Metabolic Syndrome & Disease Mechanisms

BCH 130 — Advanced Human Biochemistry · Dr. Radi

By the end of this unit, you can…

- Classify the biochemical mechanisms of endocrine disease
- Read a hormone panel as a biochemist
- Explain how the same hormone axis can fail from opposite directions (primary vs secondary vs tertiary), and predict the feedback signature of each.
- State the diagnostic criteria for metabolic syndrome (central obesity, hyperglycemia, hypertriglyceridemia, low HDL, hypertension) and explain why they cluster.

Today's route

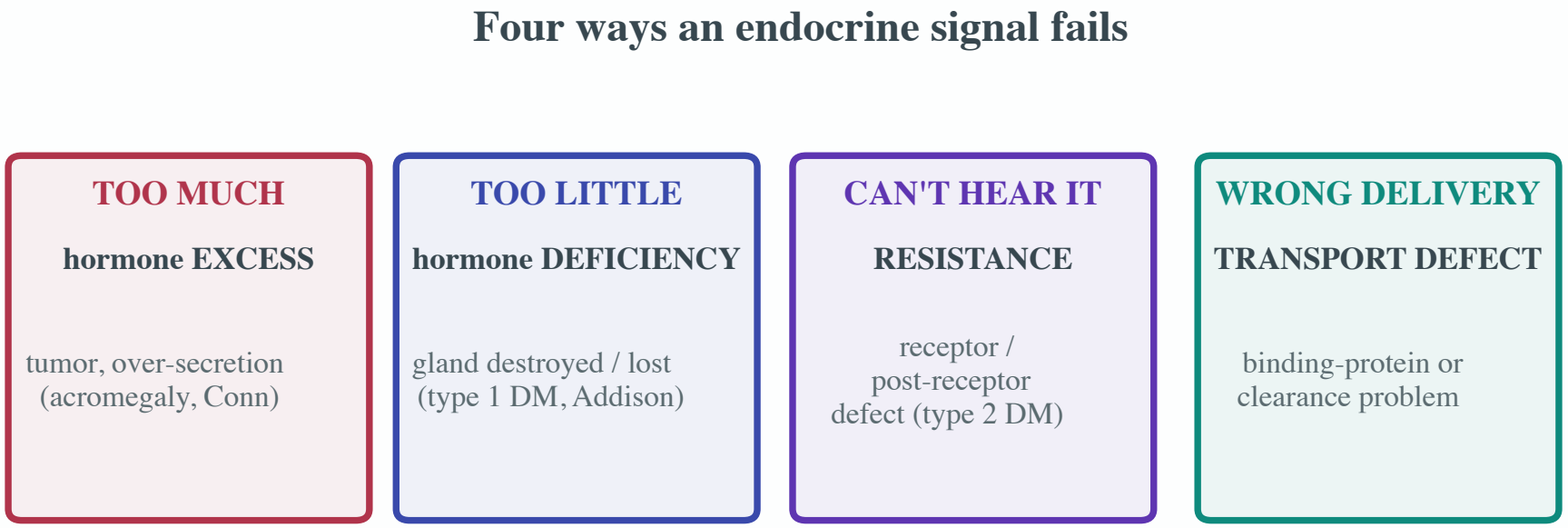
1. How Hormone Dysregulation Causes Disease
2. Metabolic Syndrome – the Cluster
3. The Biochemistry of Insulin Resistance
4. Consequences & Management

1 · How Hormone Dysregulation Causes Disease

"Welcome to the disease half of endocrinology! Before we meet a single diagnosis, let's build the lens you'll use all quarter — every hormone disease is a signal that's too loud, too quiet, ignored, or misdelivered. Name the mechanism first, and the disease explains itself."

Four ways a signal fails

You spent BCH 120 learning how hormones **work**. This course is about what happens when they **don't** — and here's the beautiful part: there are really only **four ways** to break an endocrine signal. **Too much** (a tumor screaming). **Too little** (a gland burned out). **Can't hear it** (the receptor's broken — resistance). Or **misdelivered** (a transport/clearance problem). Name the mechanism first, every single time.

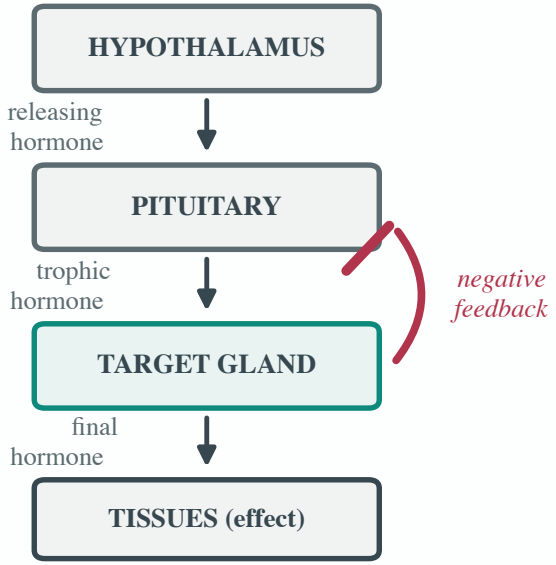


Every endocrine disease in this course is one of these four — name the mechanism first.

Read the feedback, find the culprit

A low hormone level alone tells you almost nothing. The **trophic partner** — the hormone one step upstream — is where the diagnosis hides. Low final hormone with a **HIGH** trophic signal? The gland itself failed (**primary**). Low final hormone with a **LOW** trophic signal? Look upstream — the pituitary (**secondary**) or hypothalamus (**tertiary**) went quiet. Feedback is your detective.

Where did the axis break? Read the feedback.



The feedback signature

PRIMARY (gland)
final ↓, trophic HIGH

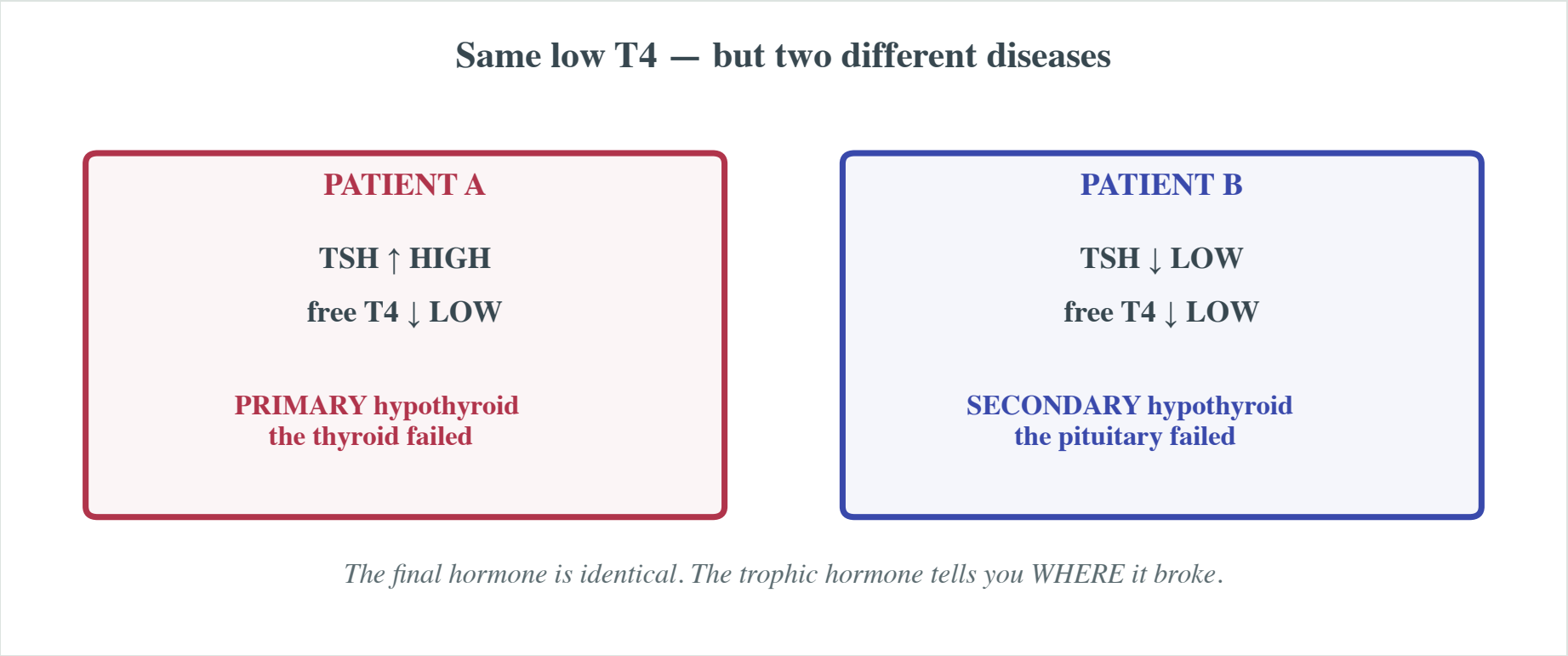
SECONDARY (pituitary)
final ↓, trophic LOW

TERTIARY (hypothal.)
final ↓, releasing LOW

Low target hormone + HIGH trophic = the gland is the problem.
Low + LOW = look upstream.

Same number, two diseases

Watch this. Two patients walk in, both exhausted, both cold, both with a rock-bottom **free T4**. Identical final hormone. But Patient A's **TSH is sky-high** — her thyroid died and the pituitary is shouting at it. Patient B's **TSH is low** — his pituitary is the one that quit. Same low T4, completely different disease, completely different fix. The trophic hormone made the call.

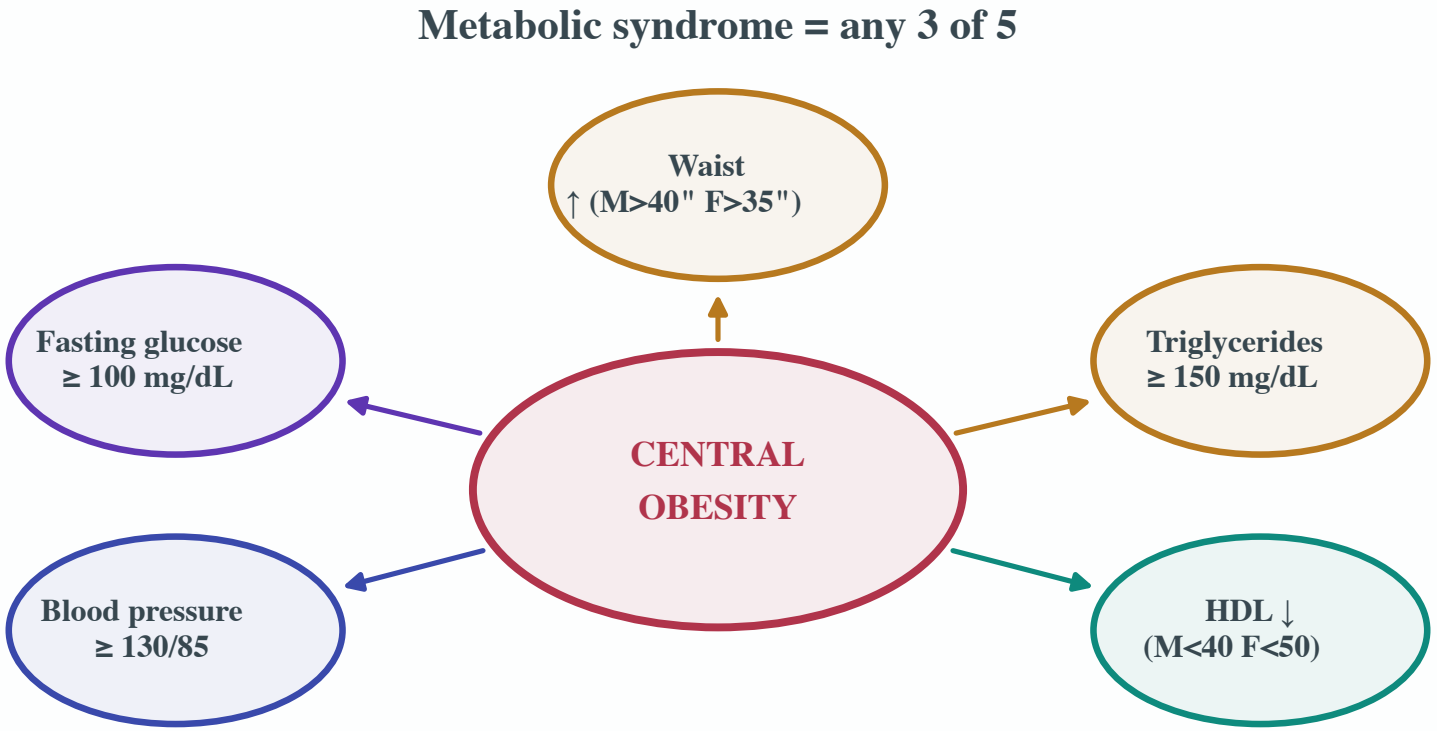


2 · Metabolic Syndrome — the Cluster

"Five risk factors that love to show up together — big waist, high sugar, high triglycerides, low HDL, high blood pressure. Individually they're nuisances; together they're a syndrome that fast-tracks you to diabetes and heart disease. And the villain tying them together is one you already know: insulin resistance."

Any three of five

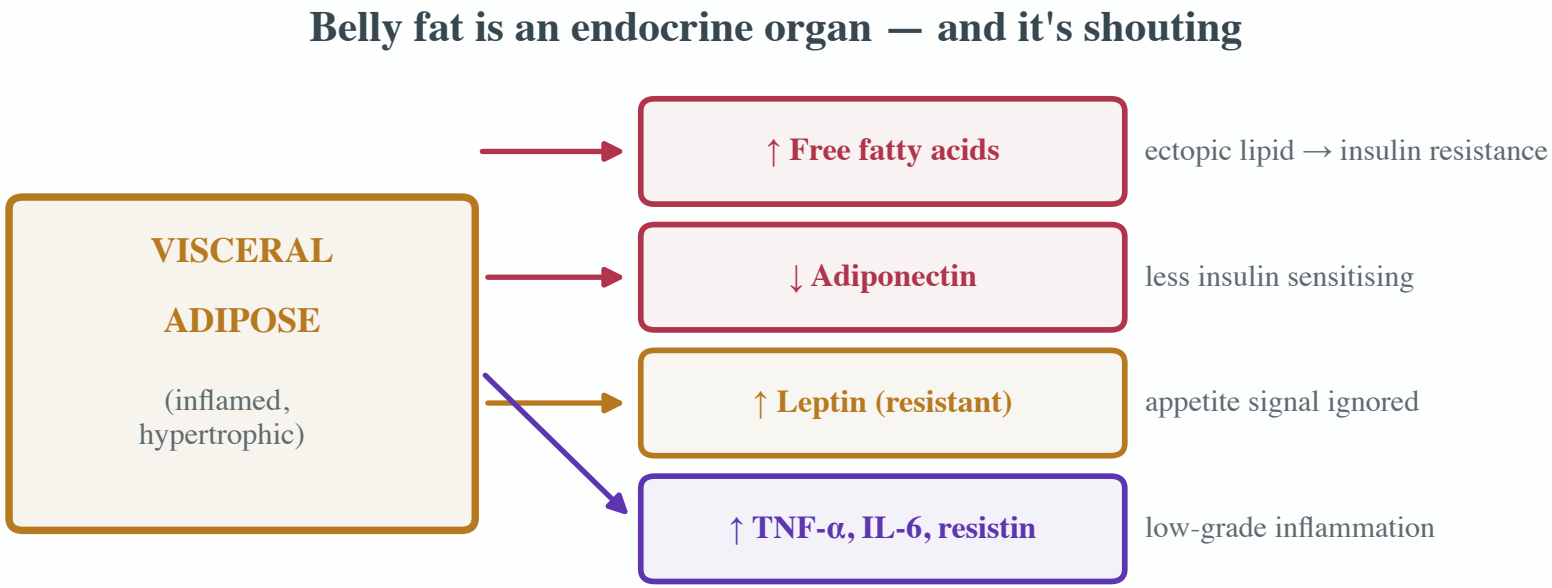
Metabolic syndrome isn't one thing — it's a **cluster diagnosis**. Hit **any 3 of these 5** and you've got it: a big **waist** (central obesity), **fasting glucose ≥ 100**, **triglycerides ≥ 150**, **HDL low** (men < 40, women < 50), and **blood pressure ≥ 130/85**. Why do they travel as a pack? Because one process — **insulin resistance** — drives all five at once.



Insulin resistance is the thread that ties all five together.

Belly fat talks back

Here's the mindset shift: **visceral fat is an endocrine organ**, not a passive storage bag. When it's inflamed and overstuffed it **secretes**, and everything it says makes the syndrome worse. It dumps **free fatty acids** (ectopic lipid → insulin resistance), drops protective **adiponectin**, pumps out **leptin** nobody listens to anymore, and releases inflammatory **TNF-α and IL-6**. The waistline isn't a symptom — it's the **source**.



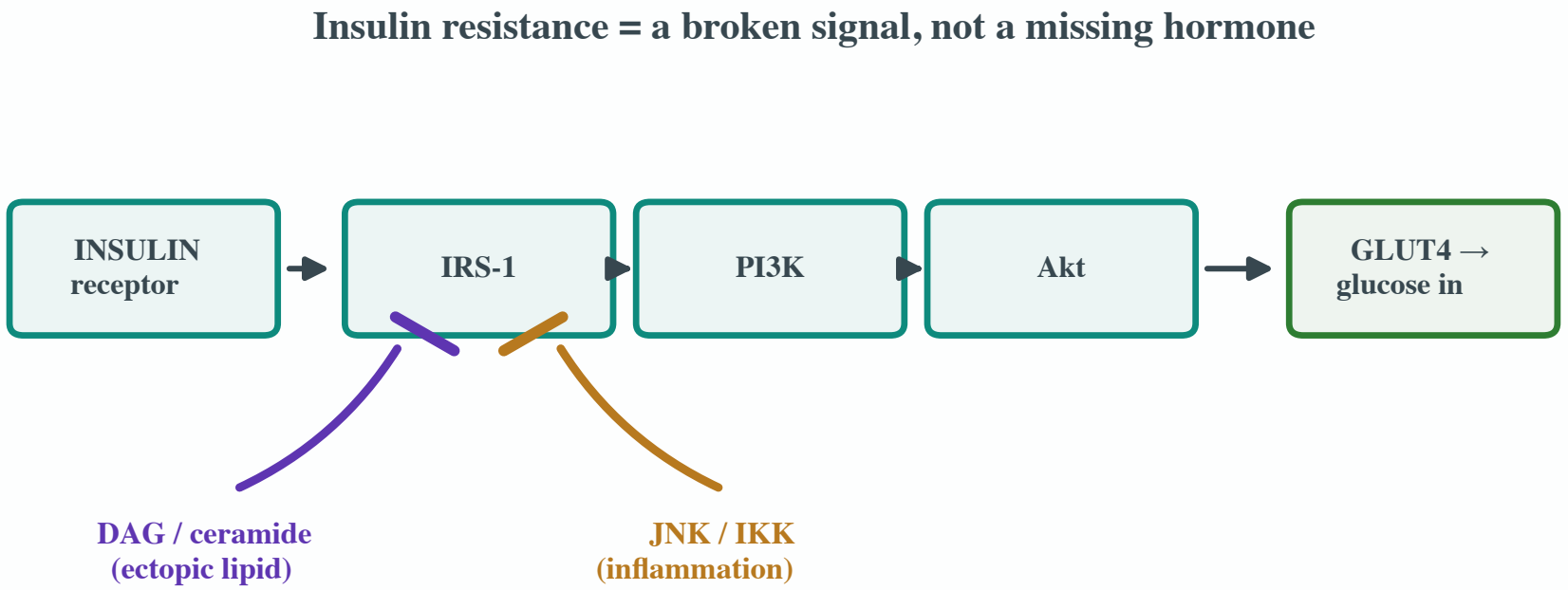
The secretome drives insulin resistance, dyslipidemia, and hypertension — the whole syndrome.

3 · The Biochemistry of Insulin Resistance

"Insulin resistance is the engine under the whole syndrome — so let's pop the hood. The hormone is present, sometimes sky-high; the problem is downstream, where the signal gets jammed. And the liver's response is so perverse it deserves its own slide."

The signal, and where it jams

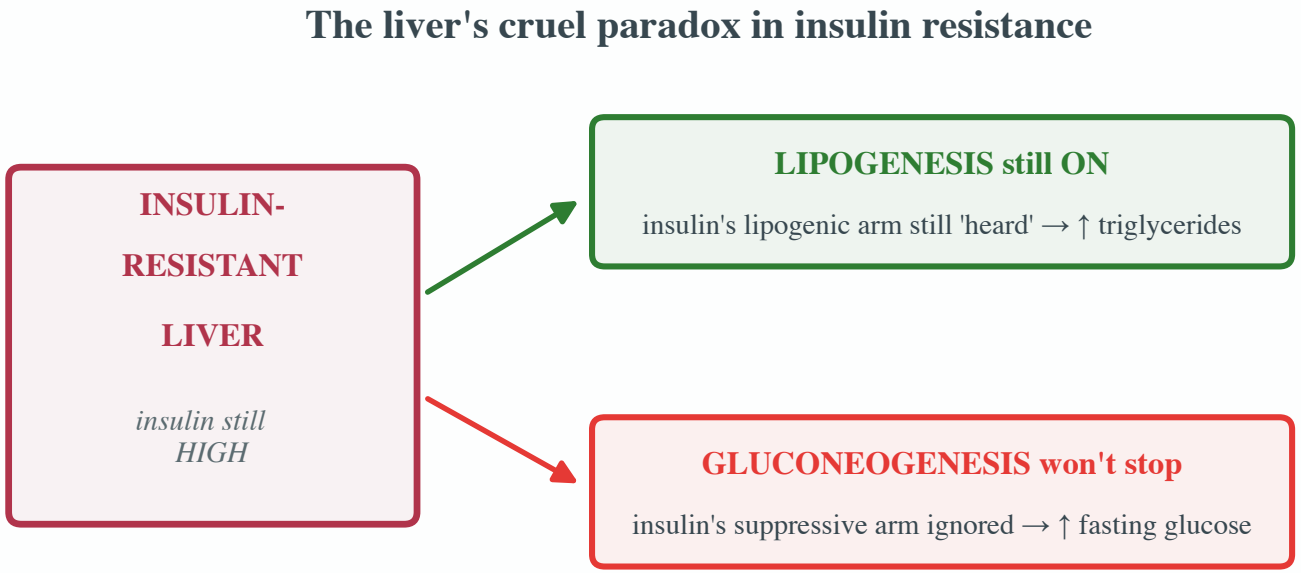
Remember the insulin cascade from BCH 120: receptor → **IRS-1 → PI3K → Akt → GLUT4** goes to the membrane and glucose comes in. In insulin resistance the hormone is **there** — the **wiring** is broken. **Ectopic lipid** (DAG, ceramide) and **inflammatory kinases** (JNK, IKK) slap inhibitory **serine phosphates** onto IRS-1. PI3K never fires, Akt stays asleep, GLUT4 never leaves home. High insulin, low effect.



Ectopic fat and inflammation both serine-phosphorylate IRS-1 — the signal dies right there.

The liver's cruel paradox

Now the twist that trips everyone up. The resistant liver isn't uniformly deaf — it's **selectively** deaf. Insulin's job to **shut off gluconeogenesis**? Ignored — so the liver keeps dumping glucose and **fasting sugar climbs**. But insulin's job to **run lipogenesis**? Still heard loud and clear — so the liver keeps making fat and **triglycerides climb**. High glucose **and** high triglycerides at once — the fingerprint of the whole syndrome.



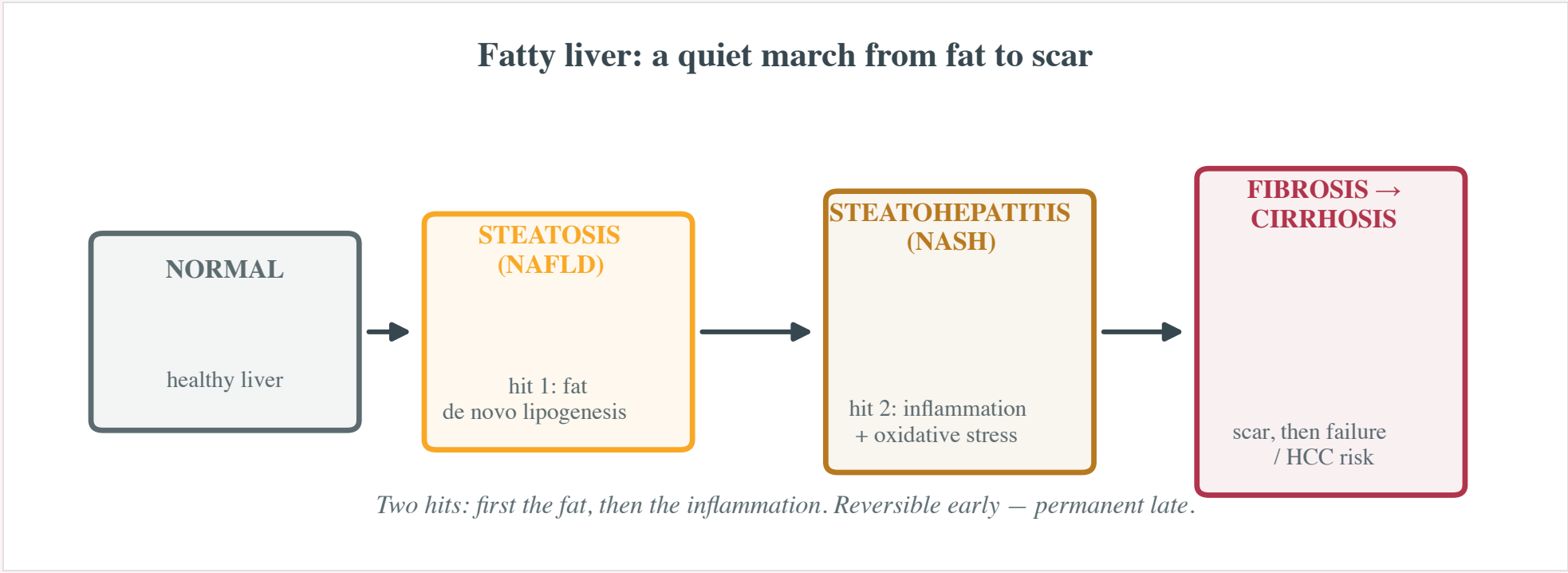
High glucose AND high triglycerides at once — the fingerprint of the syndrome.

4 · Consequences & Management

"Where does the syndrome go if we ignore it? Straight to the liver, and then to diabetes and heart disease. But here's the hopeful part: caught early, it's reversible — and every treatment we reach for maps back to a mechanism from this unit. Treat the defect, not the number."

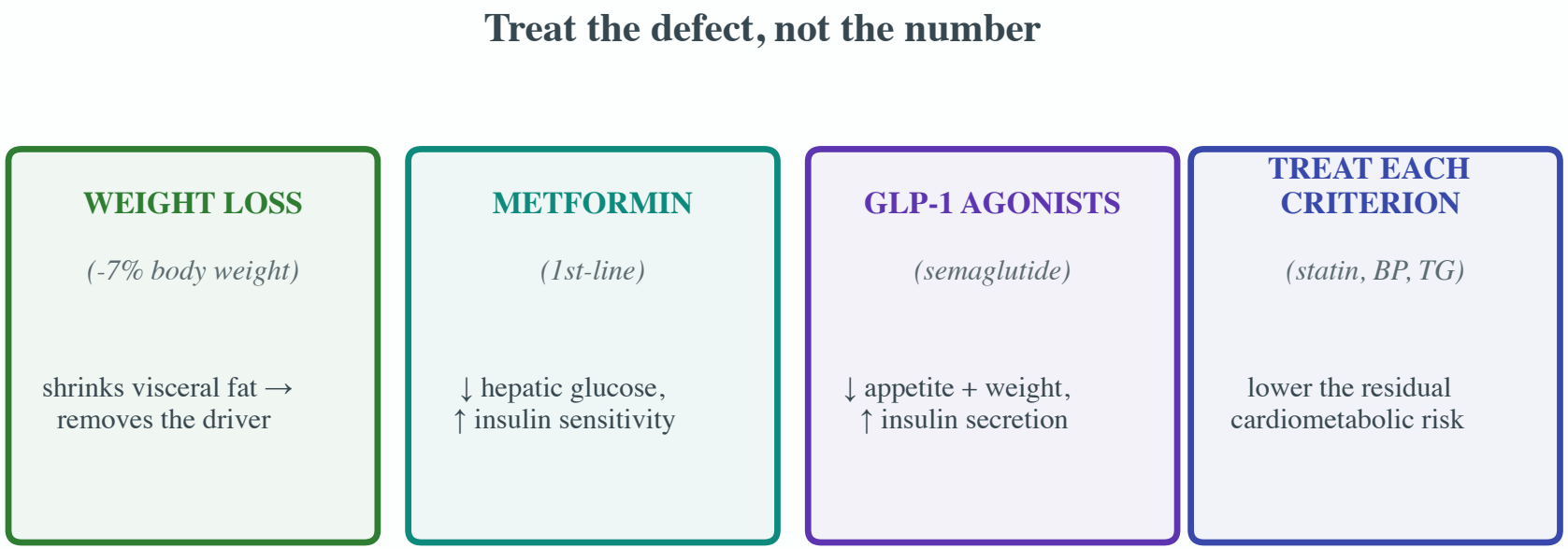
The fat lands in the liver

All that hepatic lipogenesis parks in the liver as **fatty liver (NAFLD/MASLD)** – a **two-hit** march. **Hit one:** fat accumulates (steatosis), silent and reversible. **Hit two:** inflammation and oxidative stress make **steatohepatitis (NASH)**, scarring into **fibrosis** then **cirrhosis**. The tip-off is subtle – a **mildly elevated ALT** or a bright liver on ultrasound, often with otherwise-normal labs.



Treat the defect, not the number

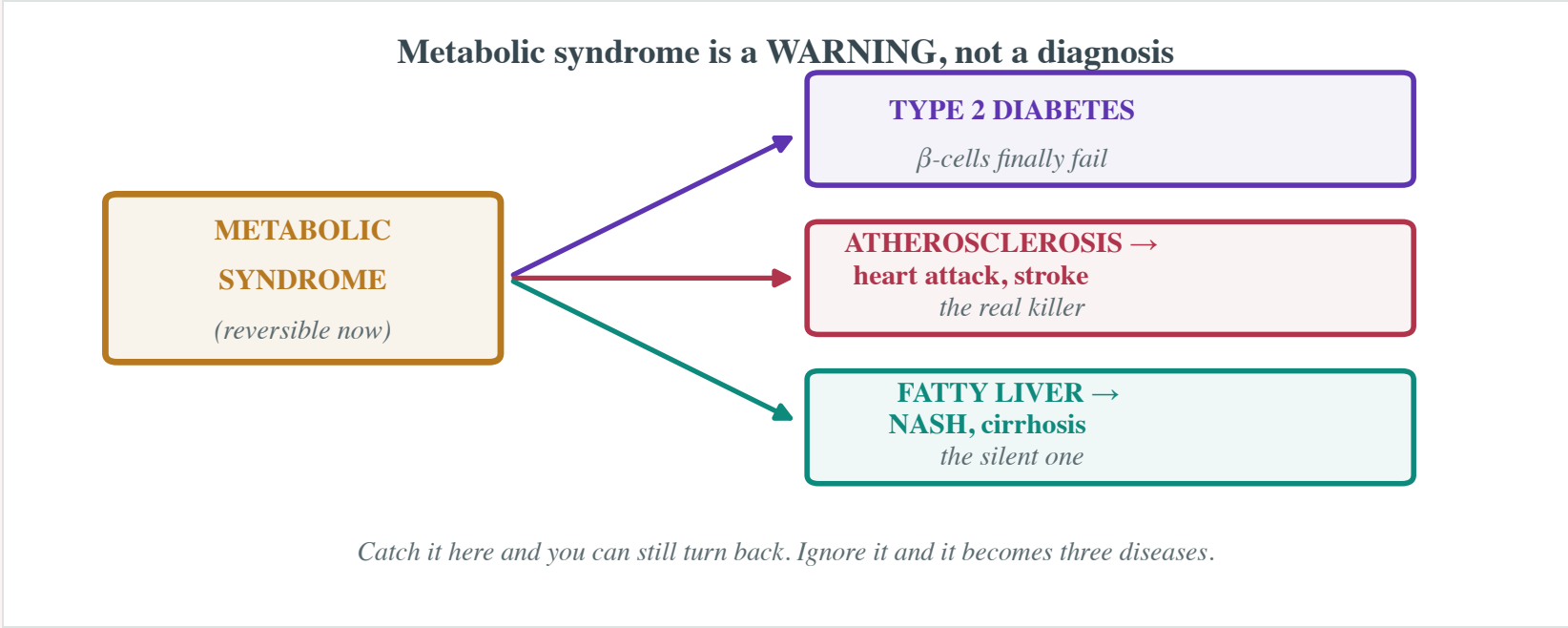
Here's the payoff of naming mechanisms first: every treatment **targets one**. **Lose ~7% of body weight** and you shrink the visceral fat that started it all — the single most powerful lever. **Metformin** quiets hepatic glucose output. **GLP-1 agonists** (semaglutide) crush appetite and sharpen insulin secretion. Then **treat each criterion** — statin, blood pressure, triglycerides — to mop up the residual risk.



Every lever here maps to a mechanism from this unit — that's the point of naming it first.

A warning, not a verdict

Leave this unit hearing metabolic syndrome as an **alarm**, not a diagnosis. Left alone it forks into **three diseases**: type 2 diabetes when the β-cells give out, **atherosclerosis** — the real killer — and fatty liver grinding toward cirrhosis. This is exactly why we open the whole course here.



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If any box stays empty, the practice site has a drill for it.
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