Diabetes & Its Complications

BCH 130 — Advanced Human Biochemistry · Dr. Radi

By the end of this unit, you can…

- Contrast the pathophysiology of type 1 (beta-cell loss, absolute insulin deficiency, ketosis-prone) and type 2 diabetes (insulin resistance + progressive beta-cell failure).
- Describe beta-cell biology and its failure
- Explain the counter-regulatory hormone response and why unopposed glucagon drives hyperglycemia and ketogenesis in insulin deficiency.
- Interpret the diagnostic tests — fasting glucose, OGTT, HbA1c (with its biochemistry and pitfalls), C-peptide, and islet autoantibodies — to distinguish diabetes types.

Today's route

1. Type 1 vs Type 2 – Two Roads to Diabetes
2. Diagnosing Diabetes – Reading the Labs
3. The Other Diabetes – Monogenic & Secondary
4. Diabetic Complications – Where the Sugar Does Its Damage

1 · Type 1 vs Type 2 — Two Roads to Diabetes

"Same diagnosis, two completely different diseases. Type 1 is a destruction story — the β-cells are gone and insulin drops to zero. Type 2 is a resistance story — insulin is loud but ignored, until the exhausted β-cells finally quit. Name the mechanism first, and the labs, the ketones, and the treatment all fall into place."

Two diseases, one name

Don't let the shared label fool you. **Type 1** is a **destruction** story — the **β-cells are gone**, insulin falls to **zero**, and with nothing to restrain fat breakdown it runs to ketones (**ketosis-prone**). **Type 2** is a **resistance** story — insulin is high but ignored, until overworked β-cells **progressively fail**. Opposite mechanisms, same hyperglycemia.

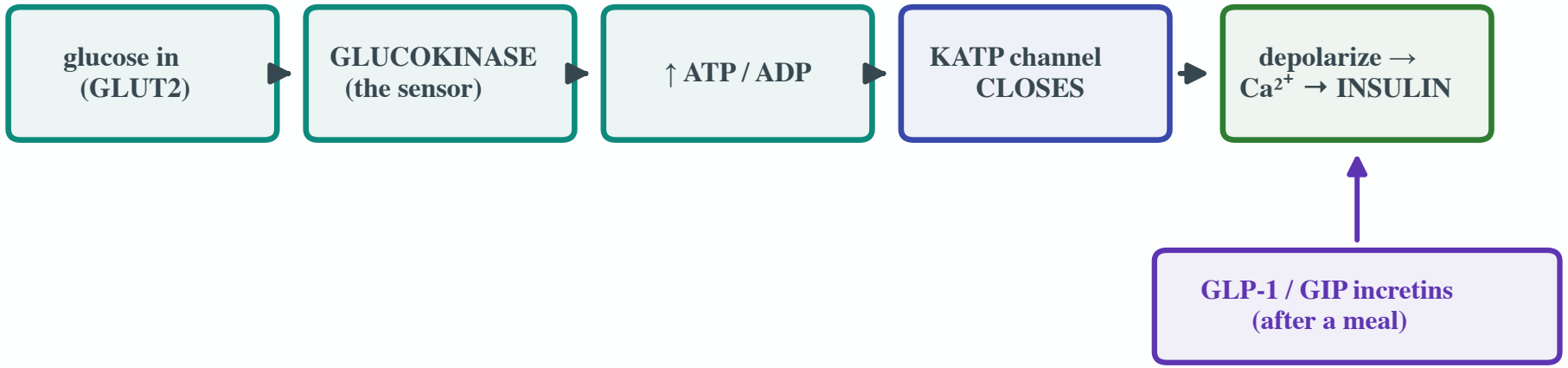
Two roads to a high blood sugar

Same endpoint — hyperglycemia — reached from opposite mechanisms.

How the β-cell knows

How does a β-cell **sense** that glucose is high? **GLUT2** lets glucose flood in, and **glucokinase** — a sensor tuned to the physiologic range — sets the pace. Burning it raises **ATP**, which slams the **KATP channel** shut, depolarizes the cell, opens **Ca^{2+}**, and releases **insulin**. Gut **incretins** amplify every meal.

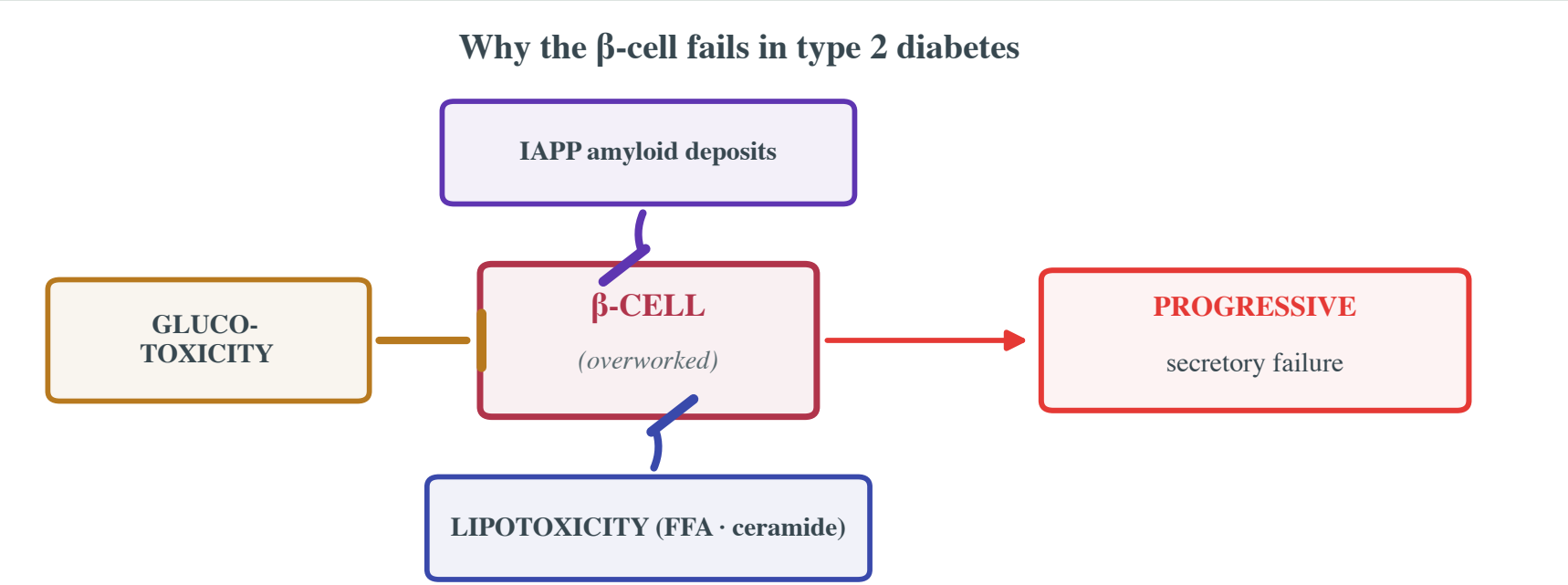
How the β-cell senses glucose and fires insulin



Glucokinase is the gatekeeper — insulin output tracks the glucose level; gut incretins amplify it.

When the β-cell burns out

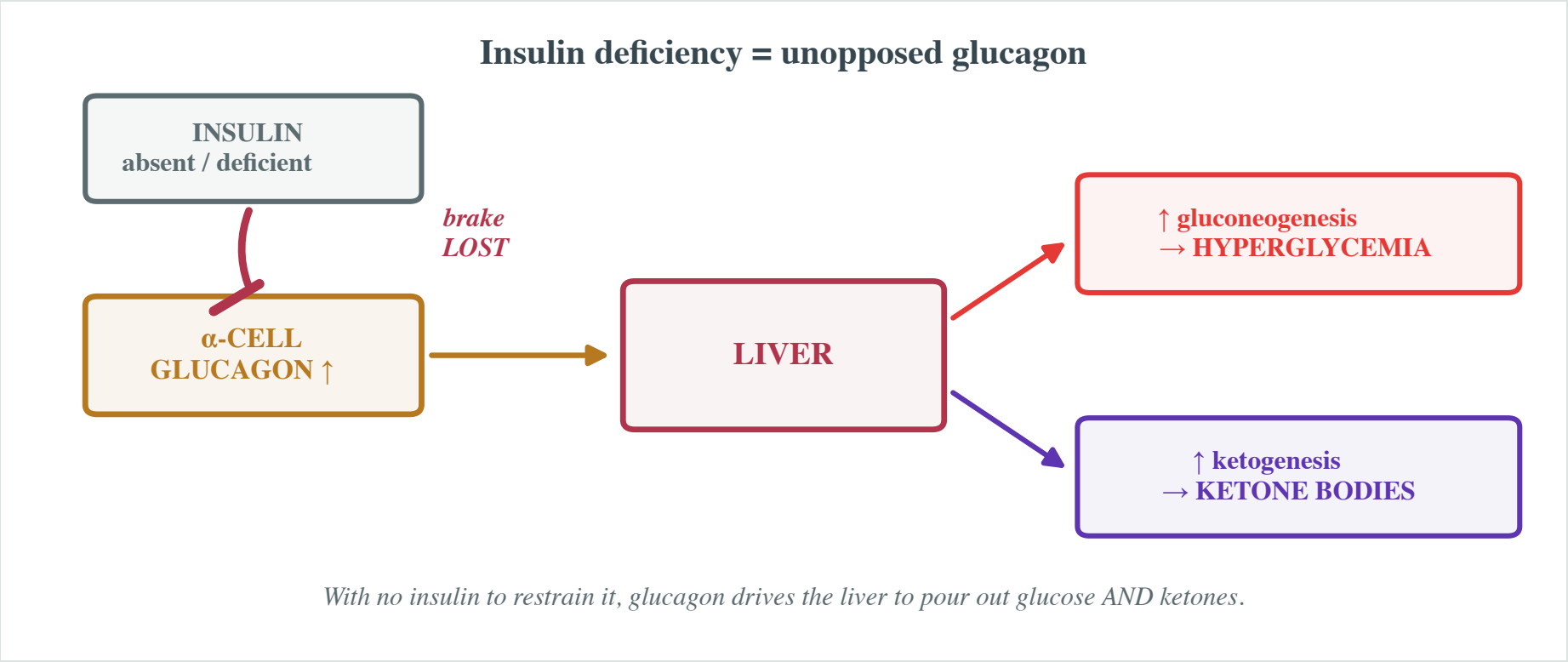
So why do Type 2 β-cells eventually quit? Three insults gang up. **IAPP amyloid** deposits choke the islet. **Glucotoxicity** — chronic high glucose — poisons the very cells meant to fix it. And **lipotoxicity** from spilled fatty acids finishes them off. That's why Type 2 is **progressive**: the insulin factory slowly wears out.



Amyloid, glucotoxicity, and lipotoxicity grind the β-cell down — T2 is a progressive disease.

The unopposed glucagon problem

Here's the twist students miss: insulin deficiency isn't just **low insulin** — it **unleashes glucagon**. Normally insulin **restrains** the α-cell; remove that brake and glucagon runs wild. The liver obeys, pouring out **glucose and ketone bodies**. That's exactly why absolute insulin loss tips straight into **ketoacidosis**.



2 · Diagnosing Diabetes — Reading the Labs

"Three numbers make the diagnosis, two more tell you which type, and one — HbA1c — is a beautiful piece of biochemistry that occasionally lies to you. Let's learn to read the panel like a biochemist: what each test measures, where the cut-offs sit, and when to trust the A1c and when to reach for something else."

Three ways to make the call

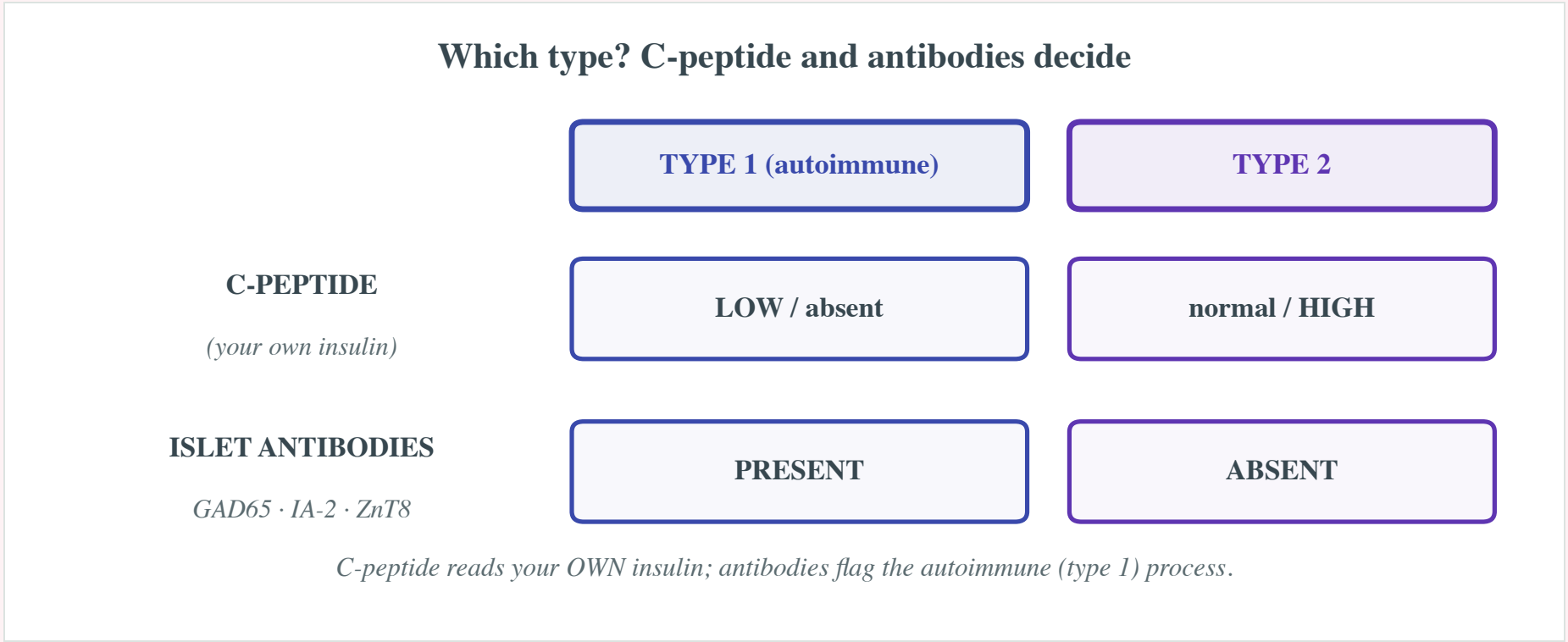
You can diagnose diabetes **three ways**, and any one clinches it: **fasting glucose ≥ 126**, a **2-hour OGTT ≥ 200** after a 75 g load, or **HbA1c ≥ 6.5%**. A **random glucose ≥ 200** plus classic symptoms counts too. Sitting just below each cut-off? That's **prediabetes** — the warning shot.

Three ways to diagnose diabetes

Any one confirms it — repeat to confirm if there are no symptoms. Prediabetes sits just below each cut.

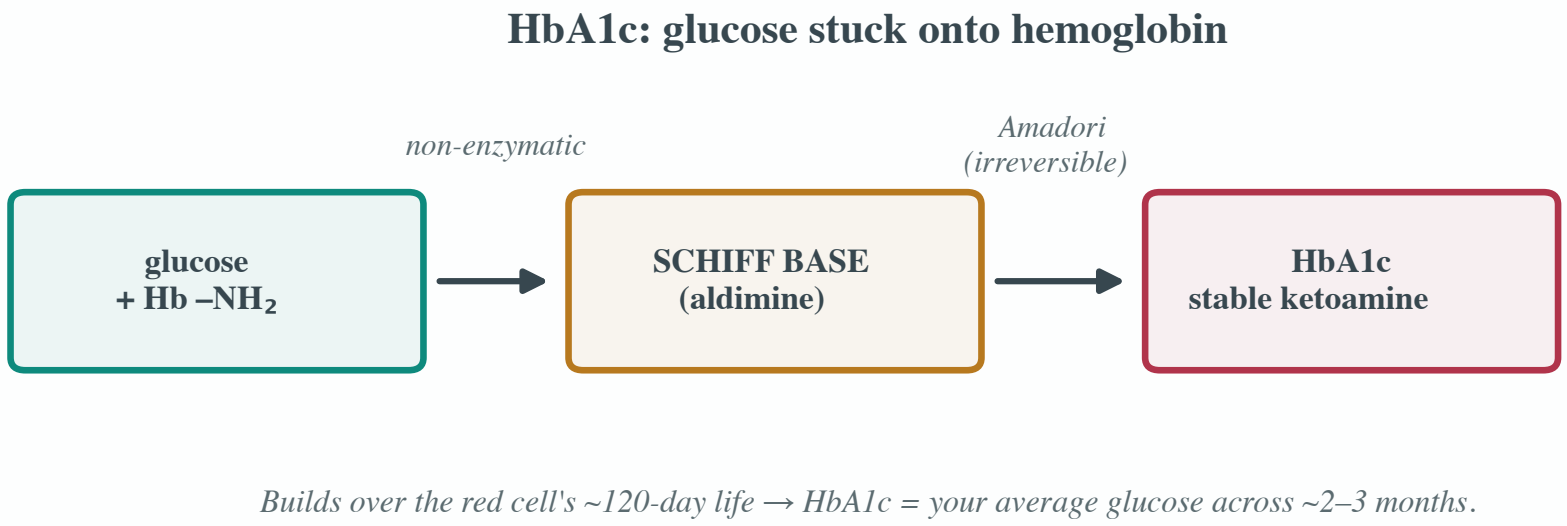
Which type is it?

The diagnosis is diabetes — but **which** type? Two tests settle it. **C-peptide** is released 1:1 with your own insulin, so **low** means Type 1 (nothing left) and **normal-to-high** means Type 2 (plenty, just ignored). **Islet autoantibodies** (GAD65, IA-2) present? That flags the **autoimmune**, Type 1 process.



HbA1c is built, not measured

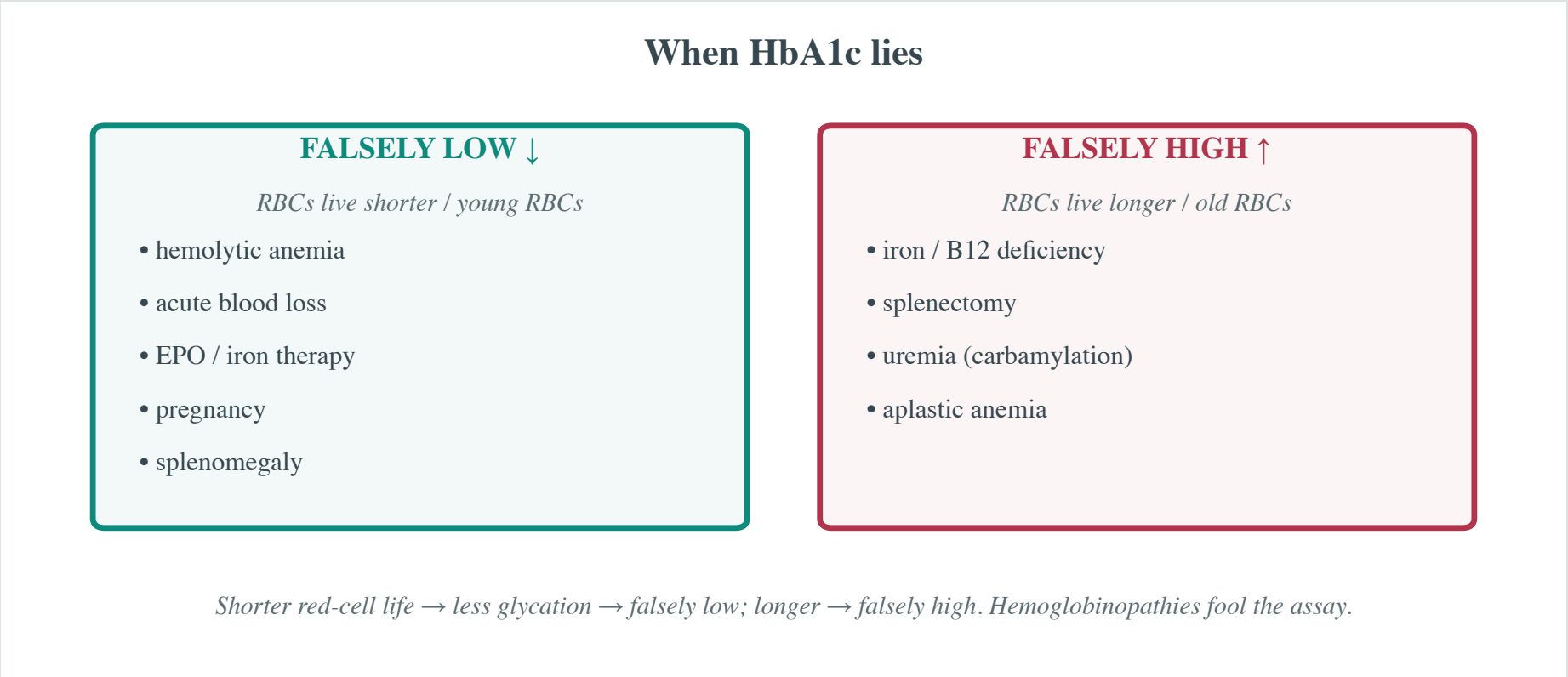
HbA1c isn't a level — it's **built**. Glucose drifts onto hemoglobin's N-terminus with **no enzyme**, forming a wobbly **Schiff base** that rearranges (the **Amadori** step) into a **stable** ketoamine. Because red cells live ~120 days, that sugar-coating records your **average glucose over 2–3 months**. Elegant, right?



Builds over the red cell's ~120-day life → HbA1c = your average glucose across ~2–3 months.

When A1c lies to you

A1c has a blind spot: it trusts the red cell's clock. **Shorten** that lifespan — hemolysis, bleeding, pregnancy, EPO — and there's less time to glycate, so A1c reads **falsely low**. **Lengthen** it — iron deficiency, splenectomy — and it reads **falsely high**. And **hemoglobinopathies** fool the assay entirely.



3 · The Other Diabetes — Monogenic & Secondary

"Not every diabetic is Type 1 or Type 2. Sometimes it's a single broken gene that tells you exactly which pill to prescribe; sometimes it's pregnancy, a wrecked pancreas, or another hormone bullying insulin. Learn to spot these, because the label changes the treatment — and occasionally cures it."

One gene, one diagnosis

Sometimes diabetes is **one broken gene**, and the gene dictates the fix. **GCK MODY** is mild and stable — often needs **nothing**. **HNF1A/4A MODY** and **KATP neonatal** diabetes respond beautifully to **sulfonylureas** — not insulin! And **mitochondrial** diabetes travels with **deafness** down the maternal line. Genotype, not glucose, guides treatment.

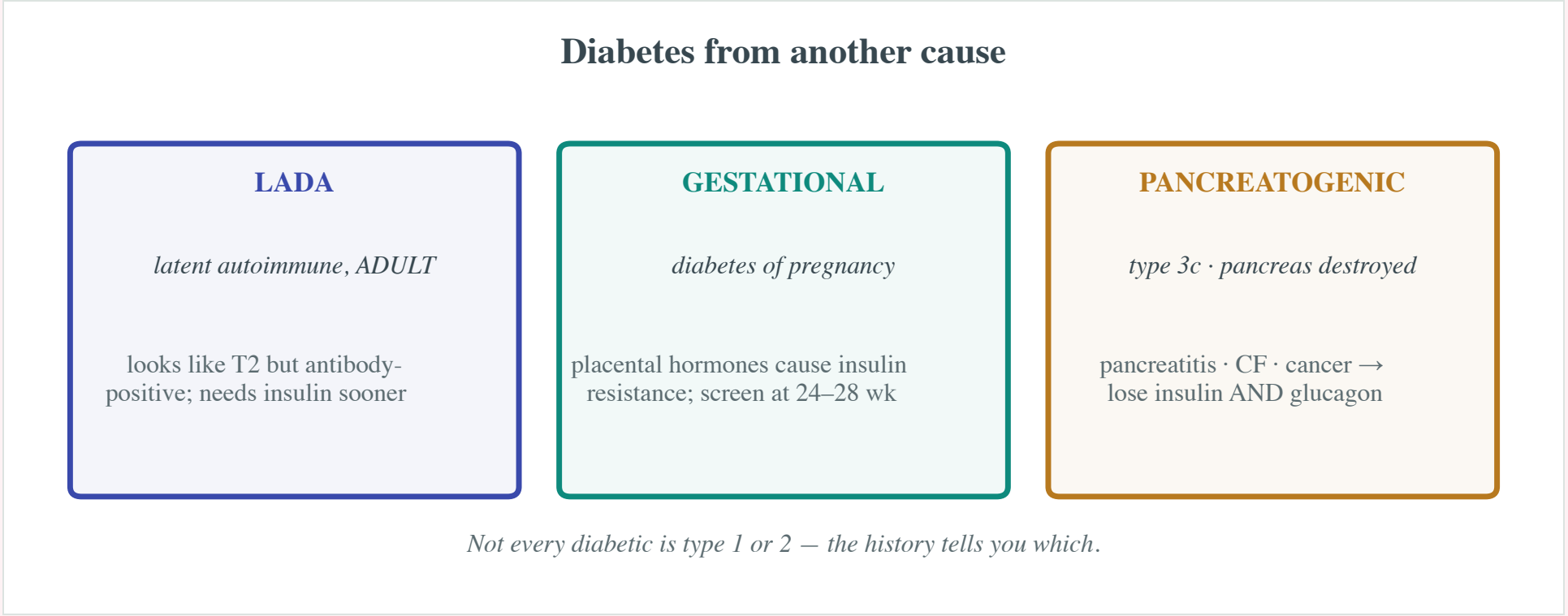
Monogenic diabetes: the gene picks the treatment

TYPE — GENE	CLUE	TREATMENT
MODY 2 · GCK	mild, stable fasting ↑	**often NONE**
MODY 3/1 · HNF1A/4A	progressive; young, familial	**SULFONYLUREA**
Neonatal · KATP	onset < 6 months old	**SULFONYLUREA**
Mitochondrial · m.3243	maternal + DEAFNESS	**avoid metformin**

Same word 'diabetes', very different genes — sulfonylureas beat insulin in the HNF1A and KATP forms.

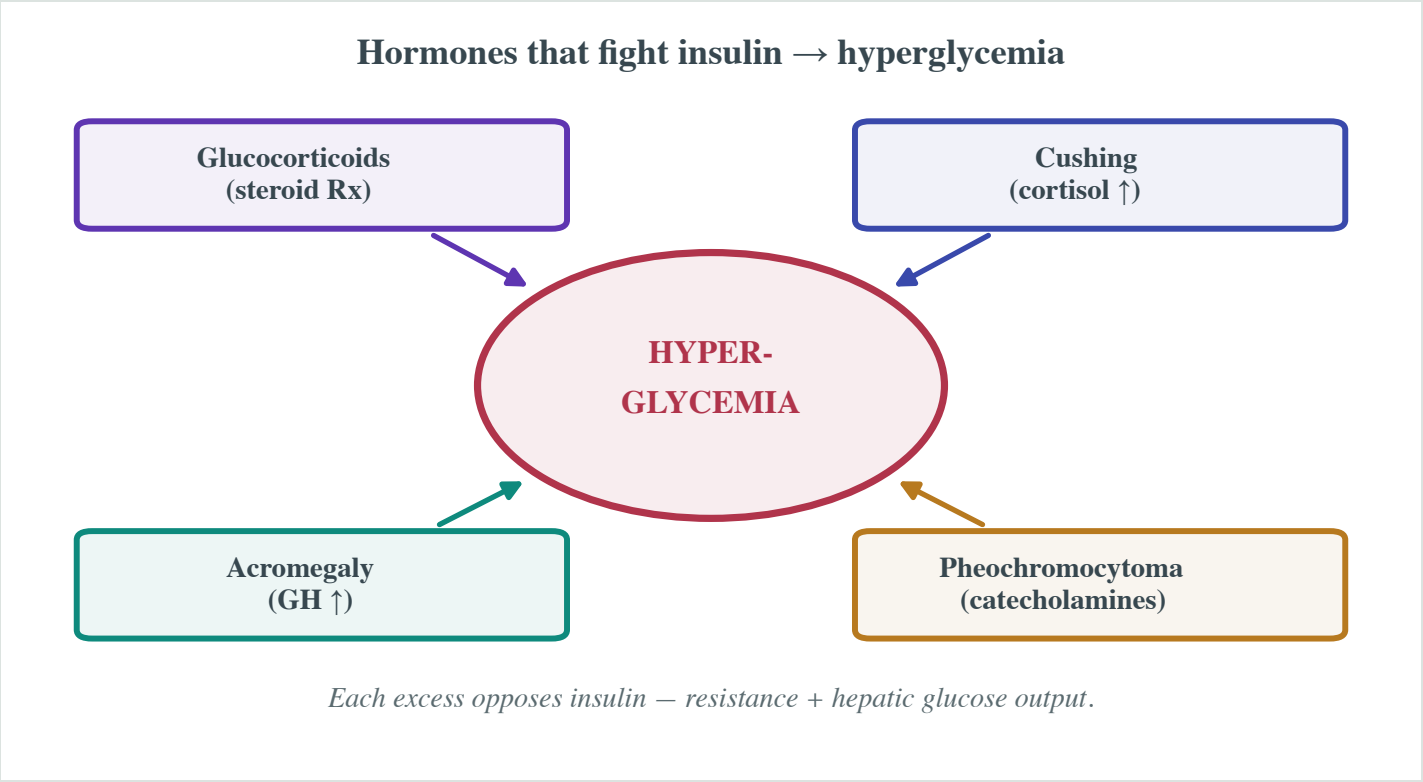
Diabetes by another route

Not every diabetic fits the big two. **LADA** is slow **autoimmune** diabetes in adults — it masquerades as Type 2 until the antibodies surface. **Gestational** diabetes rides pregnancy's built-in insulin resistance. And **pancreatogenic (type 3c)** diabetes follows a **destroyed pancreas** — losing insulin **and** glucagon at once.



Hormones that cause diabetes

Whole hormones can **cause** diabetes by fighting insulin. Pile on **glucocorticoids** — a steroid prescription or **Cushing's** cortisol — and glucose climbs. **Acromegaly's** growth hormone and a **pheochromocytoma's** catecholamines do the same. Each drives **insulin resistance** plus **hepatic glucose output**. Fix the source and the diabetes often melts away.

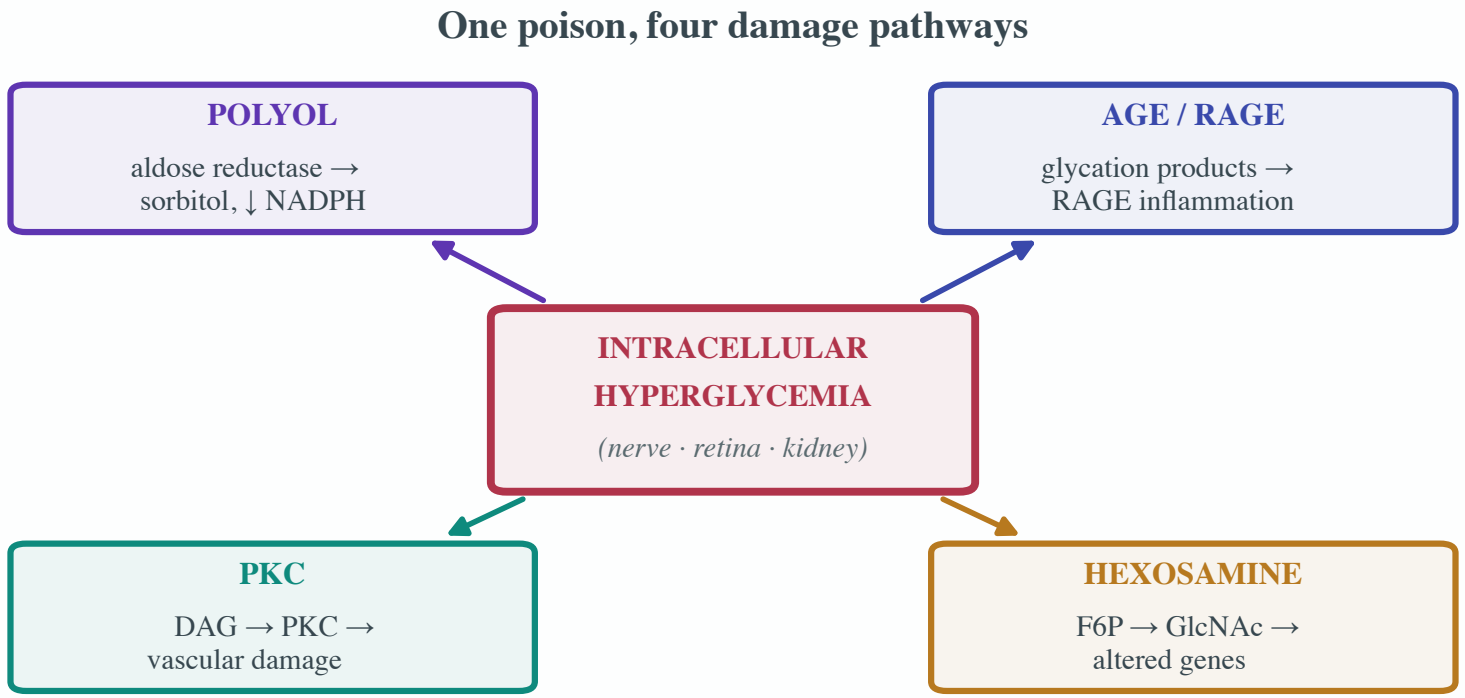


4 · Diabetic Complications — Where the Sugar Does Its Damage

"This is why we fight so hard for control. Chronic high glucose isn't just a number — it's a slow poison that fans into four biochemical pathways and cashes out as blindness, kidney failure, numb feet, and early heart attacks. And when insulin runs out fast, the emergencies arrive: DKA and HHS. Let's connect the biochemistry to the bedside."

One poison, four pathways

Why does high glucose **damage** tissue? In cells that can't throttle uptake — **nerve, retina, kidney** — glucose floods in and fans into **four pathways**: the **polyol** shunt (burning NADPH), **AGE/RAGE** glycation, **PKC** activation, and the **hexosamine** route. One upstream culprit unifies them: **mitochondrial superoxide**.

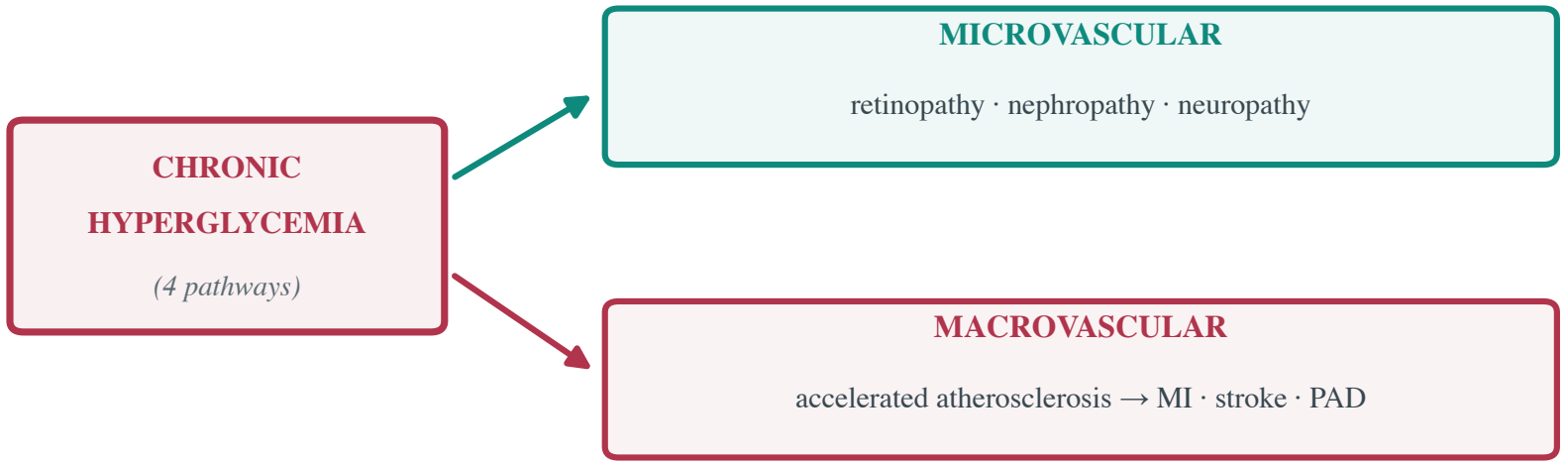


All four are driven by mitochondrial superoxide overproduction — the unifying hit.

From pathways to complications

Those pathways cash out as complications. **Microvascular** damage blinds the eye (**retinopathy**), scars the kidney (**nephropathy**), and numbs the feet (**neuropathy**). **Macrovascular** disease is **accelerated atherosclerosis** — why diabetics suffer **heart attack and stroke** years early. Tight glucose control delays all of it.

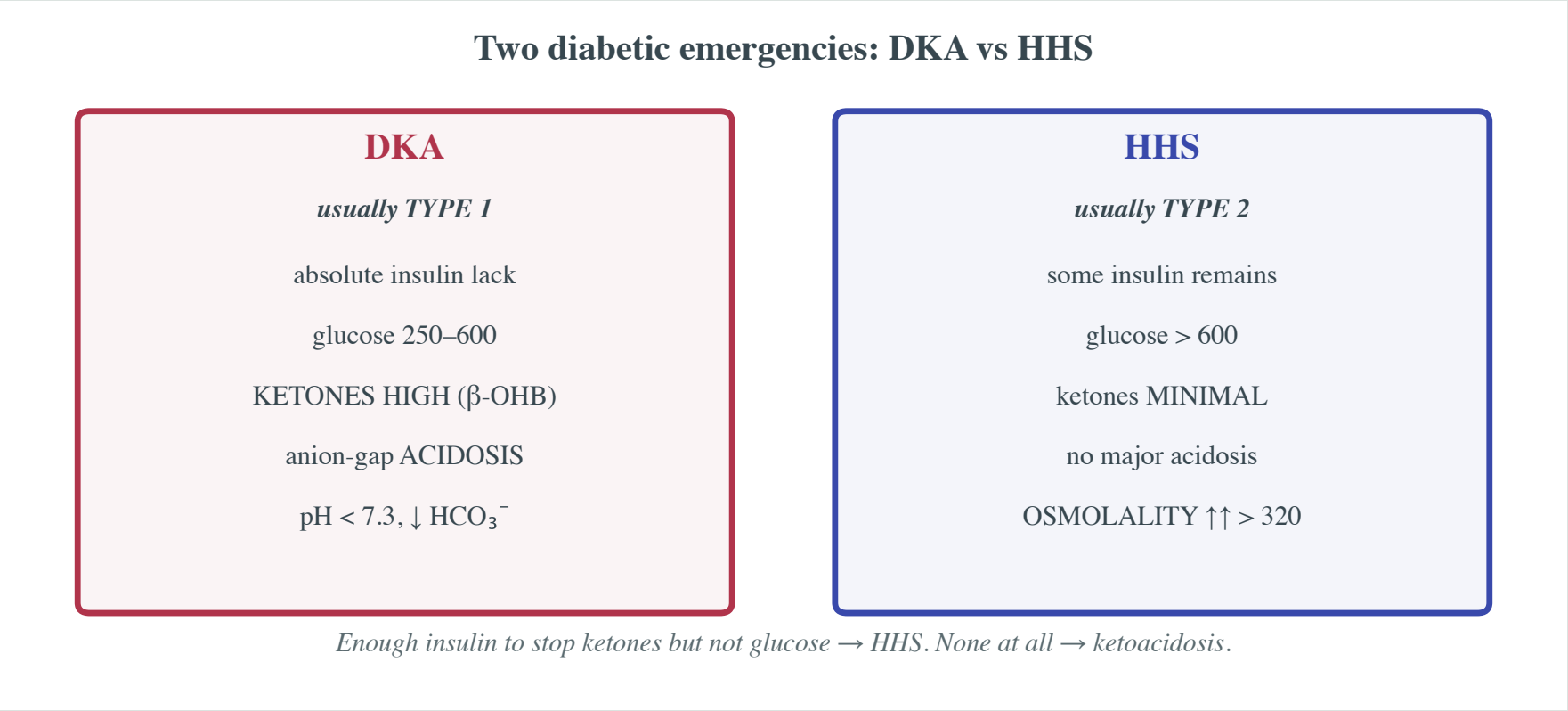
From four pathways to the diabetic complications



Small vessels blind the eye, fail the kidney, and numb the nerve; big vessels drive early MI and stroke.

DKA vs HHS: the two crises

Two emergencies, one spectrum. **DKA** hits when insulin reaches **zero** (usually Type 1): fat burns to **ketones**, blood turns acidic — an **anion-gap acidosis**. **HHS** is **just enough** insulin to block ketones but not glucose (usually Type 2): sugar soars past **600**, turning **hyperosmolar**.



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- □ interpret the diagnostic tests — fasting glucose, OGTT, HbA1c (with its biochemistry and pitfalls), C-peptide, and islet autoantibodies — to distinguish diabetes types?

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