Diabetes

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Diagnose diabetes from the glucose criteria (FPG, OGTT, HbA1c, random) and explain how HbA1c reports 2–3 months of control
- Explain type 1 diabetes — autoimmune β-cell destruction, autoantibodies (ICA/IAA/IA2/GAD), stages, and insulin therapy
- Explain type 2 diabetes — insulin resistance, risk factors, the natural history through prediabetes, and metabolic syndrome
- Describe diabetes management (the ABCs) and the Ominous Octet of type-2 defects
- Explain incretins (GLP-1, GIP; DPP-4), the kidney's SGLT glucose reabsorption, and the mechanisms of the major drugs (metformin, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 agonists / Ozempic)

Today's route

1. Diagnosing Diabetes & HbA1c
2. Type 1 Diabetes
3. Type 2 Diabetes & Prediabetes
4. Managing Diabetes & the Ominous Octet
5. Incretins, the Kidney & Diabetes Drugs

1 · Diagnosing Diabetes & HbA1c

"Diabetes is, at its core, one thing: chronically high blood glucose. Before we split it into types, let's nail down how it's diagnosed — and meet HbA1c, the clever blood test that remembers your last three months of sugar."

Diagnosing diabetes — the numbers

The diagnostic sign of diabetes is **hyperglycemia**, and there are **four ways to catch it**. **Fasting plasma glucose ≥ 126 mg/dL**. **Oral glucose tolerance test ≥ 200**. **HbA1c ≥ 6.5%**. Or a **random glucose ≥ 200** with symptoms. In between sits **pre-diabetes** — a warning zone (fasting 100–125, A1c 6.0–6.4) where risk is already rising. One confirmed test over the line makes the call.

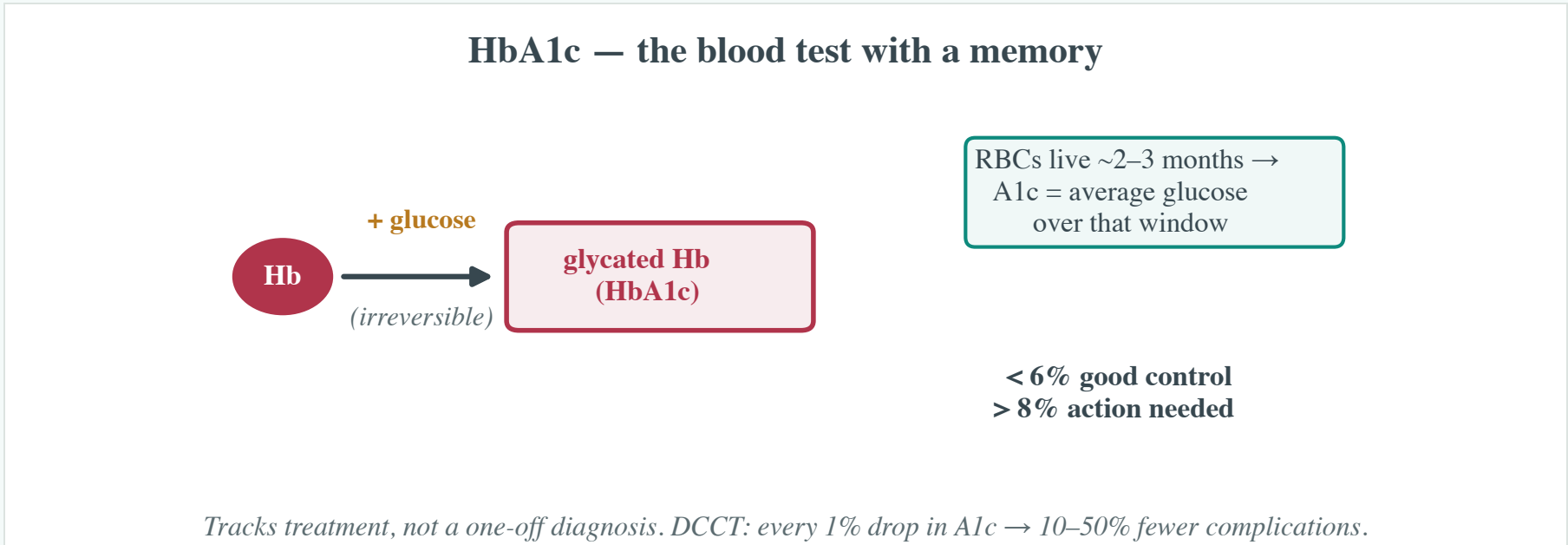
Diagnosing diabetes — it's the glucose number

TEST	DIABETES	PRE-DIABETES
Fasting glucose (FPG)	≥ 126 mg/dL	100–125
Oral tolerance (OGTT)	≥ 200 mg/dL	140–199
HbA1c	≥ 6.5 %	6.0–6.4
Random glucose	≥ 200 mg/dL	—

Hyperglycemia is THE diagnostic sign — one confirmed test over the line makes the call.

HbA1c: the blood test with a memory

Here's the elegant one. Glucose in the blood **irreversibly sticks to hemoglobin** — a bit of the sugar chemistry you saw in BCH 100 — forming **glycated hemoglobin, HbA1c**. Because red cells live **2–3 months**, the A1c is a **running average** of your blood glucose over that whole window — no single reading can hide in it. Under **6%** is good control; over **8%** means act. The **DCCT** trial proved it matters: **every 1% drop in A1c cuts complications 10–50%**.

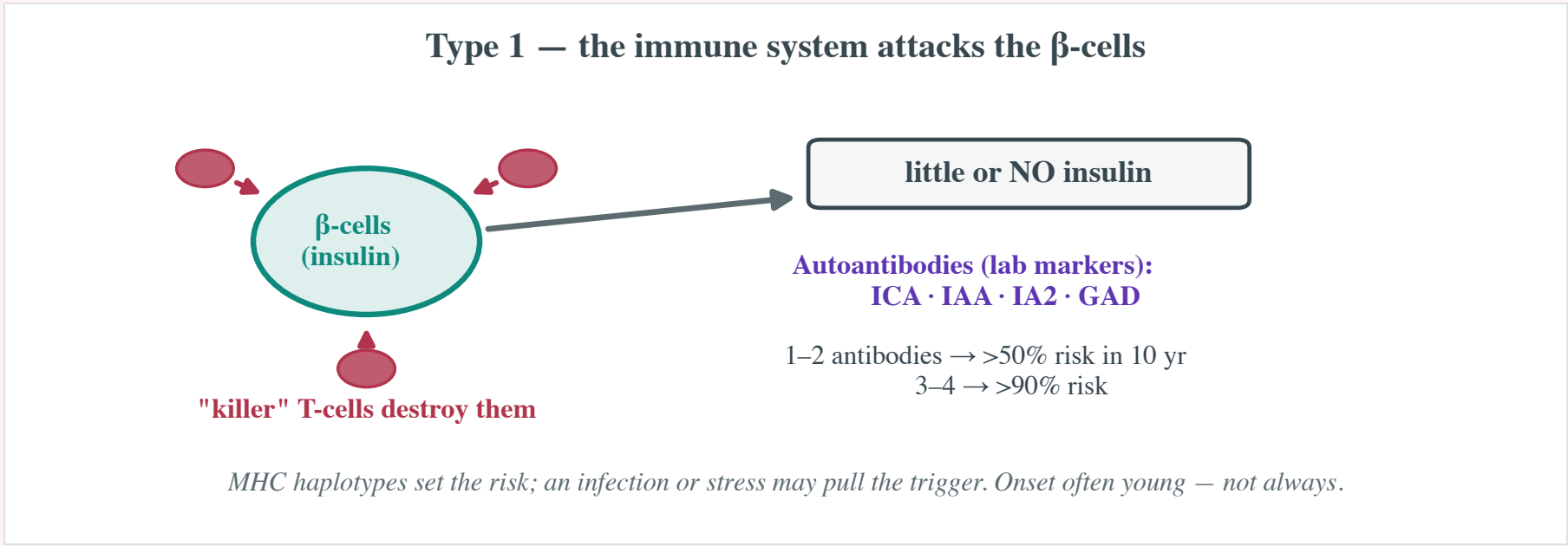


2 · Type 1 Diabetes

"Type 1 is an autoimmune tragedy with a triumphant treatment. The immune system destroys the insulin-making β-cells, so the body makes little or none — and the discovery of insulin in 1922 turned a death sentence into a manageable disease."

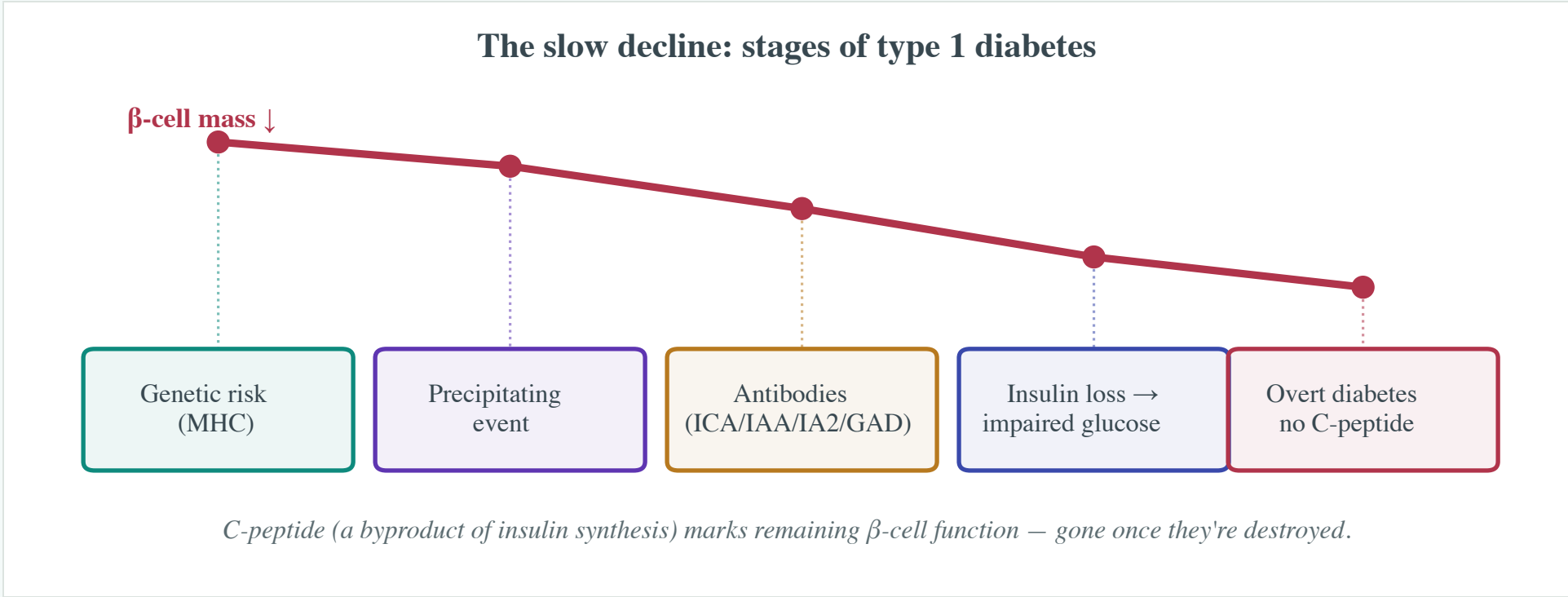
Type 1: the immune system attacks the β-cells

Type 1 diabetes is an **autoimmune** disease: the body's own **"killer" T-cells destroy the pancreatic β-cells**, so insulin falls to **little or none**. As the attack unfolds, **autoantibodies** show up in the blood and serve as **early-warning markers** — **ICA, IAA, IA2, and GAD**. Having **1–2** of them predicts >50% risk within a decade; **3–4** pushes it past 90%. **MHC haplotypes** set the genetic risk; an infection or stress may pull the trigger. (Old name "juvenile diabetes" is misleading — it can start at any age.)



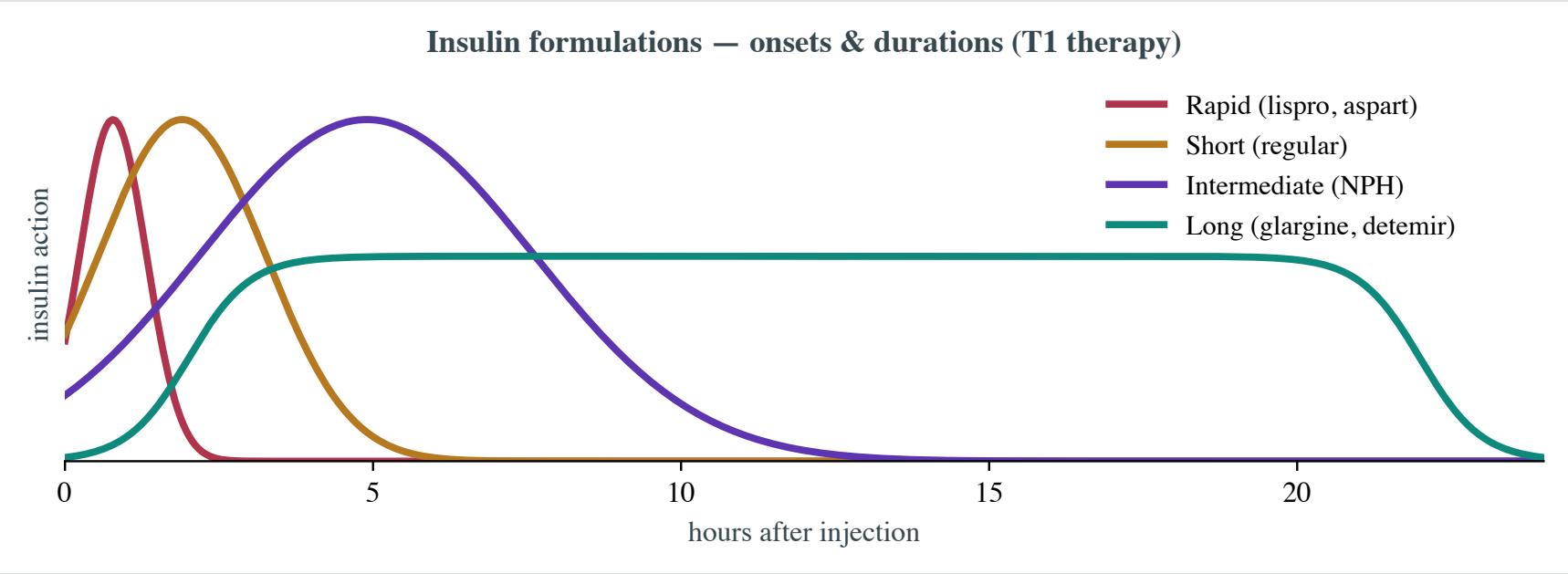
The slow decline, then the cliff

Type 1 doesn't happen overnight — it's a **staged loss of β-cell mass**. It starts with **genetic predisposition** (MHC), waits for a **precipitating event**, then **antibodies appear** while insulin is still normal. Slowly the β-cells die, glucose tolerance slips, and finally you hit **overt diabetes**. A key marker: **C-peptide** (a leftover from insulin synthesis) is **present** while β-cells work and **gone** once they're destroyed — so it reads out how much function remains.



Treatment: insulin, the 1922 miracle

Because the β-cells are gone, **insulin is mandatory** — by **injection or pump**, with **finger-stick monitoring** to dose it. When Banting and Best first gave insulin in **1922**, dying children **recovered within weeks**. Modern therapy mixes **formulations by speed** — **rapid** and **short** for meals, **intermediate** and **long** for steady background — matching the curves to the day to mimic a working pancreas.

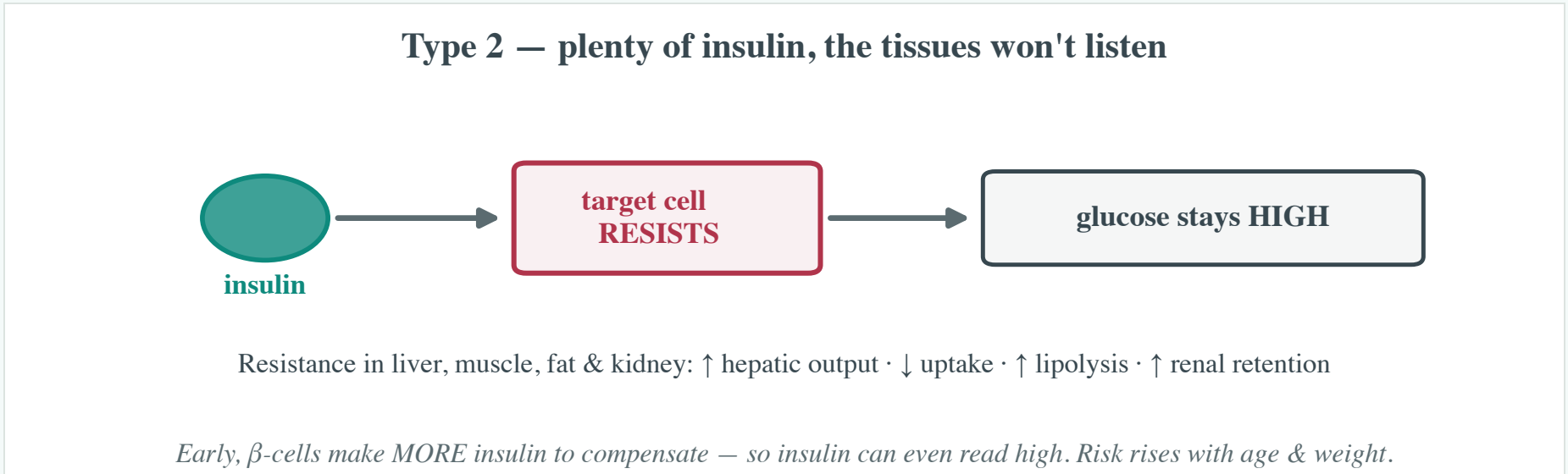


3 · Type 2 Diabetes & Prediabetes

"Type 2 is the common one — and a different beast. Here insulin is present, sometimes even high, but the tissues stop listening. It creeps in through years of prediabetes, and it's the metabolic disease of our era."

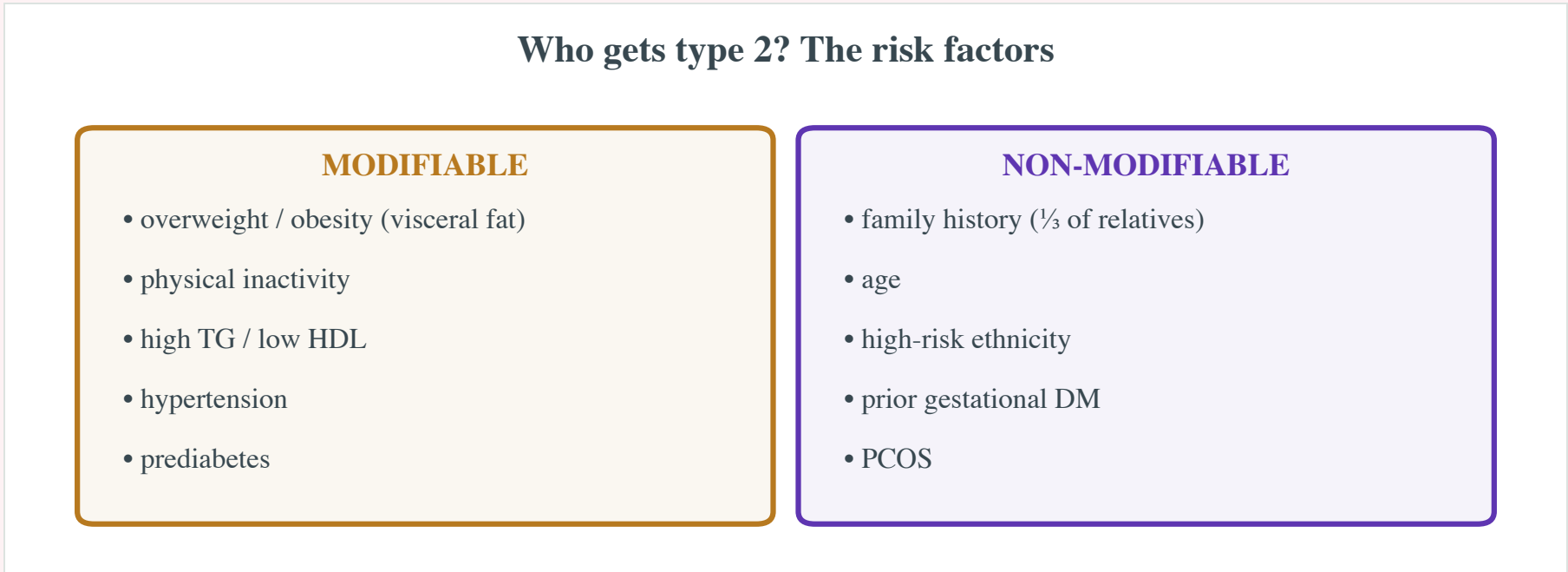
Type 2: the tissues stop listening

Type 2 diabetes is fundamentally **insulin resistance**: insulin is there — sometimes even **elevated** — but the **target tissues don't respond**, so glucose stays high. Resistance in **liver, muscle, fat, and kidney** means **more hepatic glucose output, less tissue uptake, more lipolysis, and more renal glucose retention** all at once. Early on the **β-cells compensate**, pumping out extra insulin to keep up — which is why insulin can read high. Risk climbs with **age and weight**.



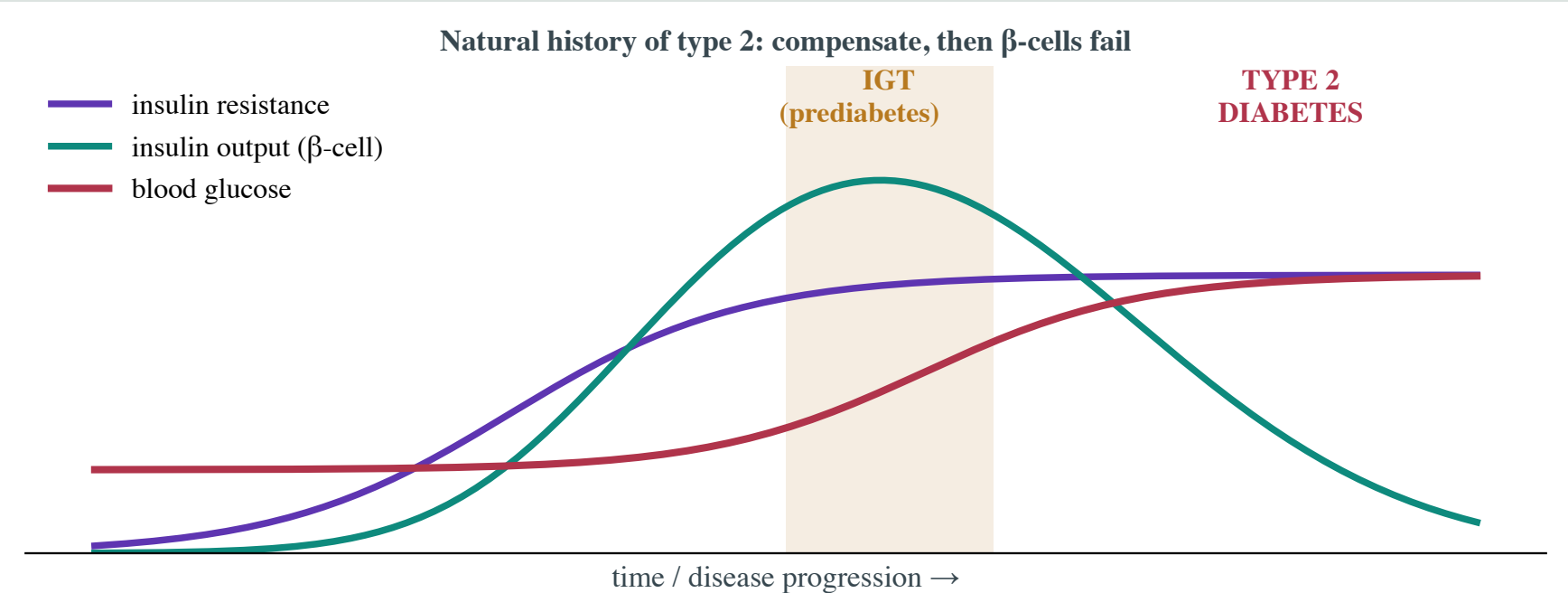
Who gets it — the risk factors

Type 2 is where **lifestyle and genes collide**. The **modifiable** drivers: **obesity** (especially **visceral fat**), **physical inactivity**, **high triglycerides / low HDL**, and **hypertension** — the cluster we call **metabolic syndrome**. The **non-modifiable** ones: a **strong family history** (about ⅓ of a patient's relatives develop it), **age**, **ethnicity**, and conditions like **PCOS** or prior **gestational diabetes**. The genetics are real but tangled — no single "diabetes gene" — so prevention leans hard on the modifiable side.



The slow slide through prediabetes

Type 2 announces itself years in advance if you know the pattern. First, **insulin resistance rises**, and the β-cells **compensate** with **more insulin** — glucose stays normal. Then the β-cells **start to fail**: glucose creeps up, especially after meals — that's **impaired glucose tolerance (IGT)**, a.k.a. **prediabetes**. When compensation can no longer keep up, **fasting and post-meal glucose climb** and it's overt **type 2 diabetes**. There's no sharp line — just a threshold of hyperglycemia where the long-term damage begins.

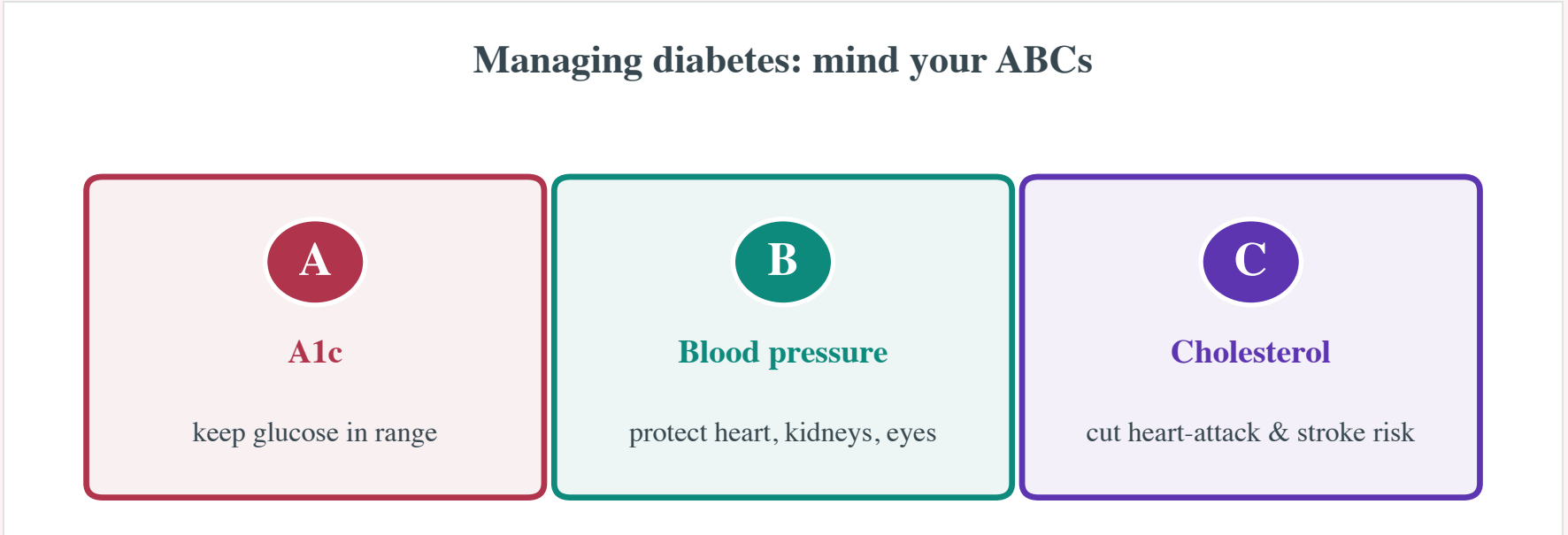


4 · Managing Diabetes & the Ominous Octet

"Treating diabetes isn't just about glucose — it's about protecting the heart, kidneys, and nerves that high sugar destroys. And to treat type 2 rationally, you need the map of everything that's broken: the Ominous Octet."

The ABCs of diabetes care

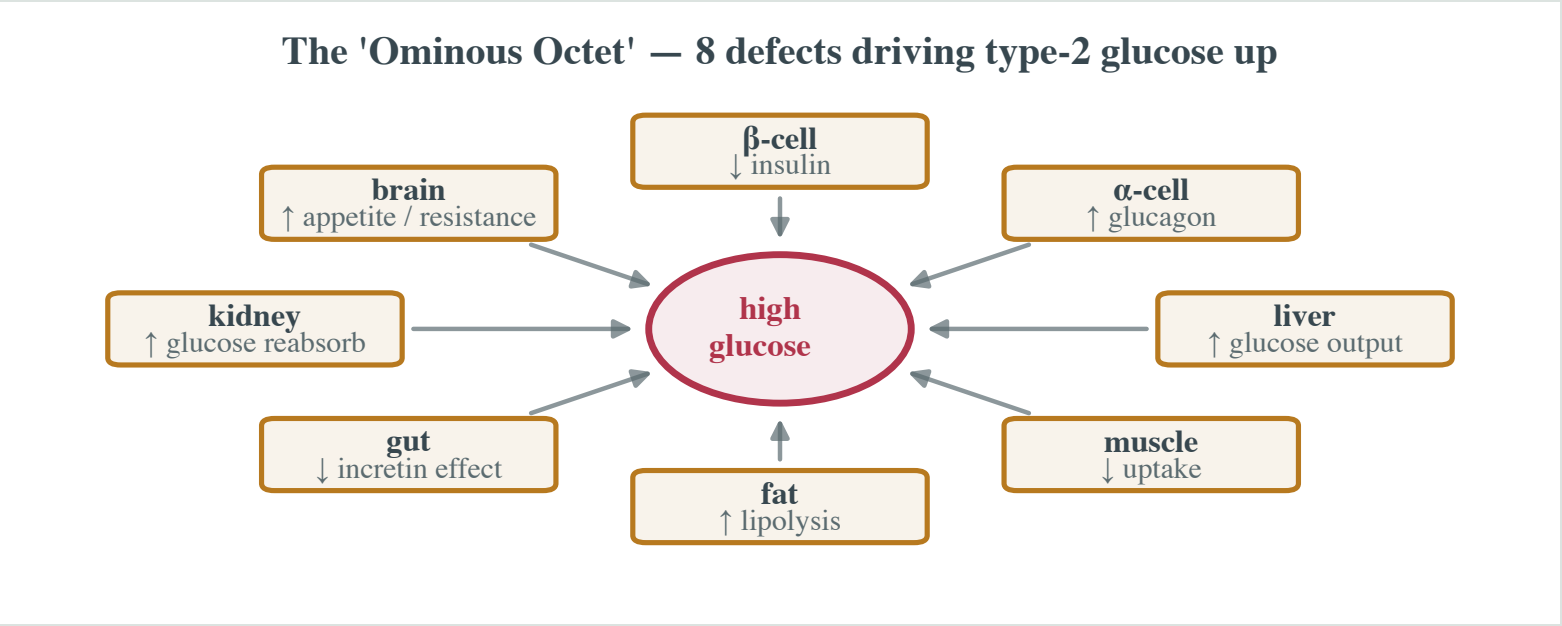
Diabetes doesn't usually kill through a high sugar reading — it kills slowly, through **heart attacks, strokes, kidney failure, and blindness**. So good management targets **three numbers**, easy to remember as the **ABCs**. **A** is **A1c** — keep average glucose in range. **B** is **Blood pressure** — protect the kidneys, eyes, and vessels. **C** is **Cholesterol** — cut cardiovascular risk. Add diet, exercise, weight control, and not smoking, and you attack the disease from every side.



Diabetes kills mostly through heart disease and stroke — control isn't just glucose, it's all three.

The Ominous Octet

Type 2 isn't one broken thing — it's **eight**, and this map (the **"Ominous Octet"**) is why. Glucose runs high because the **β-cells** make too little insulin, the **α-cells** make too much glucagon, the **liver** overproduces glucose, **muscle** underabsorbs it, **fat** floods the blood with fatty acids, the **gut** loses its incretin boost, the **kidney** reabsorbs too much glucose, and the **brain** drives appetite and resistance. Every modern drug targets a **different** one of these eight — which is exactly why they're combined.

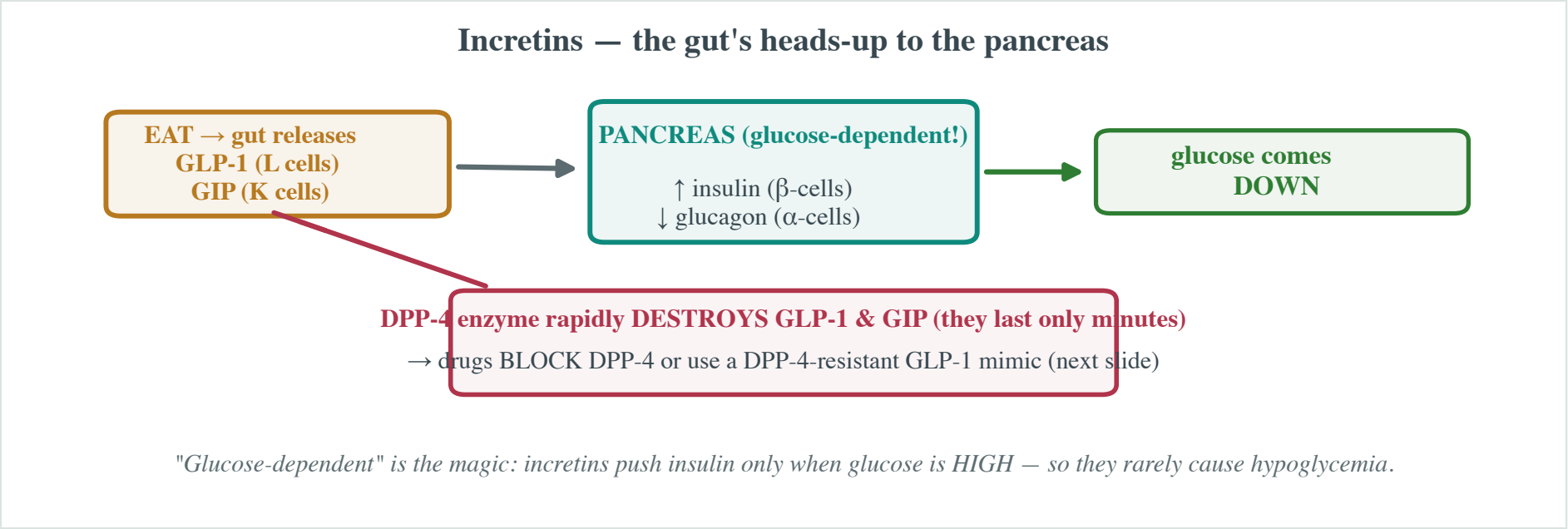


5 · Incretins, the Kidney & Diabetes Drugs

"The newest, most talked-about diabetes drugs — Ozempic, the -flozins, the -gliptins — all come straight from this biochemistry: the gut's incretin hormones and the kidney's glucose-hoarding transporters. Learn the biology and the drugs explain themselves."

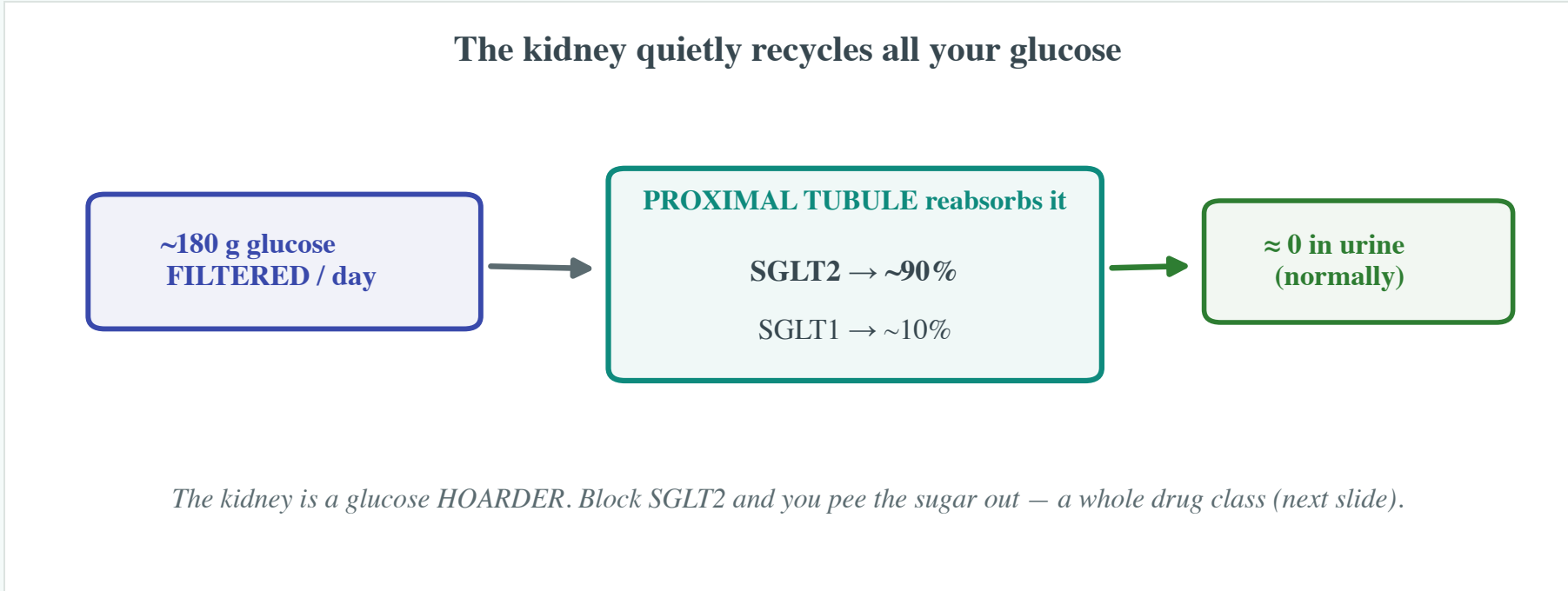
Incretins: the gut's heads-up to the pancreas

When you eat, the gut releases **incretin** hormones – **GLP-1** (from **L cells**) and **GIP** (from **K cells**) – that reach the pancreas and, **only when glucose is high**, **boost insulin** and (for GLP-1) **suppress glucagon**. That **"glucose-dependent"** part is the magic: incretins push insulin **only** when it's needed, so they rarely cause hypoglycemia. The catch: an enzyme, **DPP-4**, chews them up in **minutes**. So two drug strategies write themselves – **block DPP-4**, or build a **GLP-1 mimic that resists it**.



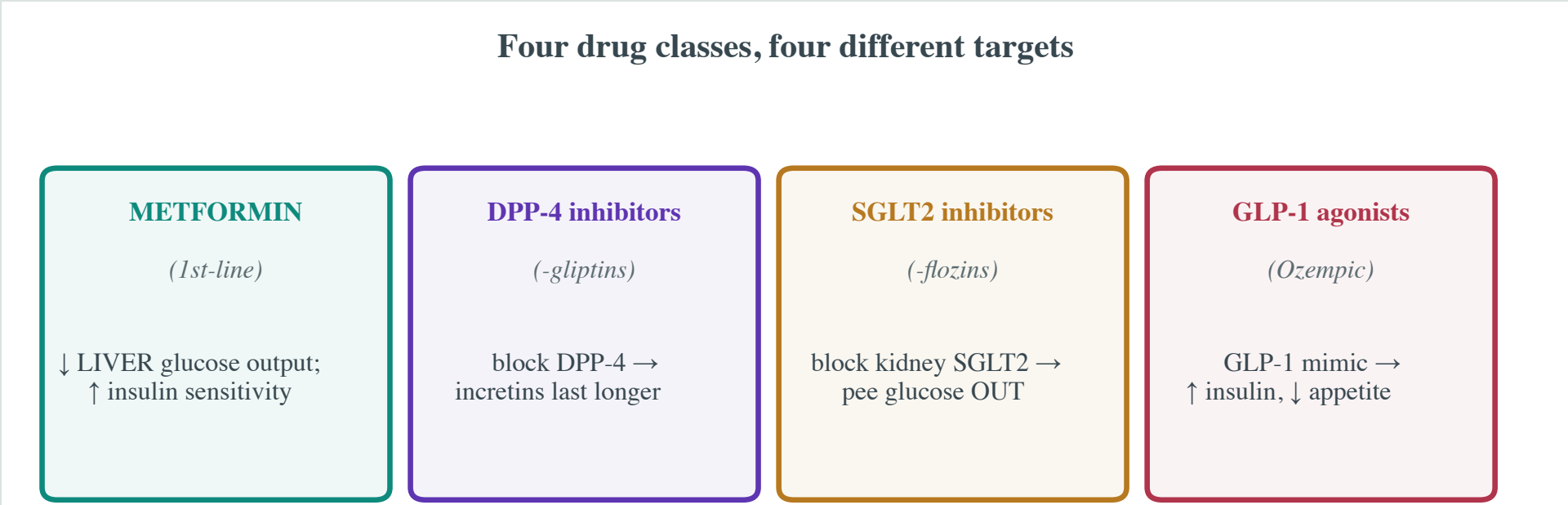
The kidney hoards glucose

Here's a target most people never think about. Your kidneys **filter ~180 grams of glucose every day** — and then **reabsorb essentially all of it** in the proximal tubule, so **none** shows up in the urine. The workhorse is **SGLT2** (sodium-glucose cotransporter 2), which grabs about **90%** (SGLT1 handles the rest). In evolution, hoarding precious sugar made sense. In diabetes, it's the last thing you want — so **blocking SGLT2** lets you literally **pee the excess glucose out**.



Four drugs, four targets

Now the payoff — each major drug hits a **different** node of the Octet. **Metformin** (first-line) tells the **liver** to make less glucose and improves insulin sensitivity. **DPP-4 inhibitors** (the **"-gliptins"**) let your own incretins **last longer**. **SGLT2 inhibitors** (the **"-flozins"**) make the **kidney dump glucose** in the urine. And **GLP-1 receptor agonists** — **Ozempic (semaglutide)** — are DPP-4-resistant incretin mimics that **boost insulin and cut appetite** (hence the weight loss). Different targets, often combined.



Can you…?

- □ diagnose diabetes from the glucose criteria (FPG, OGTT, HbA1c, random) and explain how HbA1c reports 2–3 months of control?
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If any box stays empty, the practice site has a drill for it.
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