In The Name of God

Title: Managing Dysregulated Vitamin D Metabolism in CKD: Time to Update Conventional Wisdom?

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What We know

- In CKD: Circulating 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D, the active Vitamin D hormone) declines
- PTH Goes Up
- Driving Secondary Hyperparathyroidism
- Current Guideline: No target for PTH because no RCT data
- Treatment strategy: vitamin D insufficiency / targeting 25D levels of 20-30 ng/ml
- Vitamin D supplements: cholecalciferol or ergocalciferol
- It’s hard to reach such levels because of physiological barriers
- Adipose tissue – obesity – Impaired hepatic activation - upregulation of CYP24A1 (cytochrome P450-24-hydroxylase), the vitamin D catabolic enzyme

- Standard treatment: supplements but no evidence to raise 25D sufficiently to control PTH
- Data show: 25D is inadequate In CKD patients despite treatment
- PTH rise – Switch to hormone therapy (Calcitriol)

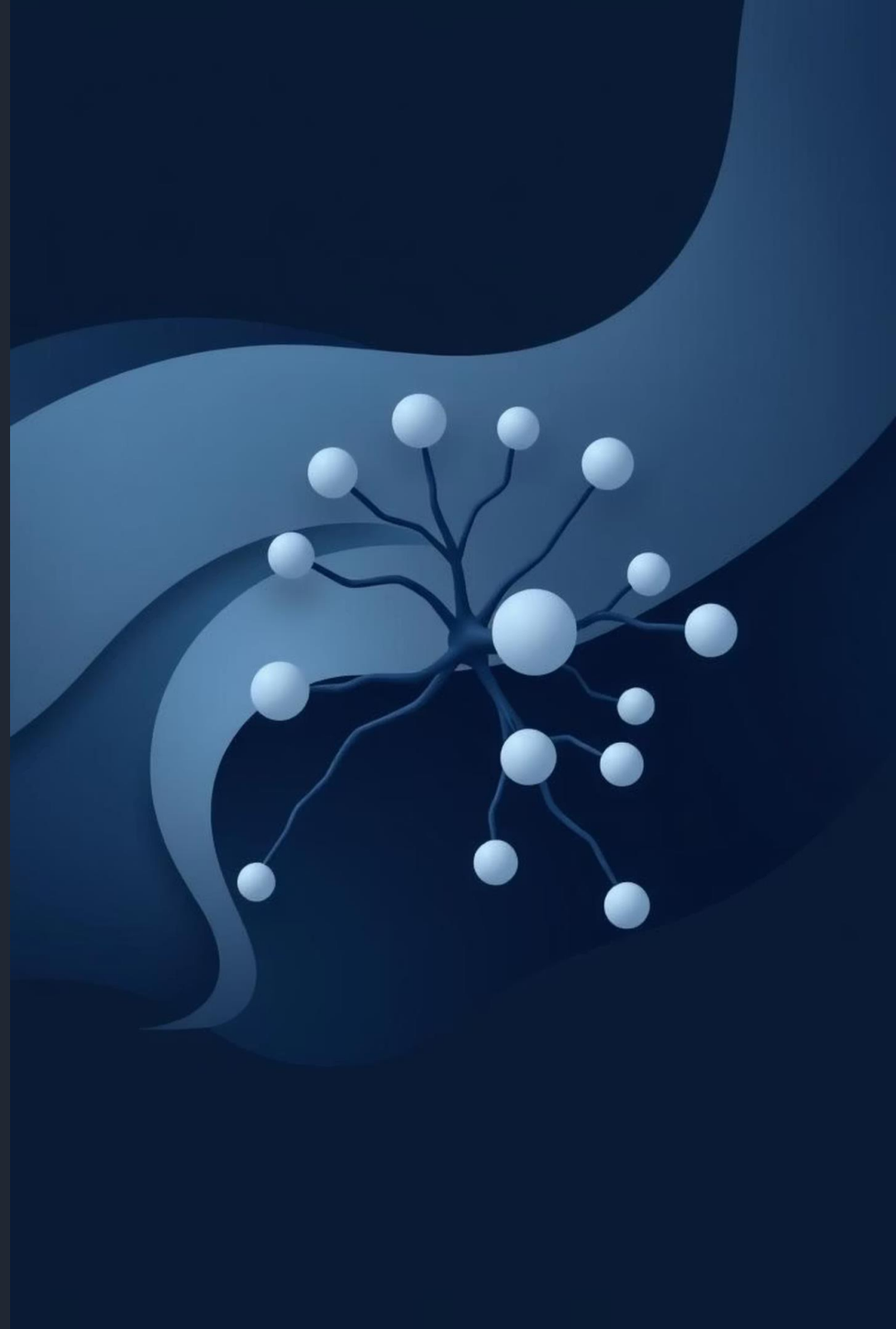
- Oral hormone therapy ➔ calcium burden – risk of hypercalcemia
- Current guideline: avoid using in non-dialysis patients
- it reaches vitamin D receptors directly in small intestine ➔ increasing active absorption of dietary calcium
- Also: increases serum phosphorus and FGF23 ➔ faster CKD progression – induction of vitamin D catabolic enzyme ➔ decreasing therapeutic responsiveness

Conventional wisdom: kidney ➔ only source of producing 1,25D
Loss of renal CYP27B1 (cytochrome P450 25D-1α-hydroxylase) in CKD ➔ hormone therapy

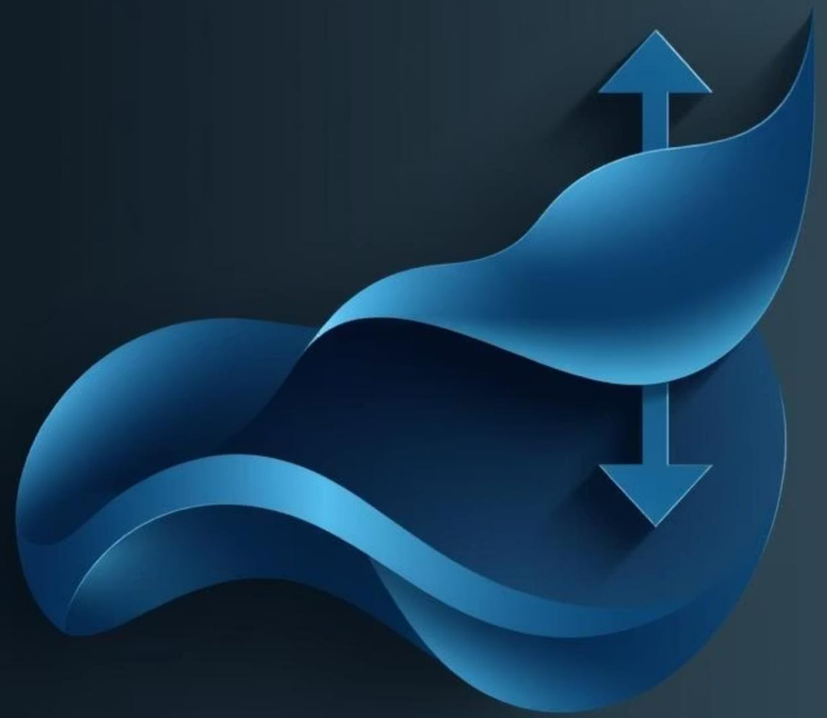
It also expressed in: parathyroid glands – lungs – skin – immune cells – bone

Extra-renal enzyme activates ➔ major alternative source of 1,25D in CKD

Demonstrated by clinical trials with extended-release calcifediol (ERC) in stage 3-4-5 CKD



- Extra-renal enzyme receives 25D with Passive Diffusion ➔ requires high concentration of 25D
- Unlike renal enzyme, no negative feedback for extra-renal ➔ 1,25D rises with 25D concentrations
- RCTs: extra-renal engagement needs raising serum 25D to ≥50 ng/mL ➔ 30% reduction in elevated PTH
- No differences in PTH-lowering response in CKD stages ➔ delivery of 1,25D to intracellular VDR in parathyroids was achieved

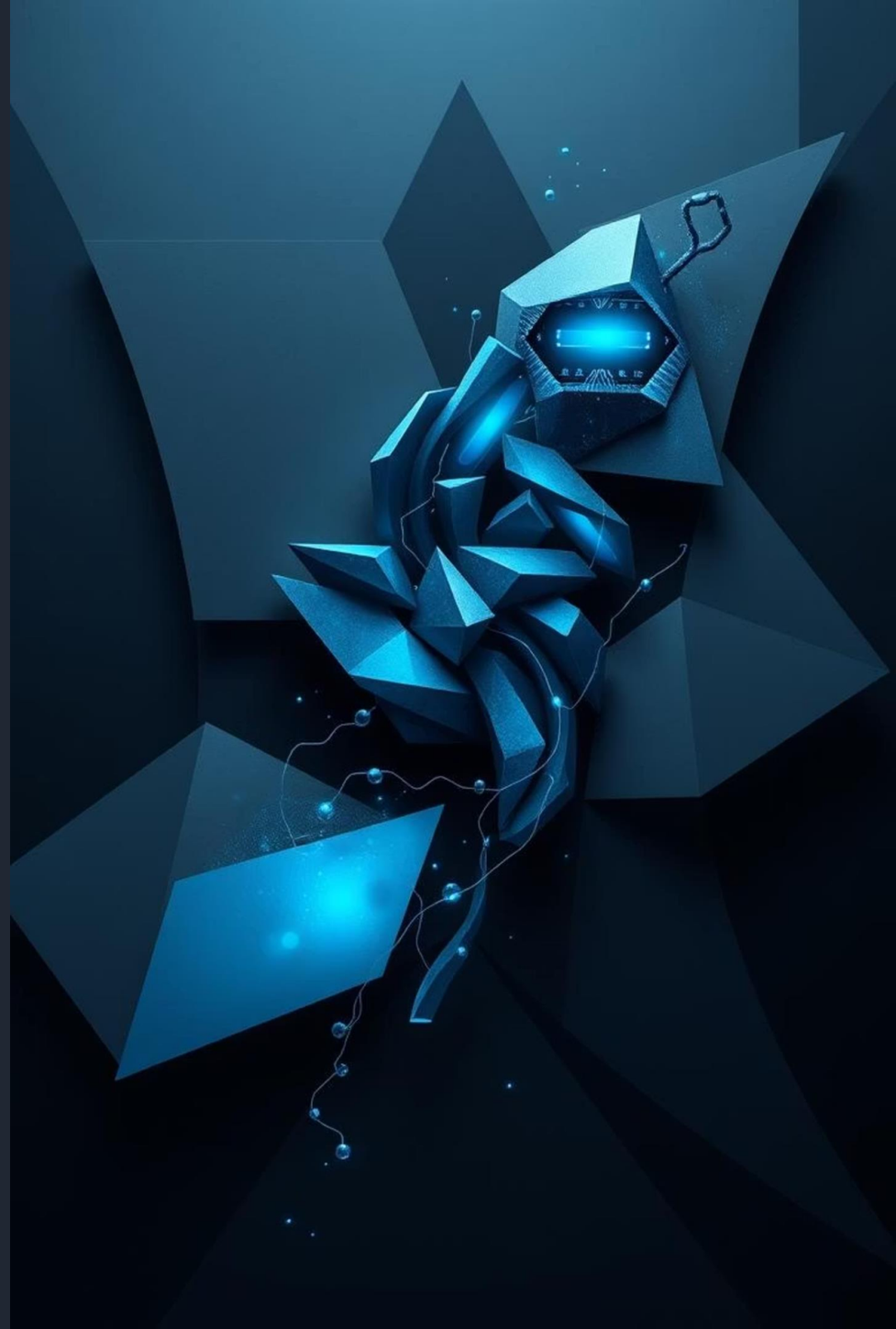


- Recent RCT: in chronic hemodialysis patients ➔ raising 25D to ≥50 ng/mL with ERC ➔ normalized circulating 1,25D from undetectable or low pre-treatment levels

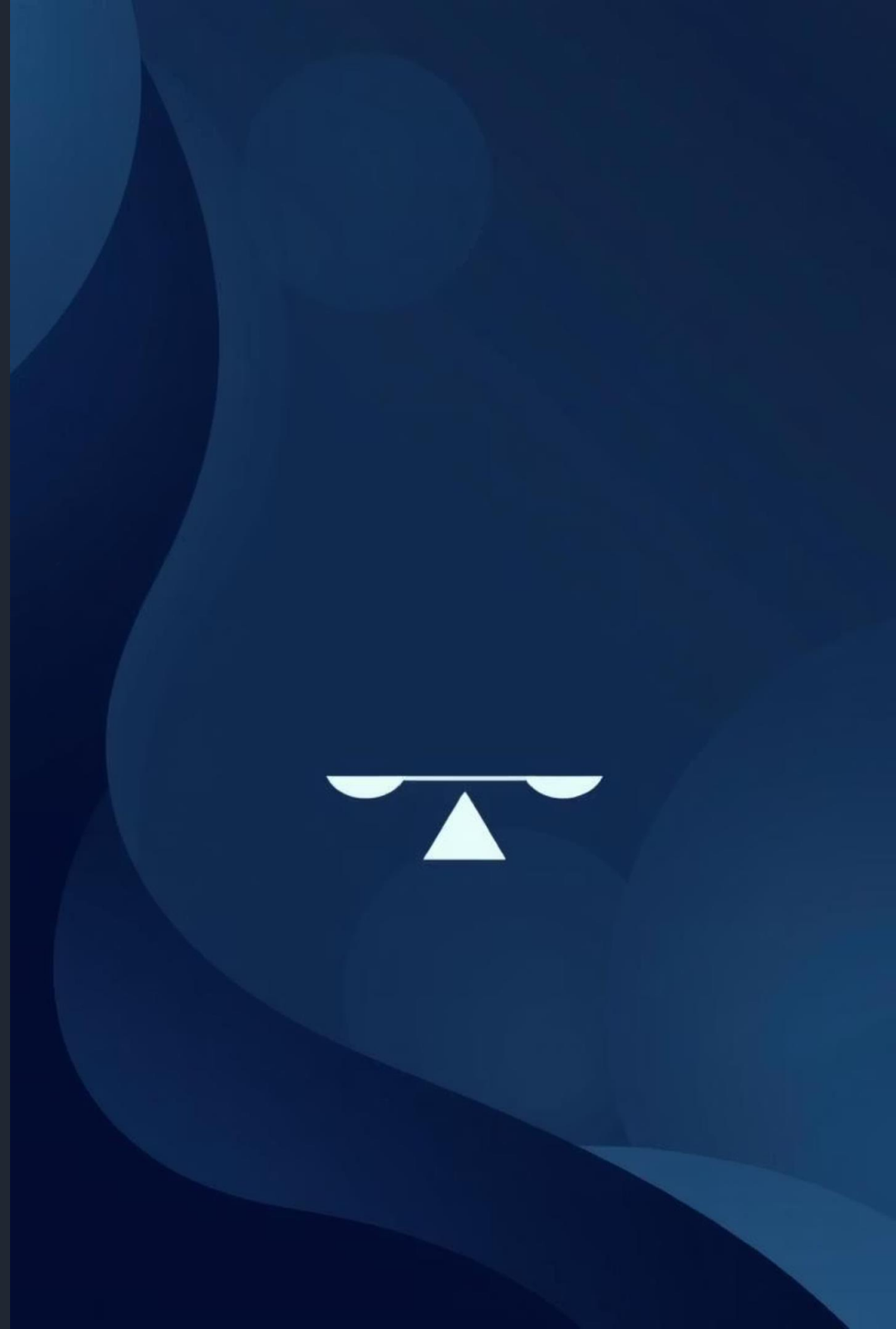
- Further increase ➔ 1,25D reached upper end of the reference range ➔ additional evidence of no negative feedback of extra-renal

- 25D repletion can be useful in CKD despite old belief

- Conventional wisdom: cautions about raising 25D to ≥50 ng/mL ➔ no extra-renal engagement
- In 2011 (the Institute of Medicine) ➔ safety concerns about 25D exposures ➔ increased risk of cancer, toxicity and mortality
- A carcinogenicity study ➔ no neoplastic changes for daily subcutaneous administration of calcifediol at ≤33 µg/kg/day for 26 weeks in transgenic mice ➔ No increased rates of hypercalcemia, hypercalciuria, elevated serum phosphorus or FGF23, or treatment-emergent adverse events with ERC versus placebo at 70 ng/ml concentrations
- However, Longer RCTs needed



- Other studies ➔ higher toxicity thresholds for 25D ➔ 60 to 250 ng/ml (not proven)
- Toxicity depends on daily rate of 25D elevation (rather than absolute exposure achieved)
- Toxicity derives from 1,25D exposure not 25D ➔ because of greater affinity (500-1000 fold)
- Fears over safety ➔ caused clinicians to avoid properly correcting vitamin D deficiency in CKD patients with 25D



- Most CKD patients are overweight ➔ 25D exposure of ≥50 ng/mL is difficult with supplements

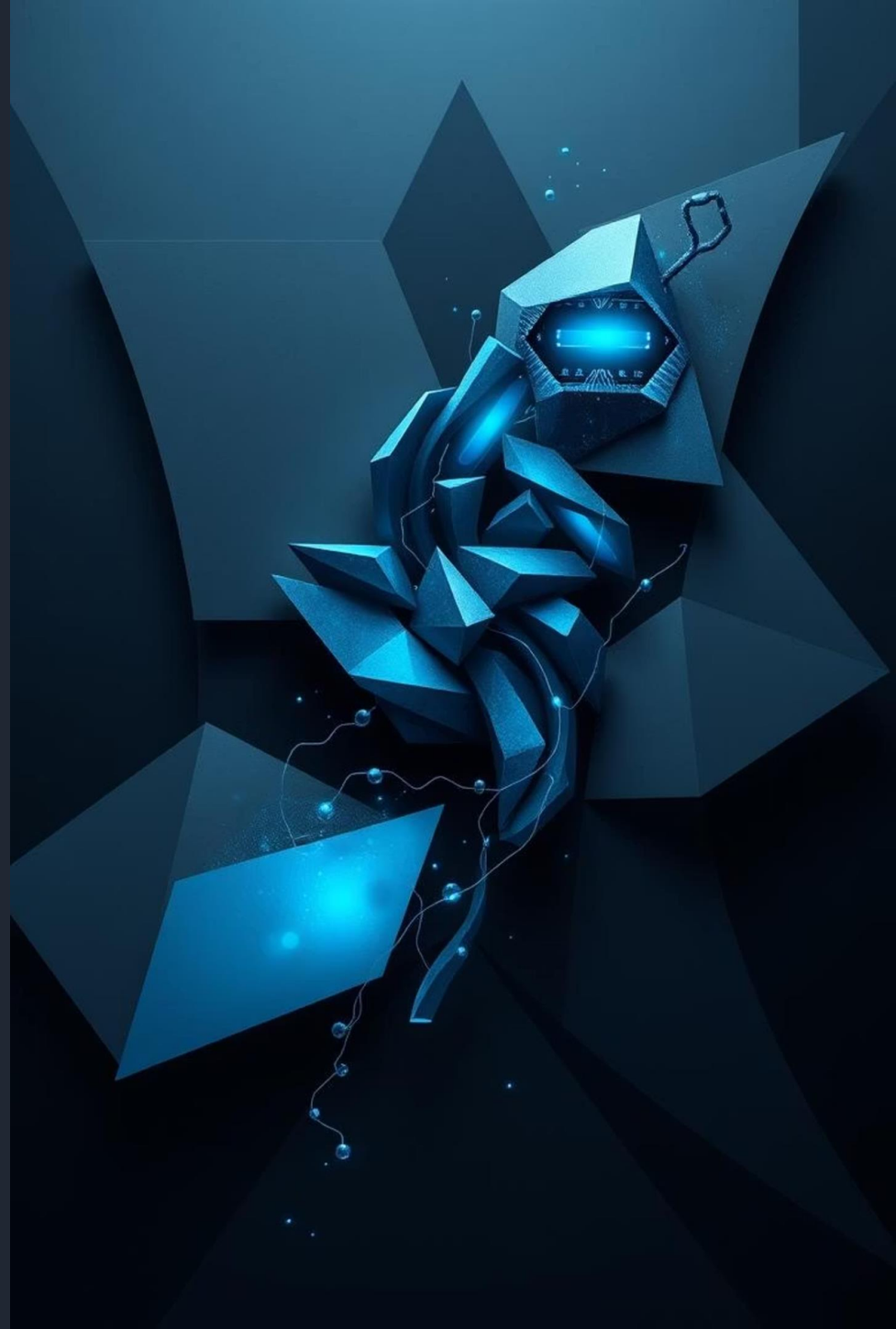
Reasons:

- Fat-soluble ➔ accumulate in adipose tissue
- Low affinities for serum vitamin D binding protein (DBP) ➔ poorly mobilized for adipose to circulation (hepatic activation)
- In CKD and obesity ➔ Hepatic 25-hydroxylase activity low ➔ 25D levels not sufficient

- In contrast: Calcifediol ➔ achieves 25D exposures of ≥50 ng/mL

Reasons:

- No hepatic activation
- Water soluble ➔ less accumulation in adipose tissue
- Binds to DBP more easily
- ERC: gradual delivery of calcifediol ➔ avoids catabolic enzyme upregulation
- ERC: slow release of calcifediol ➔ reduced first pass activation (compared to calcitriol) ➔ lower risk of increased calcium, phosphorus, and FGF23
- Recent data: ERC ➔ sustained 30% reduction of elevated PTH ➔ reduced rate of CKD progression
- Treatment with calcitriol ➔ accelerated progression



Time to update conventional wisdom?

Time to make changes in current treatment paradigm

Changes:

1: Target for 25D levels of 20-30 ng/ml should be increased to ≥50 ng/ml ➔ extra-renal enzyme activation ➔ producing 1,25D

2: Start treatment with ERC not supplements ➔ raise 25D levels

3: daily dose of ERC ➔ target a sustained ≥30% reduction of elevated PTH ➔ slowing CKD progression

Raising serum 25D with ERC ➔ generating sufficient extra-renal 1α-hydroxylation ➔ normalizing serum 1,25D levels

Thank You for Your Attention