bone density.
- **After surgery**, watch for hypocalcaemia and **hungry bone syndrome**, and for recurrent laryngeal nerve injury.

5. Teaching Points and Viva Questions

- Correct for albumin before you do anything else.
- Parathyroid hormone splits the differential in two, and an unsuppressed level in the presence of hypercalcaemia is abnormal however normal the number looks.
- Check the urinary calcium before anyone books a neck operation.
- Fluid, not furosemide, is the treatment for acute hypercalcaemia.
- Hypercalcaemia of malignancy has a suppressed parathyroid hormone, rises quickly and usually declares its cause within weeks. Primary hyperparathyroidism is mild, chronic and often incidental.

- Localisation imaging tells the surgeon where to cut. It does not tell you whether to operate.

Questions you should be able to answer:

- Her albumin is 28 g/L and calcium 2.62 mmol/L. Is she hypercalcaemic?
- Parathyroid hormone is 4.1 pmol/L with a calcium of 2.95. Interpret that.
- What must you exclude before referring her for parathyroidectomy, and how?
- She is asymptomatic. Give three findings that would still make you operate.
- A patient with lung cancer has a calcium of 3.8 mmol/L. Outline your first six hours.

Case 24 · Pituitary Disorders

CLINICAL VIGNETTE

A **44-year-old man** attends because his wedding ring no longer fits and he has gone up two shoe sizes over about three years. He sweats excessively, has headaches most days, and wakes with numb tingling hands. His wife says he snores heavily and stops breathing at night. His dentures no longer fit. He was told last year that he had hypertension and borderline diabetes.

On examination: large hands with **doughy soft palms**, prognathism with separation of the lower teeth, macroglossia, frontal bossing and deep nasolabial folds. Multiple skin tags. Blood pressure 158/94 mmHg. **Confrontation testing shows a bitemporal field defect.** Photographs from ten years ago show a strikingly different face.

Insulin-like growth factor 1 markedly raised · growth hormone fails to suppress during an oral glucose tolerance test · magnetic resonance imaging: 18 mm pituitary adenoma with suprasellar extension.

THE MOST USEFUL QUESTION IN THIS CONSULTATION

Acromegaly develops over years, and **the patient and their family cannot see it** because they adapt to the change day by day. It is frequently first suspected by a dentist, an optician or a doctor meeting the patient for the first time.

So ask about ring, shoe, hat and glove size, about dentures no longer fitting, and ask to see photographs from ten years ago. That single request often makes the diagnosis in the consultation, and it costs nothing.

1. Think in Three Layers

A pituitary lesion causes trouble in three separate ways, and you must assess all three in every patient — not just the one that brought them in.

Layer	What to look for
Mass effect	Headache; bitemporal hemianopia from chiasmal compression; diplopia from third, fourth or sixth nerve involvement in the cavernous sinus; cerebrospinal fluid rhinorrhoea
Hormone excess	Growth hormone — acromegaly · prolactin — galactorrhoea, amenorrhoea, loss of libido, erectile dysfunction, infertility · adrenocorticotrophic hormone — Cushing disease (Case 26) · thyroid-stimulating hormone — rare
Hormone deficiency	Hypopituitarism. The axes typically fail in a characteristic order: growth hormone, then gonadotrophins, then thyroid-stimulating hormone, then adrenocorticotrophic hormone — and the posterior pituitary, causing diabetes insipidus, in infiltrative or surgical disease

2. Focused History

- **Acromegaly:** the somatic changes above, plus sweating, headache, **carpal tunnel symptoms**, arthralgia, deepening voice, snoring and daytime somnolence.
- **Complications of acromegaly, all of which need looking for:** hypertension, diabetes mellitus, **obstructive sleep apnoea**, cardiomyopathy and heart failure, arthropathy, **colonic polyps with an increased risk of colorectal cancer**, and thyroid nodules.
- **Hypopituitarism:** loss of libido, erectile dysfunction or amenorrhoea, fatigue, cold intolerance, weight change, postural dizziness, loss of axillary and pubic hair, and — in a woman — failure of lactation.
- **Causes of hypopituitarism to ask about:** an adenoma and its treatment; **pituitary apoplexy**; **Sheehan syndrome after postpartum haemorrhage — ask every parous woman with unexplained fatigue and**

amenorrhoea; craniopharyngioma; infiltrative disease including sarcoidosis, tuberculosis, haemochromatosis and histiocytosis; **hypophysitis, including that caused by immune checkpoint inhibitors**; head injury; and cranial irradiation.

- Family history and features of multiple endocrine neoplasia type 1 — parathyroid, pancreatic and pituitary disease.

3. Physical Examination

- **Hands:** size, doughy soft texture, and Tinel and Phalen tests for carpal tunnel syndrome.
- **Face:** prognathism, interdental separation, macroglossia, frontal bossing, coarse features, and the bite.
- **Skin:** excessive sweating, oiliness, skin tags and acanthosis nigricans.
- **Visual fields by confrontation, and visual acuity** — then formal perimetry. Cranial nerves three, four and six.
- Blood pressure, capillary glucose, signs of heart failure, thyroid, joints, and **testicular volume and body hair distribution** for hypogonadism.

4. Investigations

- **Insulin-like growth factor 1 is the screening test for acromegaly. A random growth hormone level is useless**, because secretion is pulsatile and a normal value means nothing.
- **Confirm with failure of growth hormone suppression during an oral glucose tolerance test** — in health, glucose suppresses growth hormone.
- **Magnetic resonance imaging of the pituitary with contrast**, and formal visual field perimetry.

ASSESS ALL THE AXES, EVERY TIME

Whatever the presenting hormone, **test every axis** — the mass may be secreting one hormone while destroying the production of others.

Prolactin · 9 a.m. cortisol, with a short synacthen or insulin tolerance test if borderline · free thyroxine · luteinising and follicle-stimulating hormone with testosterone or oestradiol · insulin-like growth factor 1.

Use free thyroxine, not thyroid-stimulating hormone, to assess the thyroid axis in pituitary disease. In central hypothyroidism the stimulating hormone is low or inappropriately normal, so relying on it will miss the diagnosis entirely.

THE ONE MEASUREMENT NOT TO OMIT

Measure prolactin in every pituitary mass, because the answer may change the treatment from an operation to a tablet.

A **macroprolactinoma is treated medically with a dopamine agonist**, which shrinks the tumour and restores fields and function — surgery is not first line. Operating on one that was never measured is an avoidable harm.

Two pitfalls: the **hook effect**, in which extremely high prolactin levels give a falsely low reading unless the sample is diluted — ask the laboratory; and **stalk compression**, in which any mass causes a modest prolactin rise by interrupting dopamine inhibition. A very high level suggests a prolactinoma; a modest one suggests compression.

- **Screen for complications of acromegaly:** glycated haemoglobin, lipids, blood pressure, electrocardiogram and echocardiography, sleep study, and colonoscopy.

5. Management

- **Acromegaly: transsphenoidal surgery is first-line treatment.** Residual or persistent disease is treated with somatostatin analogues, the growth hormone receptor antagonist pegvisomant, or cabergoline; radiotherapy is reserved for refractory disease. **Monitor insulin-like growth factor 1.** Mortality is increased in active disease and returns towards normal with biochemical control — which is the argument for treating a slowly progressive cosmetic-seeming condition aggressively.
- Treat the comorbidities in their own right — the hypertension, the diabetes and the sleep apnoea will not resolve simply because the adenoma has been removed.

THE ORDER OF REPLACEMENT MATTERS

Replace hydrocortisone before levothyroxine — always.

Thyroxine increases metabolic demand and the clearance of cortisol. Giving it to a patient with unrecognised adrenocorticotrophic hormone deficiency can **precipitate an adrenal crisis**. If both axes are deficient, the glucocorticoid goes first.

Then: **levothyroxine titrated against free thyroxine, not the stimulating hormone**; sex steroid replacement; growth hormone in selected adults; and desmopressin for diabetes insipidus.

Every patient on glucocorticoid replacement needs **sick-day rules, a steroid emergency card, and an emergency injection kit** — see Case 26.

EMERGENCY: PITUITARY APOPLEXY

Sudden severe headache with vomiting, visual loss or ophthalmoplegia, meningism, and often hypotension, caused by haemorrhage or infarction into a pituitary adenoma. Precipitants include anticoagulation, surgery, pregnancy and dynamic pituitary testing.

It is missed because it looks exactly like subarachnoid haemorrhage or meningitis — and the computed tomogram may be reported as normal.

Give intravenous hydrocortisone immediately, arrange urgent magnetic resonance imaging, and refer to neurosurgery and endocrinology the same hour. The steroid is given before any confirmation, because the patient may be in adrenal crisis.

6. Teaching Points and Viva Questions

- Ask for the old photographs and the ring and shoe sizes.
- Insulin-like growth factor 1, never a random growth hormone.
- Test every axis in every pituitary mass, and use free thyroxine rather than the stimulating hormone.
- Measure prolactin — a macroprolactinoma is treated with a tablet.
- Hydrocortisone before thyroxine.
- Sudden headache with visual loss in a patient with a known adenoma is apoplexy — give steroid first.

Questions you should be able to answer:

- Why is a random growth hormone level of no use, and what do you send instead?
- Explain the anatomical basis of his visual field defect.

- His prolactin is 190 mU/L. Does that change anything? What if it were 19,000?
- His free thyroxine is low with a thyroid-stimulating hormone of 1.2. Interpret that.
- A colleague starts levothyroxine while awaiting the cortisol result. What is your concern?

Case 25 · The Chronic Complications of Diabetes

CLINICAL VIGNETTE

A **61-year-old woman** with type 2 diabetes of fourteen years attends for annual review. Her glycated haemoglobin is **9.4%**. On questioning she describes **burning numbness in both feet, worse at night**, blurred vision, frothy urine, dizziness on standing, and a feeling of fullness after a few mouthfuls with occasional vomiting. She has twice had a hypoglycaemic episode **without any warning symptoms**.

On examination: blood pressure 156/88 mmHg lying, falling to 128/74 mmHg on standing. **Monofilament sensation is absent to the mid-foot bilaterally, ankle jerks are absent, and both posterior tibial pulses are impalpable.** Under the right first metatarsal head there is a **1 cm ulcer surrounded by thick callus, which she had not noticed**. It does not probe to bone.

Retinal photography: moderate non-proliferative retinopathy with macular oedema · urine albumin-to-creatinine ratio 38 mg/mmol · estimated glomerular filtration rate 52.

WHY THIS CASE EXISTS

This patient has **six** complications and reported none of them until asked. She did not notice a foot ulcer. She has lost her warning of hypoglycaemia. Her vision is threatened and her kidneys are failing.

Complication screening is a protocol, not a clinical judgement. It is performed on a schedule, in full, whether or not the patient volunteers symptoms — because the complications that matter most are the ones that are silent until they are irreversible.

1. Retinopathy

- **The stages:** background or non-proliferative change (microaneurysms, dot-and-blot haemorrhages, hard exudates, cotton wool spots) → severe non-proliferative disease → **proliferative retinopathy** with new vessels, vitreous haemorrhage and tractional detachment.
- **Maculopathy is the commonest cause of visual loss in type 2 diabetes** and can occur at any stage, including with otherwise mild retinopathy.
- **Screening: annual retinal photography through dilated pupils**, from diagnosis in type 2 diabetes.
- **Treatment:** glycaemic and blood pressure control; **intravitreal anti-vascular endothelial growth factor therapy for macular oedema**; **panretinal photocoagulation for proliferative disease**. **Refer urgently** for new vessels, vitreous haemorrhage, or any sudden change in vision.
- **A caution:** rapid improvement in glycaemic control can **transiently worsen** retinopathy. Screen the retina before intensifying treatment substantially, and particularly before and during pregnancy.

2. Nephropathy

- **Annual urine albumin-to-creatinine ratio and estimated glomerular filtration rate.** Albuminuria usually precedes the fall in filtration.
- **Treatment:** an angiotensin-converting enzyme inhibitor or receptor blocker, a **sodium–glucose co-transporter 2 inhibitor**, and consideration of a non-steroidal mineralocorticoid receptor antagonist; blood pressure control; avoidance of anti-inflammatory drugs; sick-day rules. The management is that of Case 29.

- **Question the diagnosis** if there is haematuria, rapidly declining function, a very high protein load, or **no retinopathy** — diabetic nephropathy rarely occurs without retinal disease, and another renal diagnosis should be considered.

3. Neuropathy

Pattern	Features and management
Distal symmetrical sensorimotor	Glove-and-stocking numbness with loss of protective sensation — the reason the ulcer went unnoticed. Screen annually with a 10 g monofilament and a tuning fork.
Painful neuropathy	Burning, shooting or allodynic pain, worse at night. Treat with duloxetine, amitriptyline, gabapentin or pregabalin. Explain that relief will be partial — promising abolition guarantees disappointment.
Autonomic neuropathy	Postural hypotension · gastroparesis with early satiety, vomiting and erratic glycaemia · diabetic diarrhoea or constipation · erectile and bladder dysfunction · loss of hypoglycaemia awareness · silent myocardial ischaemia and an increased risk of sudden death.
Mononeuropathy and amyotrophy	Cranial or peripheral nerve palsies; and painful asymmetrical proximal wasting in diabetic amyotrophy.

- **Loss of hypoglycaemia awareness is itself an indication to relax the glycaemic target deliberately** until awareness returns. Chasing a low glycated haemoglobin in a patient who cannot feel a hypoglycaemic episode is dangerous.

THE FOOT — WHERE LIMBS ARE LOST

Examine both feet at every review — shoes and socks off, including between the toes — and look inside the footwear.

Risk factors for ulceration: neuropathy, peripheral arterial disease, foot deformity, callus, previous ulcer or amputation, poor vision, and renal disease.

Any ulcer is referred to a multidisciplinary foot service — within one week, and the same day if it is infected or the foot is ischaemic. Treatment is offloading, debridement, vascular assessment, imaging for osteomyelitis where the ulcer probes to bone, and antibiotics for infection rather than for colonisation.

Charcot neuroarthropathy: a **hot, swollen, red foot with palpable pulses** in a neuropathic patient, often with little pain. It is repeatedly mistaken for infection, gout or a sprain. **Immediate immobilisation and offloading; every week of delay produces permanent deformity.**

Prevention, taught explicitly: inspect the feet daily including with a mirror, never walk barefoot, check bath water with the hand or a thermometer, professional nail care, and properly fitted footwear.

4. Macrovascular Disease

- Ischaemic heart disease — **frequently silent**, which is why a diabetic patient with unexplained breathlessness, fatigue or vomiting needs an electrocardiogram; stroke; and peripheral arterial disease.

- **Treat total cardiovascular risk rather than glucose alone:** statin therapy, blood pressure control, antiplatelet therapy where indicated, smoking cessation, and an agent with proven cardiovascular benefit — a sodium–glucose co-transporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.

5. The Annual Review — What Must Actually Be Done

Domain	Action
Glycaemia	Glycated haemoglobin with an individualised target; review of hypoglycaemia frequency and awareness
Vascular risk	Blood pressure with a standing reading, lipid profile, smoking status, weight and waist
Eyes	Retinal photography through dilated pupils
Feet	Inspection, pulses, monofilament and vibration, footwear — and risk stratification
Kidneys	Urine albumin-to-creatinine ratio, creatinine and estimated filtration rate
Treatment review	Injection sites and lipohypertrophy, inhaler-style technique check for injectables, adherence, drug rationalisation
The conversation nobody has	Mood, sexual function, driving, hypoglycaemia awareness, contraception and pregnancy plans, fasting during Ramadan (Case 20), and structured education
Other	Vaccination, dental review, and screening for fatty liver disease

6. Teaching Points and Viva Questions

- Screen on a schedule. The complications that matter announce themselves too late.
- Take the shoes and socks off. That is where you find the limb-threatening problem.
- A hot swollen red foot with good pulses is Charcot, not cellulitis.
- Check the retina before you intensify glycaemic control sharply.
- Loss of hypoglycaemia awareness is a reason to loosen the target, not tighten it.
- Proteinuria without retinopathy should make you doubt that this is diabetic nephropathy.

Questions you should be able to answer:

- List this patient's complications and say which she reported spontaneously.
- Why does her ulcer matter more than her glycated haemoglobin this week?
- She has no warning of hypoglycaemia. What do you do about her targets?
- A month later the same foot is hot, red and swollen with strong pulses and no fever. What is your diagnosis?
- Her albumin-to-creatinine ratio is 300 with visible haematuria and no retinopathy. What now?

Case 26 · Cushing Syndrome and Adrenal Insufficiency

CLINICAL VIGNETTE — PART ONE

A **38-year-old woman** describes eighteen months of weight gain across the abdomen with **thinning of the arms and legs**, bruising after the slightest knock, and wide purple marks on her abdomen. She cannot rise from a chair without using her arms. Her periods have stopped, she has developed facial hair and acne, and she feels persistently low. She was recently diagnosed with diabetes and hypertension, and **fractured a vertebra lifting a bag**.

On examination: round plethoric face, an interscapular fat pad, thin skin with multiple bruises, **broad purple striae**, proximal weakness, and blood pressure 168/104 mmHg.

Overnight dexamethasone fails to suppress cortisol · late-night salivary cortisol raised · 24-hour urinary free cortisol raised · adrenocorticotrophic hormone not suppressed.

BEFORE ANYTHING ELSE

By far the commonest cause of Cushing syndrome is prescribed or purchased glucocorticoid, and the diagnosis is made by asking rather than by testing.

Ask about **oral steroids, inhalers, nasal sprays, skin creams, eye drops, joint injections, and traditional, herbal or imported remedies** — some of which contain potent steroids undeclared. Patients do not think of a cream as a drug.

Establish this before requesting a single test.

1. Cushing Syndrome — Recognising It

Distinguish **Cushing syndrome**, the clinical state of glucocorticoid excess, from **Cushing disease**, which is specifically a pituitary corticotroph adenoma.

WHICH FEATURES ACTUALLY DISCRIMINATE

Obesity, hypertension, diabetes and low mood are common and do not discriminate. **The features that do are the catabolic ones:**

Proximal myopathy · thin skin with easy bruising · wide purple striae · unexplained osteoporosis or fragility fracture in a young person · facial plethora · **unprovoked hypokalaemia** · and the combination of central weight gain with **wasted limbs**.

A patient who has gained weight all over is unlikely to have Cushing syndrome. One who has gained it centrally while their thighs have wasted, and who cannot get out of a chair, very possibly does.

Screening and pitfalls

- **Any two of: an overnight 1 mg dexamethasone suppression test, a late-night salivary cortisol, and a 24-hour urinary free cortisol.** A random serum cortisol is of no value.
- **Pseudo-Cushing states** produce genuinely abnormal results: depression, alcohol excess, obesity, poorly controlled diabetes and severe illness. Oestrogen raises cortisol-binding globulin and therefore total cortisol; shift work invalidates late-night sampling.

Then localise — and the pivotal test is the corticotrophin level

Adrenocorticotrophic hormone	Meaning and next step
Suppressed	The lesion is adrenal and is making cortisol autonomously — adenoma, carcinoma or hyperplasia. Proceed to adrenal computed tomography.
Not suppressed or raised	The disease is corticotrophin-dependent. Pituitary magnetic resonance imaging, high-dose dexamethasone and corticotrophin-releasing hormone testing, and bilateral inferior petrosal sinus sampling to separate a pituitary source from an ectopic one. Computed tomography of chest and abdomen for an ectopic tumour.

- **Features suggesting ectopic corticotrophin secretion** — small cell lung carcinoma, bronchial or pancreatic neuroendocrine tumours: rapid onset over weeks, **severe hypokalaemia with metabolic alkalosis**, marked hyperpigmentation, profound myopathy, and **weight loss rather than gain**.

Management

- **Treat the cause:** transsphenoidal surgery for Cushing disease; adrenalectomy for an adrenal tumour; resection of an ectopic source. Medical control with metyrapone, ketoconazole or osilodrostat while awaiting definitive treatment.
- **Manage the consequences actively:** diabetes, hypertension, osteoporosis, psychiatric symptoms, infection risk — and **thromboprophylaxis, because Cushing syndrome is a markedly hypercoagulable state**.
- **After successful treatment, expect adrenal insufficiency.** The remaining axis is suppressed and recovers over months. Replace glucocorticoid, taper slowly, and warn the patient about **glucocorticoid withdrawal syndrome** — aching, fatigue and low mood despite adequate replacement. Issue a steroid card.

2. Adrenal Insufficiency

CLINICAL VIGNETTE — PART TWO

A **32-year-old man** has had eight months of fatigue, anorexia and 9 kg of weight loss, with nausea, dizziness on standing and a **craving for salty food**. His wife has noticed that his skin has darkened, especially the creases of his palms and an old appendicectomy scar. He now presents collapsed with vomiting and abdominal pain three days into an influenza-like illness.

Blood pressure 78/48 mmHg · sodium 122 mmol/L · potassium 6.0 mmol/L · glucose 3.2 mmol/L · urea raised. Buccal mucosa and palmar creases are pigmented.

- **Pigmentation of the palmar creases, buccal mucosa, scars and pressure areas is the sign of primary adrenal failure**, caused by the high corticotrophin level. **It is absent in secondary, pituitary-driven insufficiency** — which is how the two are separated at the bedside.
- **The combination to recognise:** fatigue and weight loss with **hyponatraemia, hyperkalaemia and hypoglycaemia**, and postural hypotension. It is repeatedly mistaken for gastroenteritis, depression or occult malignancy.

Primary — adrenal	Secondary — pituitary or exogenous
Autoimmune adrenalitis, often with other autoimmune disease	Abrupt withdrawal of long-term glucocorticoids — by far the commonest cause of adrenal insufficiency overall
Tuberculosis — historically the leading cause and still important in this region; look for adrenal calcification	Pituitary tumour, surgery or radiotherapy; apoplexy; Sheehan syndrome
Adrenal haemorrhage — meningococcal sepsis, antiphospholipid syndrome; metastases; adrenoleukodystrophy; congenital adrenal hyperplasia	Hypophysitis, including from immune checkpoint inhibitors; infiltrative disease
Drugs — ketoconazole, etomidate, checkpoint inhibitors; fungal infection and human immunodeficiency virus	Aldosterone production is preserved, so hyperkalaemia and salt craving are absent and pigmentation does not occur

Investigation

- **A 9 a.m. cortisol** as the initial test, with **the short synacthen test as the confirmatory one**. **Corticotrophin** — high in primary, low or normal in secondary disease. Renin and aldosterone.
- **21-hydroxylase autoantibodies**; adrenal computed tomography where autoantibodies are negative, looking for **calcification, enlargement or metastases**; tuberculosis assessment.
- Screen for associated autoimmune disease — thyroid, coeliac, pernicious anaemia, type 1 diabetes.

EMERGENCY: ADRENAL CRISIS

Treat first, confirm afterwards. Do not wait for a synacthen test on a hypotensive, hyponatraemic, vomiting patient.

1. Take a sample for cortisol and corticotrophin — one tube, ten seconds.

2. Hydrocortisone 100 mg intravenously immediately, then regularly.

3. Rapid intravenous 0.9% sodium chloride; correct hypoglycaemia.

4. Treat the precipitant — usually infection.

Mineralocorticoid replacement is not needed in the acute phase, because high-dose hydrocortisone has sufficient mineralocorticoid activity. **The commonest fatal error is diagnostic delay while tests are arranged.**

Long-term management — and the education that keeps them alive

- **Hydrocortisone in divided doses** approximating the diurnal rhythm; **fludrocortisone in primary disease only**, titrated against blood pressure, postural drop, sodium and renin.
- **Sick-day rules, taught and written down: double the oral dose during febrile illness, and use parenteral hydrocortisone if vomiting or unable to take tablets.**
- **A steroid emergency card, medical alert identification, and an emergency hydrocortisone injection kit with the patient and a family member trained to use it.**
- **Stress dosing for surgery, procedures and childbirth** — and **steroids must never be omitted before an operation**, which is a recurring and preventable cause of perioperative crisis.

3. Teaching Points and Viva Questions

- Ask about every steroid, including creams, inhalers, injections and traditional remedies.

- The catabolic features separate Cushing syndrome from obesity — myopathy, thin skin, purple striae, fracture.
- Corticotrophin divides the differential: suppressed means adrenal, unsuppressed means pituitary or ectopic.
- Pigmented palmar creases mean primary adrenal failure.
- Hyponatraemia with hyperkalaemia and hypoglycaemia in a tired thin patient is Addison disease.
- Treat adrenal crisis before you confirm it, and never omit steroid before surgery.

Questions you should be able to answer:

- Which of her features would you use to argue that this is not simple obesity?
- Her corticotrophin is undetectable. What is the lesion and what imaging do you request?
- Give three findings that would suggest an ectopic source instead.
- The collapsed man's synacthen test cannot be done until tomorrow. What do you do tonight?
- He is listed for a hernia repair. What must be arranged, and what must not happen?

Case 27 · Lipid and Lipoprotein Disorders

CLINICAL VIGNETTE

A **38-year-old man** is referred after his brother had a myocardial infarction at the age of 41. His father died of a heart attack at 46. He himself has no symptoms, does not smoke, and is of normal weight.

On examination: body mass index 25 kg/m², blood pressure normal. There are **firm nodular thickenings over both Achilles tendons and over the extensor tendons of the hands**, **corneal arcus**, and xanthelasma at both upper eyelids.

Total cholesterol 9.8 mmol/L · low-density lipoprotein cholesterol 7.4 · high-density lipoprotein 1.1 · triglycerides 1.4 · thyroid function, liver function and glucose all normal.

THE PHYSICAL SIGN THAT MAKES THIS DIAGNOSIS

Tendon xanthomata are close to diagnostic of familial hypercholesterolaemia. They are not xanthelasma and not corneal arcus, both of which are common and non-specific — they are firm nodules **within the tendon itself**, classically Achilles and the extensor tendons of the hands, and they move with the tendon.

Feel for them in any patient with a very high cholesterol or a family history of premature coronary disease. **They take fifteen seconds to find and they change the diagnosis, the treatment target, and the management of the entire family.**

1. Exclude Secondary Causes First

A raised cholesterol is not a diagnosis. Before labelling a dyslipidaemia primary, exclude the treatable secondary causes — several of which resolve completely when the underlying problem is corrected.

Cause	Test or question
Hypothyroidism	Thyroid-stimulating hormone — and a common, entirely reversible cause
Nephrotic syndrome and chronic kidney disease	Urine albumin-to-creatinine ratio, creatinine, albumin
Cholestasis	Liver function tests
Poorly controlled diabetes and obesity	Glycated haemoglobin, weight
Alcohol	Quantified intake — particularly for hypertriglyceridaemia
Drugs	Thiazides, corticosteroids, oestrogens, retinoids, antiretrovirals, ciclosporin, some antipsychotics
Pregnancy	Pregnancy test

2. Familial Hypercholesterolaemia

- **Autosomal dominant**, from mutations in the low-density lipoprotein receptor, apolipoprotein B or *PCSK9*, and affecting roughly one person in 250 — which makes it one of the commonest serious inherited disorders, and one of the most under-diagnosed.

A REGIONAL CONSIDERATION

Consanguineous marriage substantially increases the likelihood of homozygous familial hypercholesterolaemia, which is far more severe: it presents in childhood with extensive cutaneous and tendon xanthomata, aortic stenosis and coronary disease in the first two decades, and it requires lipoprotein apheresis and specialist care.

So in this population the **pedigree matters twice over** — for cascade screening of an autosomal dominant condition, and for recognising the homozygous form early enough to treat it.

- **Diagnostic pointers:** low-density lipoprotein cholesterol above about 4.9 mmol/L in an adult; **tendon xanthomata**; corneal arcus or xanthelasma before the age of 45; and **premature coronary disease in the family — under 55 in men, under 65 in women — or unexplained sudden death.**
- Use a validated criteria set — the Simon Broome or Dutch Lipid Clinic Network criteria — and arrange **genetic testing with cascade screening of all first-degree relatives.**

WHAT ACTUALLY SAVES LIVES HERE

Cascade screening is the highest-value intervention in this consultation, and it is not about the patient in front of you. Each first-degree relative has a one-in-two chance of carrying the same mutation. Identifying and treating them **before their first coronary event** is the entire point, and it extends outwards through the family. Where a mutation is found, testing also allows you to **discharge the relatives who did not inherit it** — which is as valuable as finding those who did.

Treatment of affected children generally begins around the age of ten.

3. Severe Hypertriglyceridaemia — a Different Problem

- **Triglycerides above about 10 mmol/L carry a real risk of acute pancreatitis**, which is the immediate concern rather than atherosclerosis.
- Look for **eruptive xanthomata**, lipaemia retinalis, hepatosplenomegaly, and grossly **milky (lipaemic) serum**.
- Causes: familial chylomicronaemia and familial combined hyperlipidaemia, on a background of **alcohol, uncontrolled diabetes, obesity, oestrogens or retinoids** — usually a genetic predisposition unmasked by an acquired factor.
- **Treatment is a fibrate, omega-3 fatty acids, a very low fat diet, strict glycaemic control and complete alcohol abstinence.** A statin lowers cholesterol and does comparatively little for very high triglycerides.
- **Laboratory artefacts to know:** severe hypertriglyceridaemia causes **pseudohyponatraemia** and can interfere with several assays.

4. Investigation and Management

- **A full lipid profile with non-high-density-lipoprotein cholesterol. A fasting sample is not required** for routine assessment. Glycated haemoglobin, thyroid, renal and liver function, urine albumin-to-creatinine ratio, and a baseline creatine kinase.
- **Lipoprotein(a) measured once in a lifetime** in anyone with premature or familial disease — it is an independent, largely genetically determined risk factor.
- A three-generation family history, and formal cardiovascular risk assessment.

A CALCULATION NOT TO MAKE

Cardiovascular risk calculators are not valid in familial hypercholesterolaemia.

They estimate ten-year risk from current risk factors, whereas what harms this patient is **lifetime exposure to a very high cholesterol from birth**. A 38-year-old with familial disease will have a reassuring ten-year score and a severely elevated lifetime risk.

Treat on the diagnosis, not on the calculator.

- **Lifestyle for everyone:** diet, weight, physical activity, alcohol, and smoking cessation — which matters more in this patient than any milligram adjustment.
- **High-intensity statin as the foundation**, aiming for at least a 50% reduction in low-density lipoprotein cholesterol in familial disease, with absolute targets set by risk category.
- **Then add, in sequence: ezetimibe; a PCSK9 inhibitor or inclisiran; bempedoic acid. Lipoprotein apheresis** in homozygous disease and refractory cases.

STATIN INTOLERANCE

Do not accept "statin intolerant" without a structured rechallenge — the alternative is an untreated patient with a lifetime of excess risk.

Check creatine kinase; exclude hypothyroidism, vitamin D deficiency and interacting drugs; then rechallenge with a different statin, at a lower dose, or on alternate days. Most patients who report myalgia can eventually tolerate some statin, and the nocebo effect is well documented.

True rhabdomyolysis is rare and is a different matter entirely — stop the drug and investigate.

- **Stop statins in pregnancy** and manage with diet, with specialist input; plan pregnancies in women on lipid-lowering therapy.

5. Teaching Points and Viva Questions

- Exclude thyroid, renal, hepatic, diabetic, alcohol and drug causes before calling it primary.
- Feel the Achilles tendons. Tendon xanthomata are close to diagnostic.
- Risk calculators do not apply in familial hypercholesterolaemia.
- Cascade-screen the family — that is where the benefit is, and consanguinity makes it matter more.
- Triglycerides above 10 mean pancreatitis risk and a fibrate, not a statin.
- Investigate statin myalgia and rechallenge rather than abandoning treatment.

Questions you should be able to answer:

- Which physical sign here is close to diagnostic, and how does it differ from xanthelasma?
- His ten-year cardiovascular risk score is 4%. How do you interpret that?
- What do you do about his brother, his sister and his children?
- A different patient has triglycerides of 34 mmol/L. What is the immediate risk and the treatment?
- He returns saying the statin gives him aching legs. Set out your approach.