Calcium, Phosphorus & Bone

BCH 120 — Metabolic & Endocrine Biochemistry · Dr. Radi

By the end of this unit, you can…

- Explain calcium's structural and regulatory roles, its distribution (99% in bone; free ionized fraction regulated), balance, and the consequences of hypo-/hypercalcemia
- Describe bone as a composite (collagen osteoid + hydroxyapatite; cortical vs trabecular) and the remodeling cells (osteoblasts, osteoclasts, osteocytes; the RANKL/OPG switch)
- Explain PTH — its source, negative-feedback control, and its action on bone (indirectly via osteoblast RANKL), kidney, and intestine to raise calcium and lower phosphate
- Describe calcitonin and PTHrP, and the metabolic bone diseases (osteoporosis, Paget's, osteomalacia/rickets) with treatments (bisphosphonates)
- Trace vitamin D activation (skin → liver → kidney; PTH-driven) and distinguish inert D_3 from active calcitriol
- Explain calcitriol's action through the nuclear VDR — intestinal calcium absorption and its wider physiology, and deficiency disease

Today's route

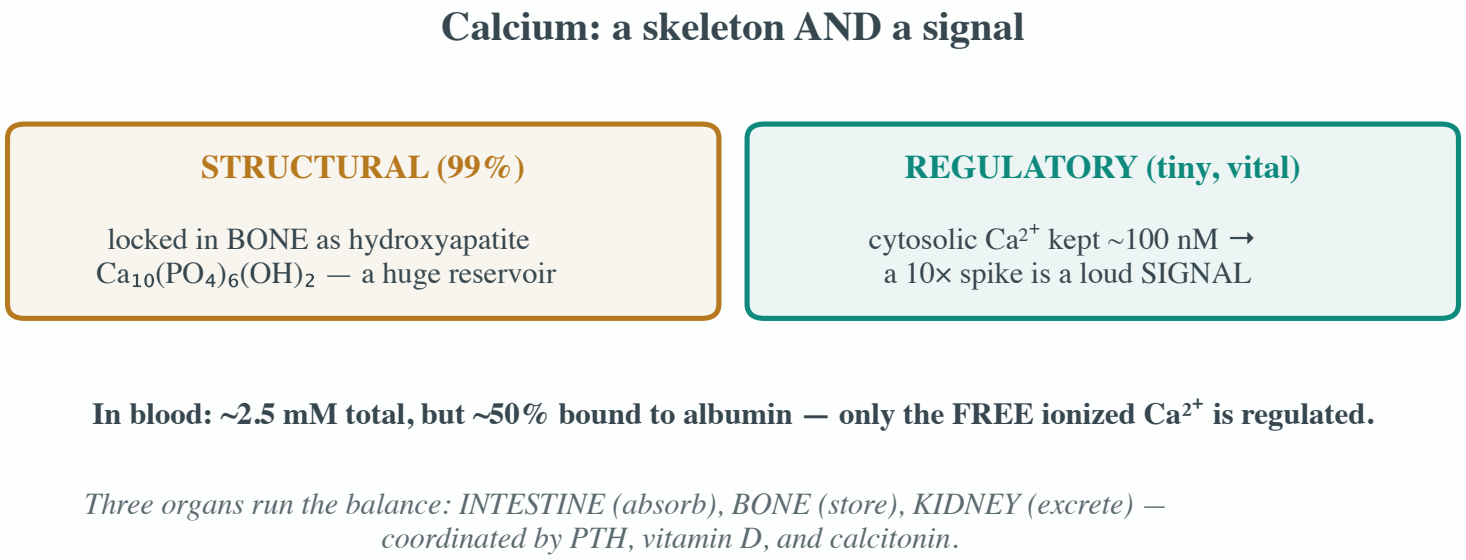
1. Calcium – Roles & Distribution
2. Bone Structure & the Remodeling Cells
3. Parathyroid Hormone (PTH)
4. Calcitonin, PTHrP & Bone Disease
5. Vitamin D – Synthesis & Activation
6. The VDR & Vitamin D's Actions

1 · Calcium — Roles & Distribution

"Calcium does two completely different jobs: it's the hard mineral in your bones AND the fastest signal in your cells. Because the second job depends on a razor-thin blood level, the body defends calcium more tightly than almost anything else."

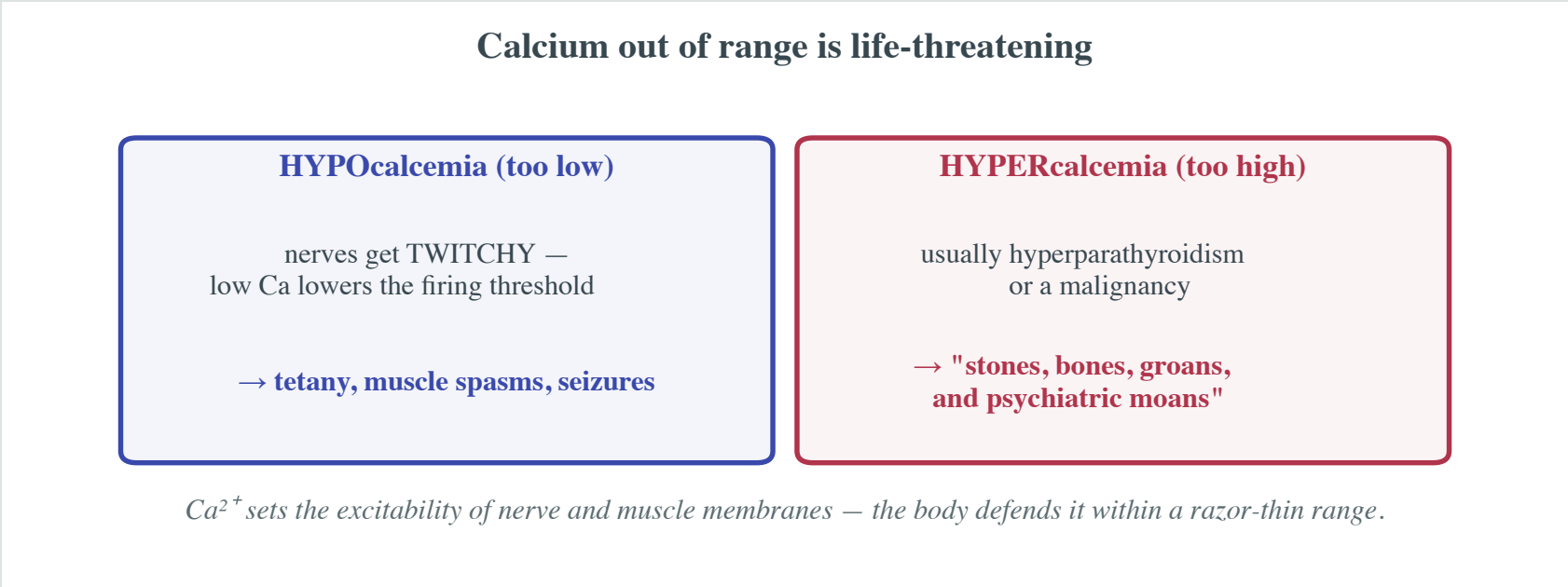
A skeleton and a signal

Calcium leads a double life. Its **structural** role: **99%** of your calcium is locked in **bone** as **hydroxyapatite crystals** — a massive reservoir. Its **regulatory** role: cells keep **cytosolic Ca^{2+} absurdly low (~100 nM)** so that a sudden influx is a **loud signal** (you saw this in unit 1). In the blood, total calcium is ~2.5 mM, but **half is bound to albumin** — only the **free ionized Ca^{2+}** is biologically active and regulated. Three organs run the balance: **intestine, bone, kidney**.



Off the rails: hypo- vs hypercalcemia

Because calcium sets the **excitability of nerve and muscle membranes**, straying outside its narrow range is dangerous. **Hypocalcemia** (too low) makes membranes **hyper-excitable** – it lowers the firing threshold toward the resting potential – causing **tetany, muscle spasms, and seizures** (often from hypoparathyroidism or vitamin D deficiency). **Hypercalcemia** (too high, usually **hyperparathyroidism or malignancy**) gives the classic **"stones, bones, groans, and psychiatric moans."** The body would rather rob your skeleton than let blood calcium drift.

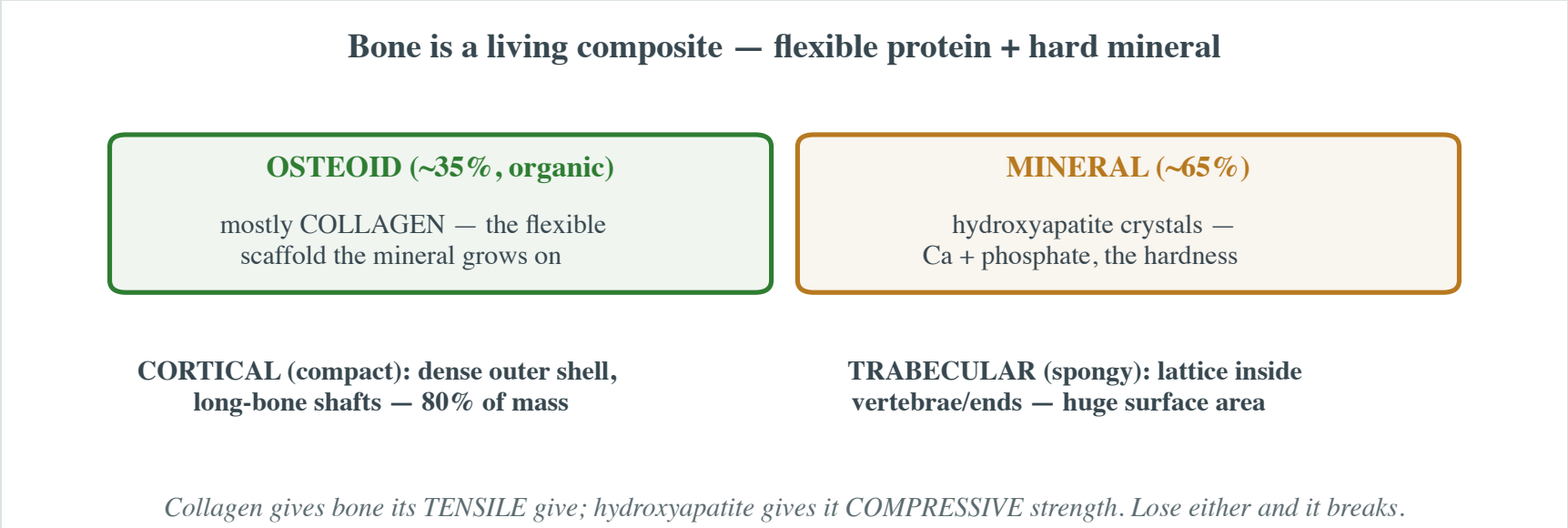


2 · Bone Structure & the Remodeling Cells

"Bone isn't dead scaffolding — it's a living composite that's constantly torn down and rebuilt. Understand the two cell types and the one molecular switch between them, and you understand osteoporosis, Paget's, and half of calcium metabolism."

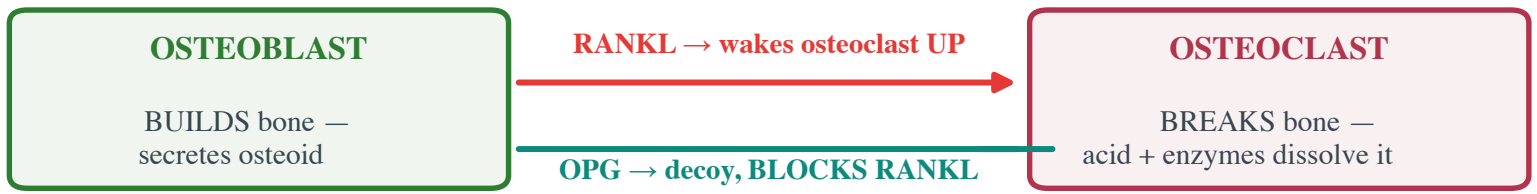
Bone is a composite material

Bone gets its remarkable properties from **two components working together**. The **organic osteoid** (~35%) is mostly **collagen** — the flexible protein scaffold that gives bone its **tensile give**. The **mineral** (~65%) is **hydroxyapatite** — calcium-phosphate crystals grown onto that scaffold, providing **compressive hardness**. It comes in two architectures: **cortical (compact)** bone, the dense outer shell of long-bone shafts (80% of mass), and **trabecular (spongy)** bone, an internal lattice with huge surface area. Lose the collagen and it shatters; lose the mineral and it bends.



Build vs. break — and the switch

Bone is in constant **remodeling**, run by opposing cells. **Osteoblasts BUILD** — they secrete and mineralize osteoid. **Osteoclasts BREAK** — multinucleate cells (from the monocyte line) that dissolve bone with **acid and enzymes**, freeing calcium. The elegant control: the **osteoblast bosses the osteoclast**, secreting **RANKL** (which **activates** it) and **OPG** (a decoy that **blocks** RANKL). Their **ratio sets bone mass** — and it's where PTH and many drugs act.



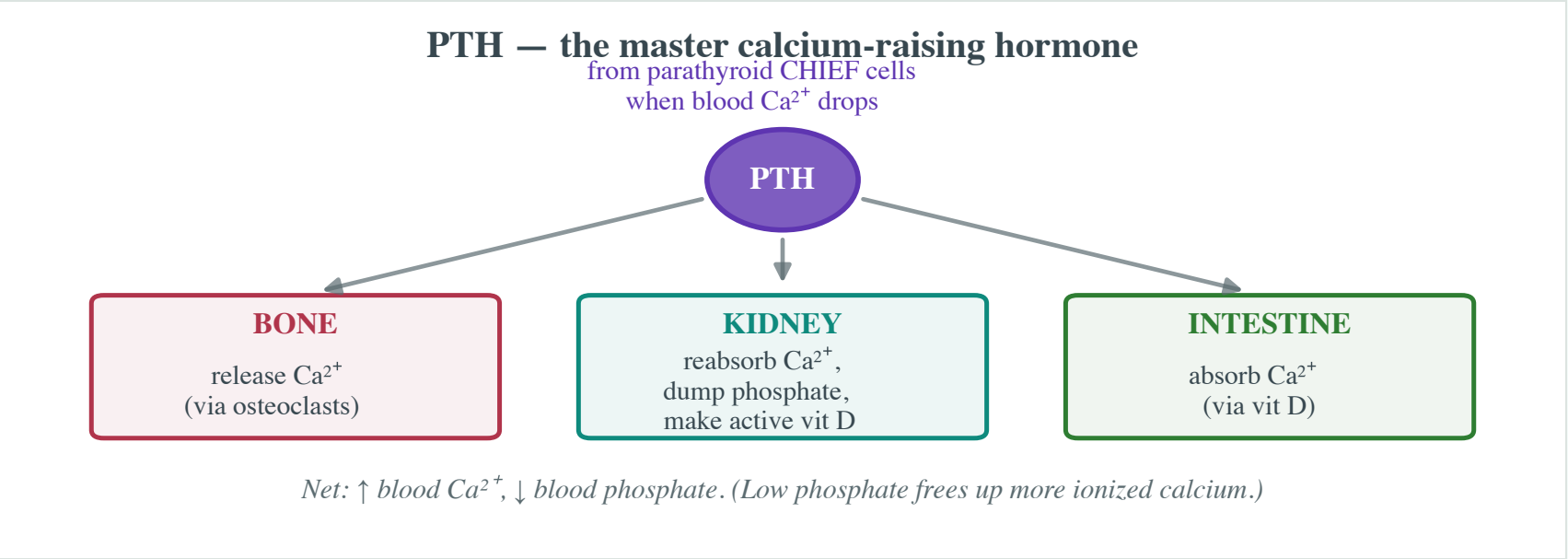
(Osteocytes = retired osteoblasts buried in the matrix, sensing strain and directing remodeling.)

3 · Parathyroid Hormone (PTH)

"PTH is THE guardian of blood calcium. When calcium drops, four tiny glands on the back of your thyroid fire this hormone, which cleverly works three organs at once to pull calcium back up – and does it through a surprising indirect trick on bone."

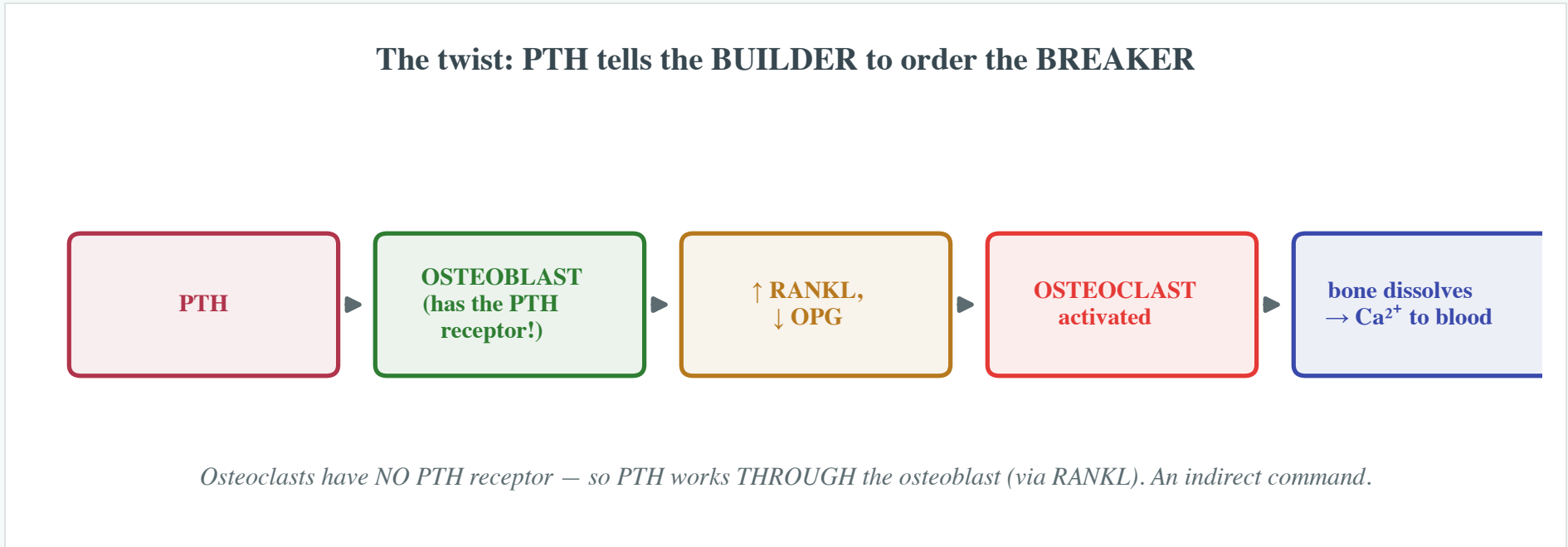
PTH: the calcium-raiser

Parathyroid hormone is the **principal regulator** of blood calcium, made by the **chief cells** of the four **parathyroid glands** on the back of the thyroid. It's an 84-amino-acid peptide (the **N-terminal 34** residues carry all the activity — that fragment is even used as a drug). Its whole mission when **calcium falls** is to **raise it**, working **three organs**: pull Ca^{2+} from **bone**, make the **kidney** keep Ca^{2+} (and make active vitamin D), and — through that vitamin D — boost **intestinal** absorption. Net: **↑ calcium, ↓ phosphate**.



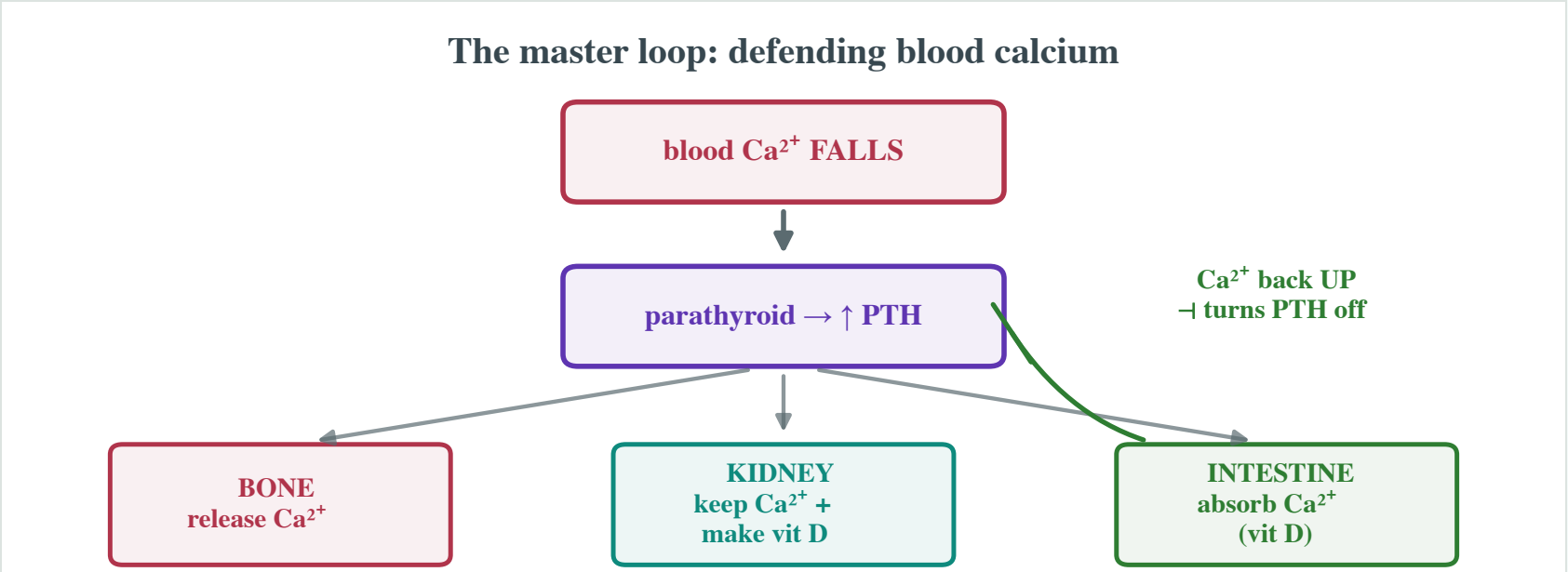
The twist: PTH works bone indirectly

Here's the fact students always get wrong. To dissolve bone, PTH does **not** talk to the osteoclast — the **osteoclast has no PTH receptor**. Instead PTH binds the **osteoblast** (the **builder**), which responds by cranking up **RANKL** and dropping **OPG** — and **that** wakes the **osteoclast** to resorb bone and release calcium. The builder orders the demolition. (And the whole cascade runs on **cAMP** — which is why a **Gαs defect** causes **pseudohypoparathyroidism**, where PTH is present but the tissues can't hear it.)



The master calcium loop

Put it together and you get the loop that runs your whole calcium life. Blood **Ca^{2+} falls** → the **parathyroid senses it** (via its calcium-sensing receptor) and releases **PTH** → PTH acts on **bone, kidney, and intestine** (the last two through **active vitamin D**) → **calcium rises** → and the rising calcium **switches PTH back off**. Classic negative feedback, three organs deep. **PTH and vitamin D push calcium up; calcitonin nudges it down** — but PTH is the one that matters.



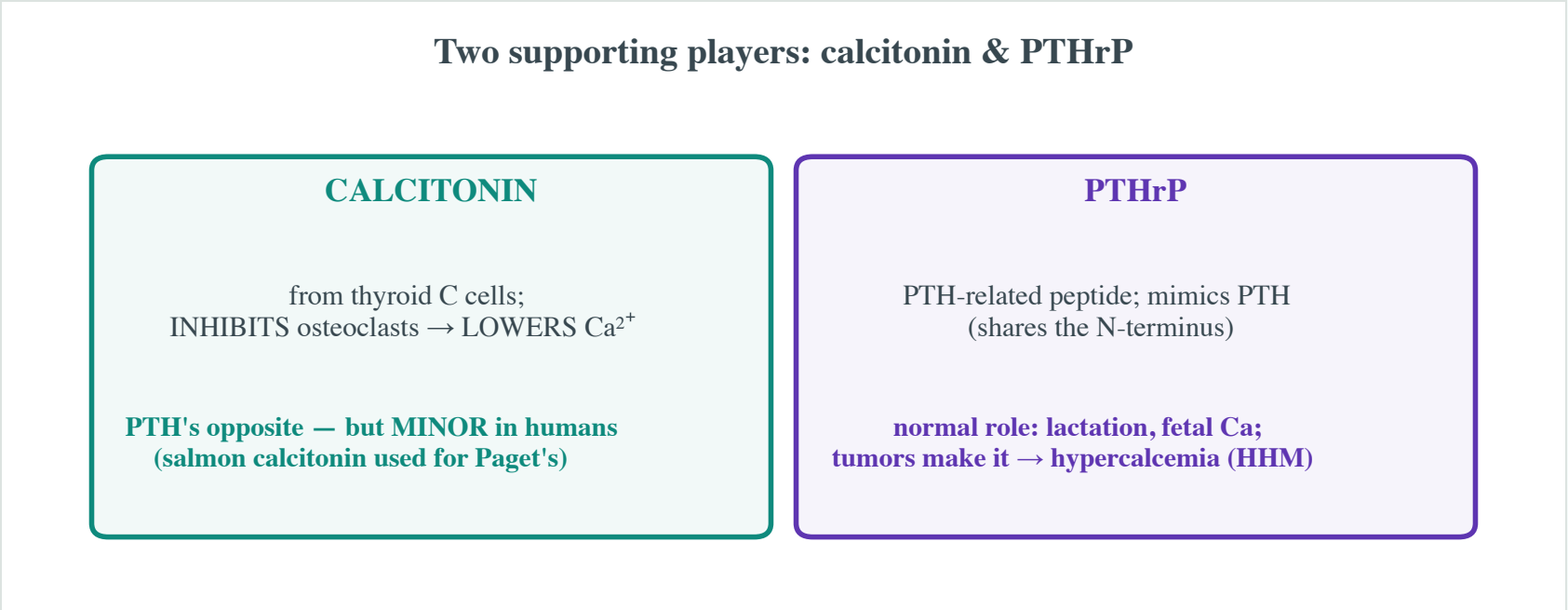
Three organs, one goal: hold ionized calcium steady. PTH + vitamin D raise it; calcitonin nudges it down.

4 · Calcitonin, PTHrP & Bone Disease

"PTH has a mirror-image partner (calcitonin) and a look-alike cousin (PTHrP) — and when the whole remodeling system tips out of balance, you get the metabolic bone diseases: osteoporosis, Paget's, and rickets."

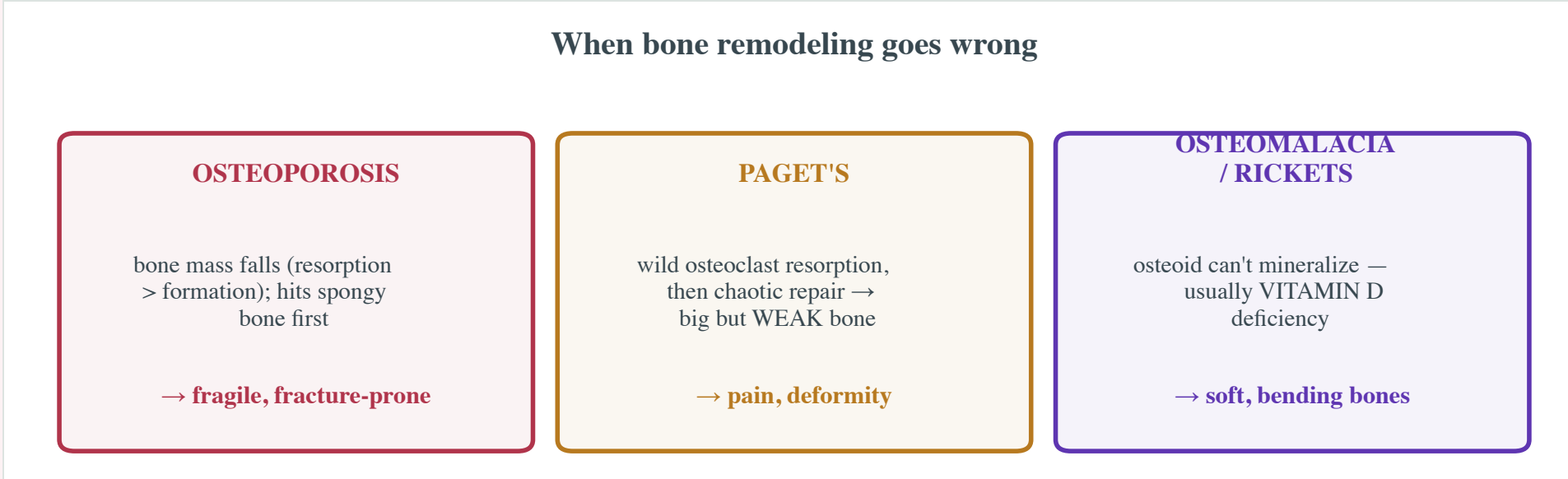
The supporting cast: calcitonin & PTHrP

Two more peptides round out the calcium story. **Calcitonin** — from the thyroid's **C cells** — is PTH's **opposite**: it **inhibits osteoclasts** and **lowers** blood calcium. But here's the catch: in humans it's **minor** (thyroidectomy barely affects calcium), though **salmon calcitonin** is used as a drug for Paget's. **PTHrP** (PTH-related peptide) is a **look-alike** that shares PTH's active N-terminus. Normally it works in **lactation and fetal calcium transfer**, but **tumors** can secrete it, mimicking PTH to cause **hypercalcemia of malignancy**.



When remodeling goes wrong

Tip the build-vs-break balance and you get the **metabolic bone diseases**. **Osteoporosis** — resorption outpaces formation, so **bone mass falls** (spongy bone first) and bones become **fragile and fracture-prone**. **Paget's disease** — chaotic **over-resorption then disordered repair**, giving bone that's **bigger but weaker**, with pain and deformity. **Osteomalacia** (**rickets** in kids) — the osteoid **can't mineralize**, usually from **vitamin D deficiency**, leaving bones **soft and bending**. The anti-resorption drugs, especially **bisphosphonates** (which force osteoclast **apoptosis**), slow the loss.

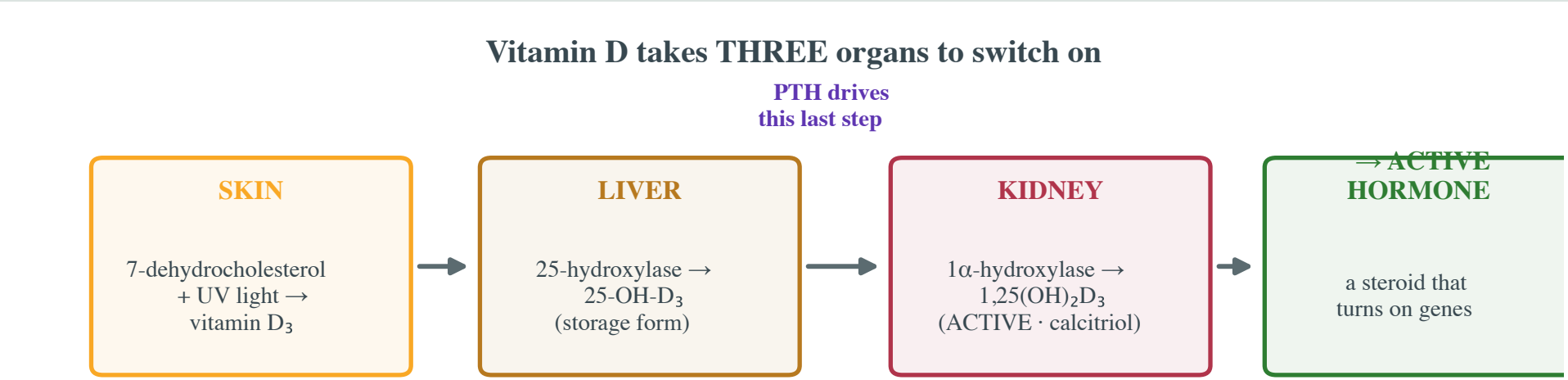


5 · Vitamin D – Synthesis & Activation

"Here's a twist: 'vitamin D' isn't really a vitamin, and the stuff you swallow is biologically inert. It takes three organs and two chemical edits to turn it into calcitriol – a genuine steroid hormone. Understand that activation and vitamin D makes sense."

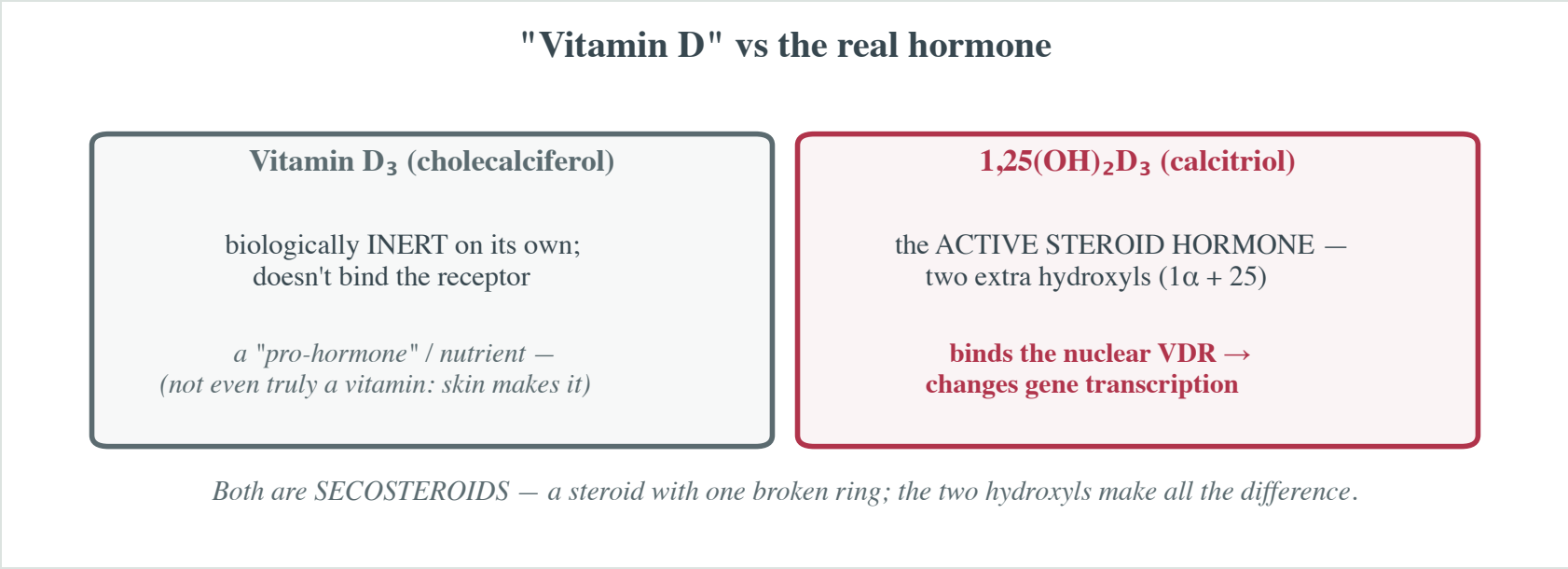
Three organs to switch it on

Vitamin D activation is a **three-organ relay**. In the **skin**, UV light converts **7-dehydrocholesterol** into **vitamin D_3 (cholecalciferol)**. The **liver** adds one hydroxyl (**25-hydroxylase → 25-OH-D_3**), the main storage/circulating form. Then the **kidney** adds the crucial second hydroxyl (**1α-hydroxylase → 1,25$(OH)_2D_3$**, calcitriol) – the **active** hormone. That final kidney step is the **regulated** one: **PTH turns it ON**, and the active vitamin D then **feeds back to turn PTH off**. Skin makes it, liver stores it, kidney activates it.



D_3 is inert; calcitriol is the hormone

Don't confuse the supplement with the hormone. **Vitamin D_3 (cholecalciferol)** — what's in your pill and made in your skin — is **biologically inert**: it doesn't bind the receptor. It's a **pro-hormone** (and, since your skin makes it, not even truly a "vitamin"). Only after the liver-then-kidney hydroxylations does it become **1,25(OH)$_2$D$_3$ (calcitriol)**, the **active steroid hormone** that binds the **nuclear VDR** and changes gene transcription. Both are **secosteroids** — a steroid with one **broken ring** — but those **two hydroxyls** make all the difference.

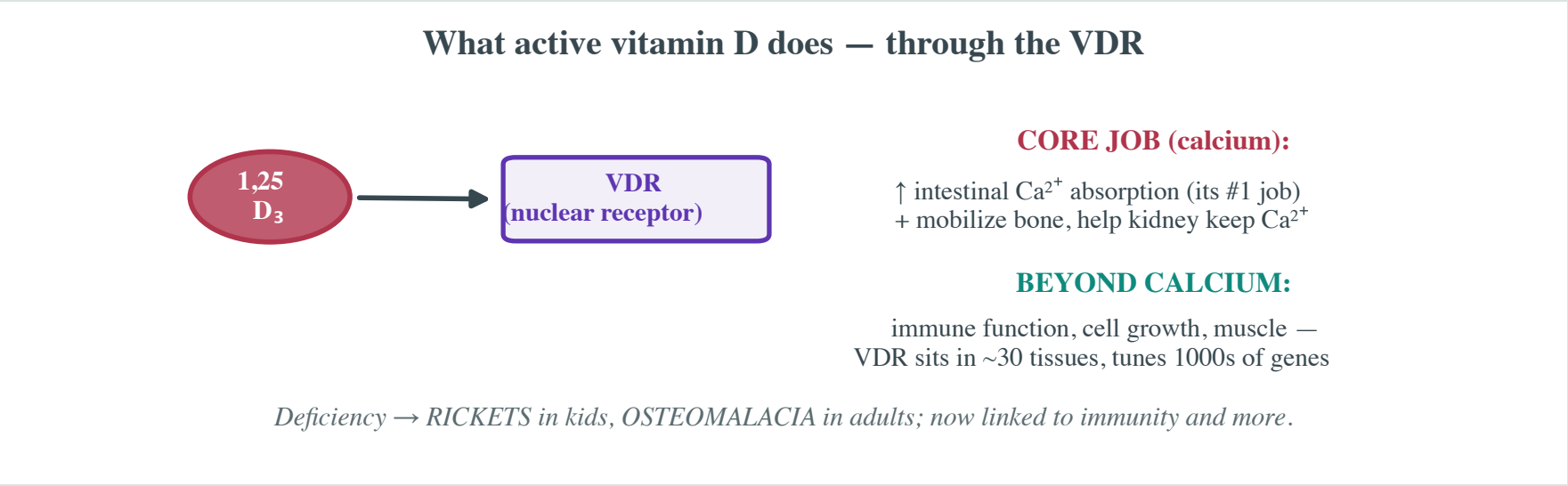


6 · The VDR & Vitamin D's Actions

"Active vitamin D is a steroid hormone, so it works like one — through a nuclear receptor that rewrites gene expression. Its headline job is raising calcium, but the same receptor sits in dozens of tissues, which is why vitamin D keeps showing up everywhere in medicine."

One receptor, calcium first — then everything

Calcitriol acts like the steroid it is: it binds the **vitamin D receptor (VDR)**, a **nuclear receptor** that pairs up and changes **gene transcription** (the mechanism from unit 1). Its **core job is calcium**, and its **number-one action is boosting intestinal Ca^{2+} absorption** — plus helping mobilize bone and letting the kidney hold calcium. But the **VDR sits in ~30 tissues** and tunes **thousands of genes**, so vitamin D reaches far **beyond calcium** — immune function, cell growth, muscle. Deficiency gives **rickets** in kids and **osteomalacia** in adults, and low levels are now linked to much more. A true endocrine system, hiding inside a "vitamin."



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

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