# PTH-Lowering Agents

Dr Reyhane Motamedi fard

Assistant Professor Of Nephrology

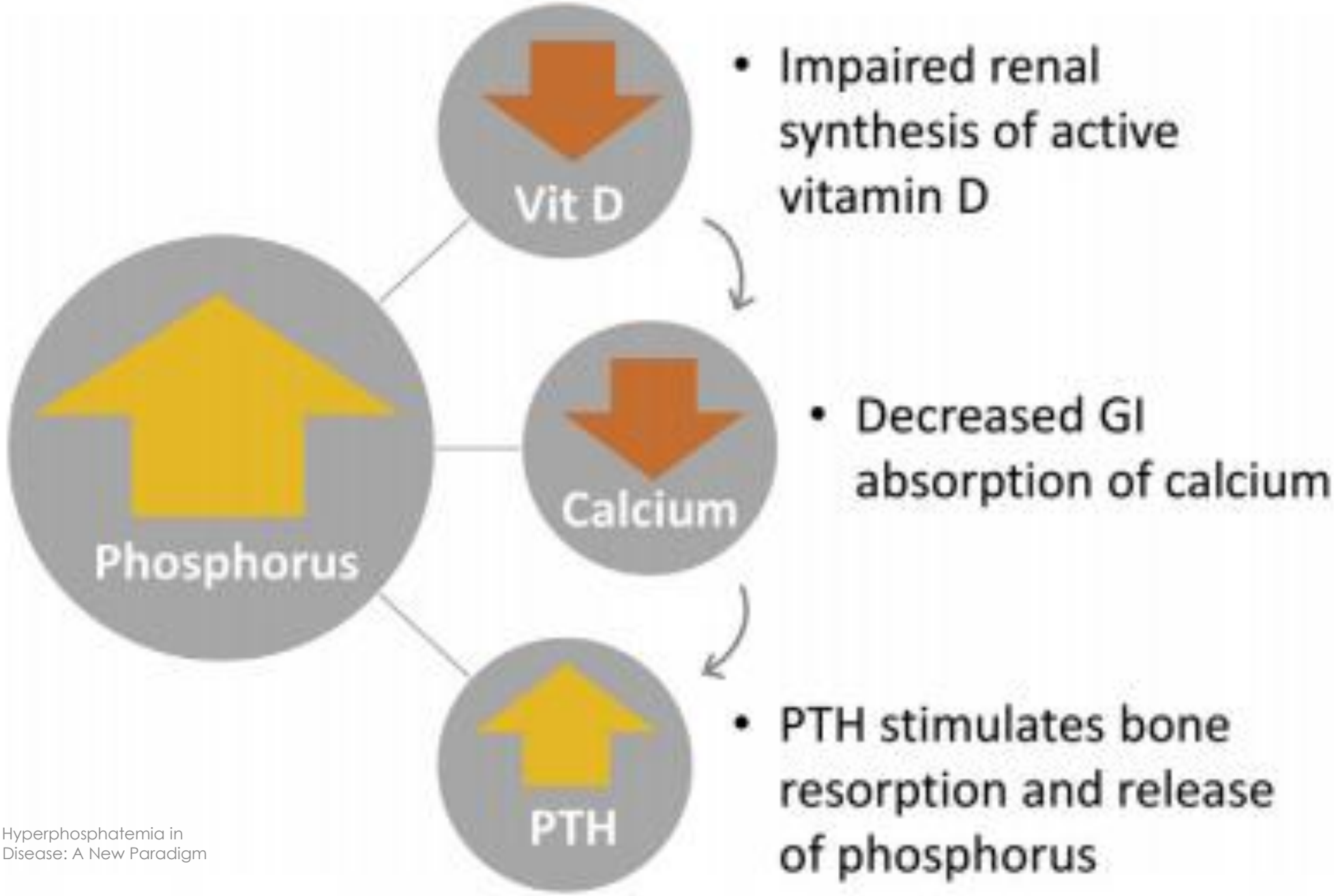
Isfahan University Of Medical Sciences

# Introduction

- Secondary hyperparathyroidism (SHPT) is a complication of CKD
- Elevations in (iPTH) concentration are observed early in the development of CKD
- Imbalances in mineral metabolism imbalances are associated with increased rates of mortality and morbidity rates in CKD patients

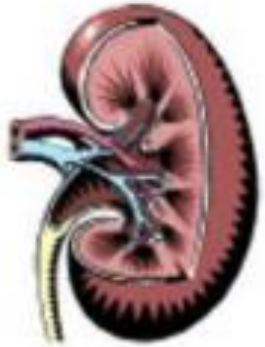
# Introduction

- Calcitriol synthesis decreases in direct response to the decline in kidney function
- Calcitriol has a direct inhibitory effect on pre-proparathyroid hormone gene transcription, and a deficiency in this hormone results in a cascade of events that include decreased calcium absorption and an increase in parathyroid hormone (PTH) production


Vit D
Phosphorus
Calcium
PTH
• Impaired renal synthesis of active vitamin D
• Decreased GI absorption of calcium
• PTH stimulates bone resorption and release of phosphorus

Source of High Phosphorus

Treatments and Limitations



## KIDNEY

Loss of kidney function and impaired renal excretion of phosphorus

Regular dialysis:

Dialyzer removes phosphorus from the blood

- Dialysis removal not sufficient to reach target range

## GUT

Dietary phosphorus absorption

Dietary changes:

Reduce intake of phosphorus and phosphate additives

- Increased protein requirement necessitates dietary phosphorus

Phosphate binders:

Reduce phosphorus absorption

- High pill burden and adverse GI effects

## BONE

Bone resorption releases stored phosphorus

Vitamin D:

Increases calcium and suppresses PTH

- Can increase phosphorus absorption from gut

Calcimimetics:

Suppress PTH-induced bone turnover and phosphorus release

- Possible hypocalcemia and GI symptoms

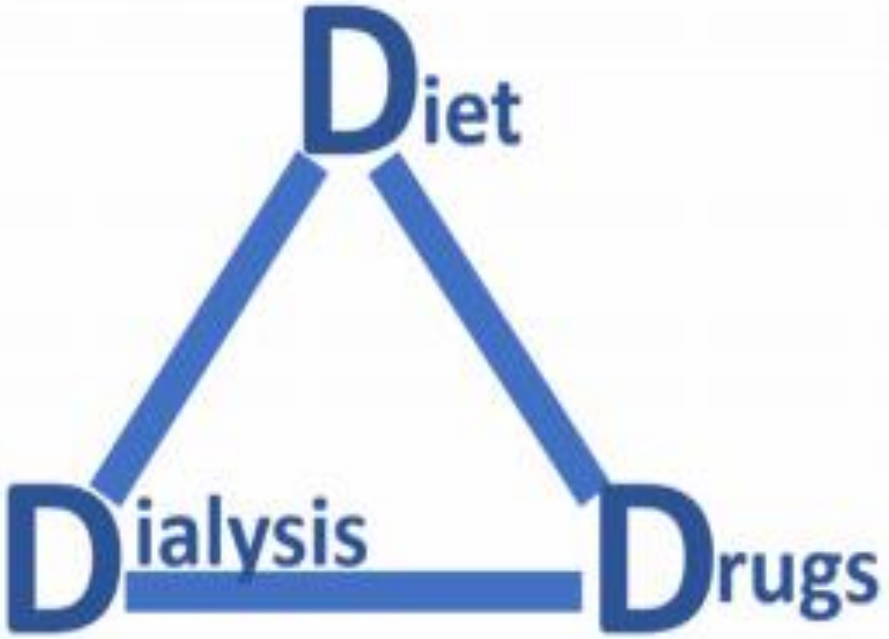
Management of Hyperphosphatemia in End-Stage Renal Disease: A New Paradigm

# Box 2. Novel Paradigm for Hyperphosphatemia Management in CKD-MBD

**Conventional Approach**

- Dietary intervention
- Phosphate binders
- Active/analog vitamin D
- Calcimimetics

All 3 key labs should be taken into account before making changes to the treatment plan, and first-line drug treatment may include a combination of phosphate binders, vitamin D, and calcimimetics.




| 2017 KDIGO Guide for Key CKD-MBD Labs | |
|---|---|
| **Lab** | **Goal** |
| **Calcium** | Avoid hypercalcemia |
| **Phosphorus** | Reduce toward the normal range |
| **PTH** | 2x – 9x the upper limit of normal |

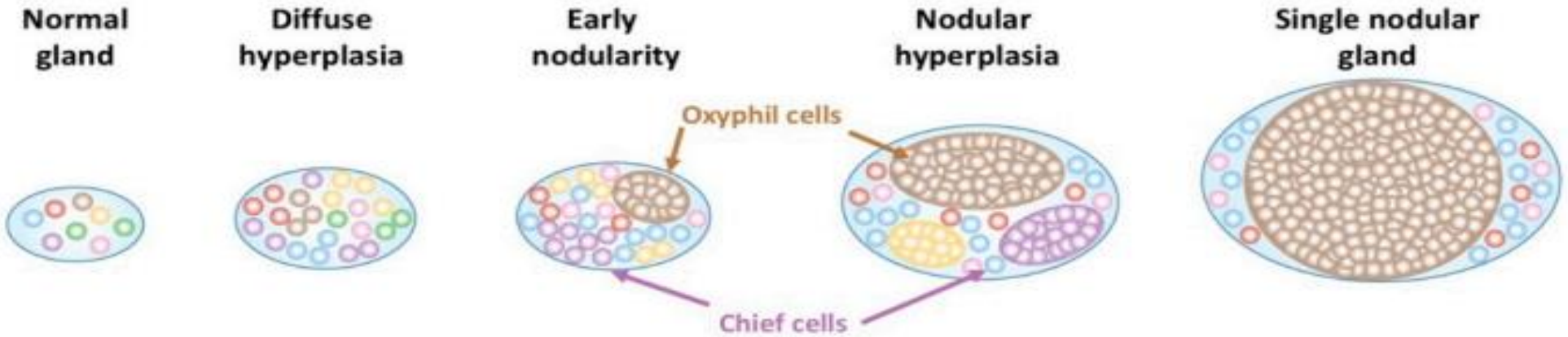
Management of Hyperphosphatemia in End-Stage Renal Disease: A New Paradigm

## Aggravating factors

| | |
|---|---|
| ⇧ Phosphate | ⇩ α-klotho |
| ⇩ Calcium | ⇧ FGF-23 |
| ⇩ Vitamin-D | Acidosis |

⇧ Oxyphil
⇩ α-klotho
⇩ FGFR1

⇧⇧ Oxyphil
⇩⇩ α-klotho
⇩⇩ FGFR1




**Diffuse hyperplasia** → **Polyclonal nodular hyperplasia** → **Monoclonal nodular hyperplasia**

**Polyclonal nodular hyperplasia**

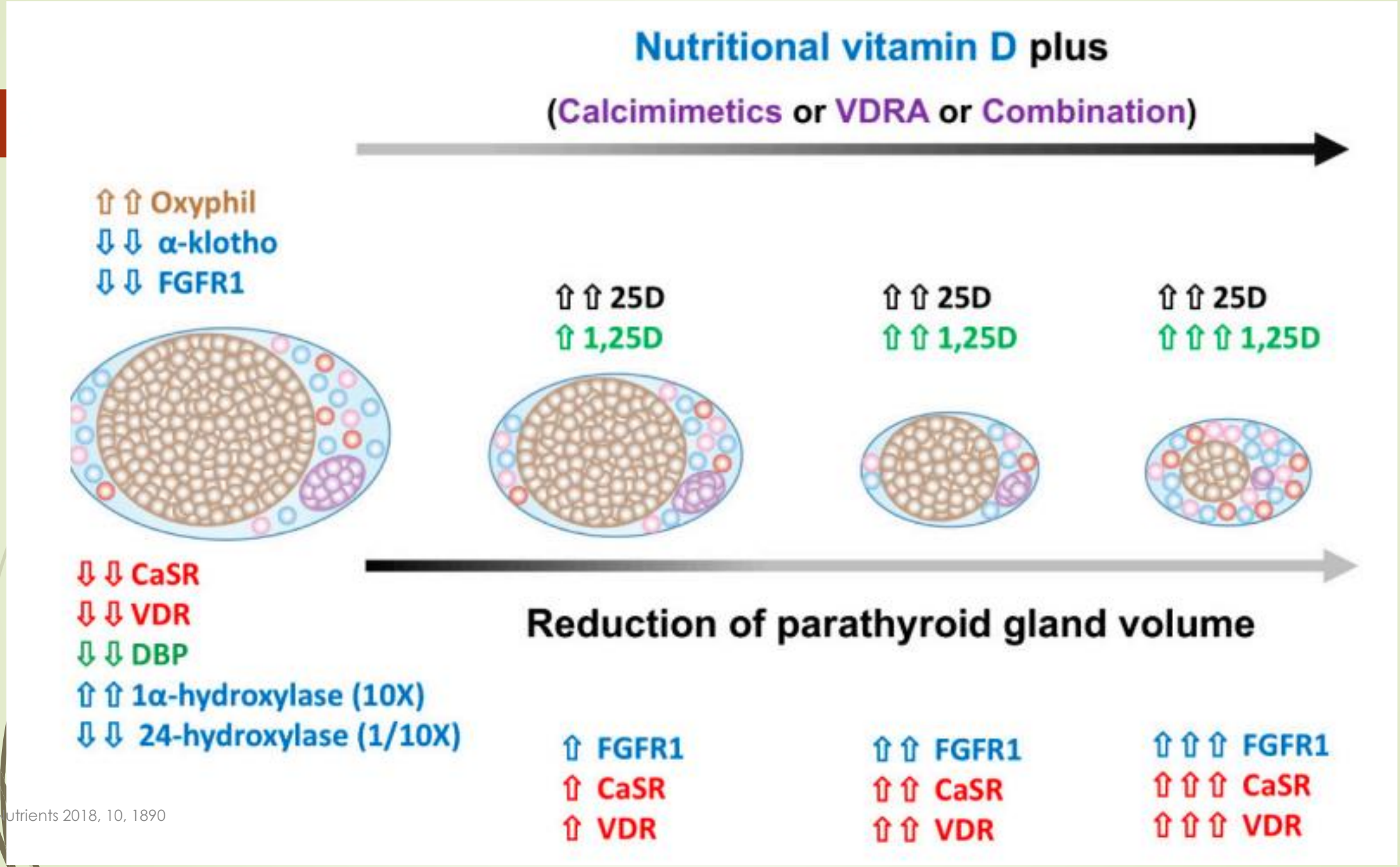
⇩ CaSR
⇩ VDR
⇩ DBP
⇧ 1α-hydroxylase
⇩ 24-hydroxylase

**Monoclonal nodular hyperplasia**

⇩⇩ CaSR
⇩⇩ VDR
⇩⇩ DBP
⇧⇧ 1α-hydroxylase (10X)
⇩⇩ 24-hydroxylase (1/10X)

**" Vitamin D hunger state"**

Nutrients 2018, 10, 1890




Nutrients 2018, 10, 1890

# Treatment of secondary hyperparathyroidism

- Calcitriol and calcimimetics can effectively reduce PTG volume in SHPT and concurrently increase VDR and CaSR expression to improve the efficient SHPT treatment
- NVD supplement meets the demand of parathyroid 25D requirement and lower PTH by dramatically increasing intra-gland 1,25D

# Treatment of secondary hyperparathyroidism

- Decreased renal production of calcitriol (1,25vitamin D3), hypocalcemia, and hyperphosphatemia are the major contributing factors to the development of secondary hyperparathyroidism
- Management of secondary hyperparathyroidism has included the use of active vitamin D or vitamin D analogs for the suppression of parathyroid hormone (PTH) secretion

Kidney International, Vol. 63 (2003), pp. 1483–1490

# PTH-Lowering Agents

- Vitamin D Vitamin D sterols and calcimimetics are specific PTH-lowering agents that act directly on the parathyroid gland to inhibit PTH secretion
- calcitriol and other active vitamin D sterols, paricalcitol, doxercalciferol, and other analogs, are effective in reducing PTH levels

Curr Osteoporos Rep (2019) 17:333–342

# Nutritional Vitamin D

- NVD, both the cholecalciferol and calcifediol supplements are effective in increasing the total and free 25D level and are associated with serum PTH level declin
- The 2017 KDIGO Guideline suggests that VDD should be corrected if CKD stage 3 to 5 not yet dialysis patients have a progressive or persistently high PTH level
- NVD had a positive effect as an adjuvant therapy with calcitriol and calcimimetics in treating SHPT in dialysis patients

# Nutritional Vitamin D

- Suppression of PTH secretion with native vitamin D to control SHPT may not be enough and the use of active vitamin D analogs or other PTH-lowering agents is required
- Native vitamin D continues to be used in CKD patients as other actions beyond treatment of SHPT have been considered

Curr Osteoporos Rep (2019) 17:333–342

# Calcitriol

- Calcitriol is a classic treatment to control PTH levels in patients with SHPT
- Both oral and parenteral forms of calcitriol have been effective in treating and preventing secondary hyperparathyroidism
- Current clinical practice is focused on developing therapies that do not cause increased body burdens of calcium and phosphorus

Kidney International, Vol. 63 (2003), pp. 1483–1490

# 25-dihydroxyvitaminD2 (Paricalcitol)

- Paricalcitol, a selective vitamin D analogue, was demonstrated to only have a minor effect on vitamin D receptors in the intestine and bone
- Paricalcitol has been proved to be an effective treatment to control PTH levels and reduce absorption of calcium and phosphorus
- Paricalcitol was shown to be effective at reducing PTH concentrations without causing significant hypercalcemia or hyperphosphatemia

Experimental
and Therapeutic
Medicine
July 24, 2020 https://doi.org/10.3892/etm.2020.9044

# Paricalcitol

- Paricalcitol is able to effectively inhibit PTH synthesis and parathyroid hyperplasia, but its effect on the intestine and bone is only 1/10 of that of calcitriol

Experimental
and Therapeutic
Medicine
July 24, 2020 https://doi.org/10.3892/etm.2020.9044

# Calcimimetics

- Calcimimetics activate the calcium-sensing receptor to inhibit calcium-regulated PTH secretion, effectively mimicking or potentiating the effects of extracellular calcium
- By reducing PTH, calcimimetics also decrease bone resorption and thus decrease the contribution of serum phosphorus from bone

# Calcimimetics

- Natural calcimimetics such as magnesium and other inorganic compounds act directly at the CaSR in the parathyroid gland, decreasing PTH secretion(calcimimetics type 1)
- other positive allosteric modulators of the CaSR, classified as type II, bind to a site distinct from the physiological ligand, rendering the CaSR more sensitive to calcium, so that inhibition of PTH secretion is achieved at lower calcium concentration

# Calcimimetics

- calcimimetics offer minimal (cinacalcet) to no (etelcalcetide) pill burden
- Etelcalcetide shows some advantages over cinacalcet
  - Stronger efficacy profile
  - Longer half-life ( three times a week at the end of hemodialysis )
  - Intravenous mode of administration

# Cinacalcet

- Cinacalcet, a second-generation calcimimetic agent, is a positive allosteric modulator of the calcium-sensing receptor that increases its sensitivity to extracellular calcium by lowering the threshold for activation by extracellular calcium ions
- This mechanism lowers PTH synthesis and secretion

Kidney Blood Press Res 2019;44:1327–1338

# limitations of calcimimetics

- Hypocalcemia
- Nausea/vomiting
- Diarrhea

✓Improvement in GI tolerability of cinacalcet

can be achieved by administration with meals

# Paricalcitol OR Cinacalcet

- Cinacalcet significantly decreased the serum calcium levels compared with paricalcitol
- serum phosphate levels were relatively higher with paricalcitol compared with cinacalcet
- paricalcitol was more cost-effective than cinacalcet and that paricalcitol was simultaneously more effective in achieving the target levels of PTH

Experimental
and Therapeutic
Medicine
July 24, 2020 https://doi.org/10.3892/etm.2020.9044

# Case presentation

- بیمار اقای ۴۷ ساله مورد ESRD از سال ۱۳۷۴ در سن ۲۱ سالگی به علت نا مشخص
- بیمار در ابتدا ۱۱ ماه همودیالیز شده است
- در سال ۷۵ پیوند کلیه از غریبه زنده
- در سال ۹۴ با تشخیص لنفوم ۱۲ جلسه کمو تراپی شده است
- به دنبال کموتراپی و تغییر داروها دچار افزایش کراتینین شده و مجددا در سال ۹۵ تحت همودیالیز قرار میگیرد

# Case presentation

- در ازماتیشات سال ۹۶

- PTH : 804 ( 12_65 )
- Ca : 8.9
- Ph : 6.2

- سیناکلست با دوز ۳۰ میلی گرم روزانه
- سولامر۸۰۰ با دوز ۲ عدد با صبحانه ۲ با ناهار ۱ با شام شروع شد
- کلسیم تجویز نشد

# Case presentation

- PTH بیماردر ویزیت های بعدی همچنان بالا بود و دوز سیناکلست افزایش داده شد
- PTH : 1470 ( 12_65 )
- Ca : 7.3
- Ph : 4.5
- سیناکلست با دوز ۶۰ میلی گرم با صبحانه یک عدد و باشام دو عدد
- سولامر ۲ عدد با صبحانه ۱ با شام
- بیمار سیناکلست را به این صورت تحمل نکرد و با دوز ۳۰ میلی گرم ۳ عدد صبح ۳ عدد شب ادامه داده شد

# Case presentation

- سال ۹۷
- PTH : 345 ( 12_65 )
- Ca : 5.5
- Ph : 3.9
- سیناکلست کاهش دوز داده شد یک روز ۱۵۰ میلی گرو و روز بعد ۱۲۰ میلی گرم
- سولامر۸۰۰ قطع
- کلسی تریول ۰/۲۵ میلی گرم هفته ای ۲ بار ۳ عدد

# Case presentation

- سال ۹۷

- PTH : 880 ( 12_65 )
- Ca : 7.5
- Ph : 3.4

- افزایش دوز سیناکلست تا ۱۵۰ میلی گرم روزانه
- کلسیم روزانه ۵ عدد با شکم خالی
- افزایش کلسیتریول ۲ بار در هفته هر بار ۴ عدد

# Case presentation

- سال ۹۸

- PTH : 367 ( 12_65 )
- Ca : 8.7
- Ph : 3.6

- کلسیتریول ۰/۲۵ هفته ای ۲ با ۶ عدد
- کلسیم کربنات روزانه ۳ عدد + پودر سوپراکل ۱۰۰۰ یک عدد شکم خالی
- سیناکلست ۳۰ میلی گرم ۴ عدد روزانه

# Case presentation

- سال ۹۸

- PTH : 134 ( 12_65 )
- Ca : 8.5
- Ph : 3.7

- سیناکلست ۳۰ میلی گرم از ۴ عدد به ۳ عدد کاهش یافت
- کلسیتریول ۰/۲۵ دو بار در هفته هر بار ۵ عدد ( کاهش دوز )

# Case presentation

- سال ۹۹

- PTH : 103 ( 12_65 )
- Ca : 8.7
- Ph : 7.07

- سولامر ۸۰۰ سه عدد با هر وعده غذایی ( شروع )
- کلسیتریول ۰/۲۵ میلی گرم ۲ بار در هفته ۳ عدد ( کاهش دوز )

# Case presentation

- سال ۹۹
- در طی چندین ماه فسفر کاهش یافت
- دوز سولامر کاهش داده شد

- PTH : 332 ( 12_65 )
- Ca : 8.9
- Ph : 4.3

- سولامر ۲ عدد با صبحانه ۳ با ناهار
- کربنات کلسیم ۳ عدد با شام
- کلسیتریول هفته ای ۲ بار یک عدد

# Case presentation

سال ۱۴۰۰

PTH : 507 ( 12_65 )

Ca : 8.7

Ph : 2.7

سولامر قطع شد

کلسیم ۳ عدد روزانه با شکم خالی

کلسیتریول هفته ای ۲ بار ۱ عدد

# Case presentation

سال ۱۴۰۰

PTH : 185 ( 12_65 )

Ca : 9

Ph : 4


Thank
You