Role of *nutritional vitamin D* in the treatment of *renal hyperparathyroidism*

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Taiwan Society of Nephrology  
Deputy Superintendent,  
Fu-Jen Catholic University Hospital
I have **no** relevant financial relationship to disclose any **COI** for this research presentation within the period of 36 months.
Objectives

✓ 1. Mineral and hormonal disruption
  ✓ Ca, InP, PTH, vit-D, FGF23/Klotho
  ✓ Renal outcome
    ✓ Nutritional vit-D

● 2. Nutritional vit-D and Bone turnover
  ➢ Vit-D in high bone turnover
  ➢ Vit-D in low bone turnover

● 3. Nutritional vitamin-D in SHPT
  ➢ PTG: 1α-Hydroxylase/24-Hydroxylase/DBP
  ➢ Cholecalciferol for SHPT
Pathogenesis of secondary hyperparathyroidism in CKD

Chronic kidney disease

↓ 25(OH)D

Phosphate retention

↑ FGF23

↓ 1,25(OH)₂D

↓ 25(OH)D

↓ Ca²⁺

↑ PTH

↑ Pi excretion in the urine

Secondary hyperparathyroidism

↑ Ca²⁺

↑ Pi

↑ FGF23

FGF23, an endocrine nexus between hormones and mineral ions

Disturbances in mineral hormones and bone turnover with the progression of CKD

Harmful

Beneficial

Kidney International 2016; 89, 289-302
Nephrol Dial Transplant. 2012; 27: 2650-2657
Control of parathyroid hormone
Synthesis and Secretion

1. $1,25\text{(OH)}_2D$ pg/mL
2. $\alpha$-hydroxylase
3. $25\text{(OH)}D$ ng/mL
4. $25\text{(OH)}D$
5. $\text{Pi}$
6. Acidosis

Bilezikian, J. P. et al. (2016) Primary hyperparathyroidism
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.33
CaR and VDR Expression Decrease as Parathyroid Gland Hyperplasia Progresses

**Progression of PTG hyperplasia proceed the ↓ of VDR & CaSR**

Circulating Levels of 25(OH) Vitamin D and Parathyroid Hormone in nondialysis CKD

Piecewise linear regression model

Nonparametric regression

N=929
Vitamin D metabolism and nomenclature

Native Nutritional Vitamin D$_3$

UV-B radiation
Skin
7-dehydrocholesterol
Cholecalciferol
Liver
Calcifediol or calcidiol
25-hydroxyvitamin D$_3$
Kidneys
Calcitriol
1,25-dihydroxyvitamin D$_3$

Active
h1/2: ½ day

# Frequency of Monitoring for CKD-MBD

<table>
<thead>
<tr>
<th>CKD STAGE</th>
<th>STAGE 3  (30–59 mL/min/1.73 m²)</th>
<th>STAGE 4  (15–29 mL/min/1.73 m²)</th>
<th>STAGE 5  (&lt;15 mL/min/1.73 m²)</th>
<th>STAGE 5 DIALYSIS  (&lt;15 mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERUM CALCIUM</strong></td>
<td>Every 6–12 months (G 3.1.2)</td>
<td>Every 3–6 months (G 3.1.2)</td>
<td>Every 1–3 months (G 3.1.2)</td>
<td>Every 1–3 months (G 3.1.2)</td>
</tr>
<tr>
<td><strong>SERUM PHOSPHORUS</strong></td>
<td>Every 6–12 months (G 3.1.2)</td>
<td>Every 3–6 months (G 3.1.2)</td>
<td>Every 1–3 months (G 3.1.2)</td>
<td>Every 1–3 months (G 3.1.2)</td>
</tr>
<tr>
<td><strong>PTH</strong></td>
<td>On baseline level &amp; CKD progression (G 3.1.2)</td>
<td>Every 6–12 months (G 3.1.2)</td>
<td>Every 3–6 months (G 3.1.2)</td>
<td>Every 3–6 months (G 3.1.2)</td>
</tr>
<tr>
<td><strong>ALKALINE PHOSPHATASES</strong></td>
<td>Every 12 months or more often when PTH is ↑ (G 3.1.2)</td>
<td>Every 12 months or more often when PTH is ↑ (G 3.1.2)</td>
<td>Every 12 months or more often when PTH is ↑ (G 3.1.2)</td>
<td>Every 12 months or more often when PTH is ↑ (G 3.1.2)</td>
</tr>
<tr>
<td><strong>25(OH)D</strong></td>
<td>Measure and repeat testing on baseline values and therapeutic interventions. Correct vitamin D deficiency and insufficiency using treatment strategies recommended for the general population. (G 3.1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Kidney Int. 2009; 76 (Suppl 113): S1-S130*
Treatment of abnormal PTH levels in CKD-MBD
2017 KDIGO guideline

- **4.2.1:** In patients with CKD G3a-G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

- **4.2.4:** In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).

## Vitamin D sterols for the treatment of SHPT

<table>
<thead>
<tr>
<th>Nutritional vitamin D</th>
<th>Vitamin D analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergocalciferol</td>
<td>Paricalcitol</td>
</tr>
<tr>
<td></td>
<td>19-nor1,25(OH)_2D_3</td>
</tr>
<tr>
<td></td>
<td>Doxercalciiferol</td>
</tr>
<tr>
<td></td>
<td>1α(OH)D_2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutritional vitamin D</th>
<th>Vitamin D analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecalciferol</td>
<td>Calcitriol</td>
</tr>
<tr>
<td>Calcifediol 25(OH)D</td>
<td>1,25(OH)_2D_3</td>
</tr>
<tr>
<td></td>
<td>Alfacalcidol</td>
</tr>
<tr>
<td></td>
<td>1α(OH)D_3</td>
</tr>
<tr>
<td></td>
<td>Maxacalcitol</td>
</tr>
<tr>
<td></td>
<td>1α,25(OH)_222oxaD_3</td>
</tr>
</tbody>
</table>

**Deserve further explore**
Atmospheric pollution and vitamin D status

Haze scores, regarded as a surrogate marker of solar UVB radiation reaching ground level.

A filter that only allowed UVB radiation (285-310 nm) to be detected by the sensor’s light detecting diode.

<table>
<thead>
<tr>
<th>Mori Gate High pollution area n=26</th>
<th>Gurgaon Low pollution area n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>16 (4.1)</td>
</tr>
<tr>
<td>Haze score</td>
<td>2.1 (0.5)</td>
</tr>
<tr>
<td>Gender</td>
<td>15 males, 11 females</td>
</tr>
<tr>
<td>Ca (mg %)</td>
<td>9.7 (0.9)</td>
</tr>
<tr>
<td>ALP (IU/l), median (range)</td>
<td>498 (116–3739)</td>
</tr>
<tr>
<td>25(OH)D₃ (ng/ml)</td>
<td>11.7 (7)</td>
</tr>
<tr>
<td>25(OH)D₂ (ng/ml)</td>
<td>2.4 (0.6) (n=5)</td>
</tr>
<tr>
<td>Total 25(OH)D (ng/ml)</td>
<td>12.4 (7)</td>
</tr>
<tr>
<td>1,25(OH)₂D (pg/ml)</td>
<td>73.7 (30)</td>
</tr>
<tr>
<td>PTH (pg/ml), median (range)</td>
<td>25 (5–284)</td>
</tr>
</tbody>
</table>
# Natural sources of vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Content in vitamin D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild salmon</td>
<td>600–1000 IU</td>
</tr>
<tr>
<td>Farmed salmon</td>
<td>100–250 IU</td>
</tr>
<tr>
<td>Sardines (canned)</td>
<td>300–600 IU</td>
</tr>
<tr>
<td>Mackerel (canned)</td>
<td>250 IU</td>
</tr>
<tr>
<td>Tuna (canned)</td>
<td>236 IU</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>400–1000 IU per tablespoon</td>
</tr>
<tr>
<td>Shiitake mushrooms (fresh)</td>
<td>100 IU</td>
</tr>
<tr>
<td>Shiitake mushrooms (dried)</td>
<td>1600 IU</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>20 IU per yolk</td>
</tr>
<tr>
<td>Fresh mushrooms</td>
<td>76 IU</td>
</tr>
<tr>
<td>Vegetable are grown by fertilizer</td>
<td>52 IU</td>
</tr>
<tr>
<td>Cheese (e.g., Emmental)</td>
<td>44 IU</td>
</tr>
</tbody>
</table>

*Per 100 grams, unless otherwise specified.
CYP24 expression is elevated in uremic kidney
異化作用の酵素

Upregulation of basal CYP24 mRNA expression is independent of vitamin D status in uremic rats

Kidney International 2010; 78: 463-472
CYP24A1 is increased 2-3 fold in renal proximal tubules of diabetic mice

Comparison of constitutive gene expression in hMSCs from a hemodialysis subject and a control subject
25-Hydroxy-vitamin D levels for each center by solar radiation

500 children from 12 European countries with CKD stages 3-5
Main steps of vascular ageing and CKD

Lancet Diabetes Endocrinol. 2018 Apr; 6(4): 319-331
Role of Local Versus Systemic Vitamin D Receptors in Vascular Calcification

活性vit-D 易引發血管钙化

![Graphs and images showing calcium content in non-uremic and uremic conditions with and without calcitriol treatment, and comparison between VDR−/− allograft and VDR+/+ aorta.](image)
Coronary artery calcification (CAC) & valve calcification in young adults with childhood onset of ESRD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Heidelberg Oh et al. [2]</th>
<th>Berlin Briese et al. [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CAC</td>
<td>34/37 (92%)</td>
<td>4/40 (10%)</td>
</tr>
<tr>
<td>With cardiac valve calcification</td>
<td>12/37 (32%)</td>
<td>0/40 (0%)</td>
</tr>
<tr>
<td>Nb of dialysis/transplanted</td>
<td>15/26</td>
<td>9/31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>25/14</td>
<td>22/18</td>
</tr>
<tr>
<td>Duration of ESRD (years)</td>
<td>12.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Time on dialysis</td>
<td></td>
<td>2.9</td>
</tr>
<tr>
<td>Time on transpl</td>
<td></td>
<td>9.2</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>108</td>
<td>97</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>109</td>
<td>109</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>6.2</td>
<td>17</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>364</td>
<td>155</td>
</tr>
<tr>
<td>Ca × P product (mmol²/l²)</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Cumulative Ca × OPB dose (kg); (per year)</td>
<td>27; (2)</td>
<td>4; (0.8)</td>
</tr>
<tr>
<td>Cumulative 1α OH vit D dose (µg); (per year)</td>
<td>13,300; (1)</td>
<td>383; (130)</td>
</tr>
<tr>
<td>Cumulative Cholecalciferol dose (10⁶ IU); (per year)</td>
<td>?</td>
<td>13; (2.1)</td>
</tr>
</tbody>
</table>

**使用できる限り早く vit-D 血管の石灰化を始めることが容易**
1,25-Dihydroxyvitamin D₃ Inhibits the Hepatic Production of 25-Hydroxyvitamin D

活性vit-D 可减少 營養性vit-D

Classical vitamin D metabolism

Vitamin D undergoes sequential steps of metabolic activation and degradation with a cascade of cytochrome P450 enzymatic reactions

![Diagram showing the classical vitamin D metabolism pathway](image-url)
Vitamin-D in the Body

Lu revised, CJASN 2012; 7: 358-365
Diastolic BP is inversely associated with serum 25(OH)D at baseline

Annualized change in eGFR expressed across three ranges of 25(OH)D levels

167 children, median eGFR 51 ml/min, after a median 8 months on ACEi

Significant associations of proteinuria with poor vitamin D status

Defined as 25(OH)D < 30 ng/mL

Takayuki Hamano, Osaka University
The effect of cholecalciferol for lowering albuminuria in chronic kidney disease: a prospective controlled study

Cholecalciferol 666 IU/day

Cholecalciferol administration reduced the uACR by −53%.

No changes of antihypertensive medication

* p<0.001 vs baseline

p=0.704 vs baseline

* p=0.004 vs baseline

p=0.621 vs baseline

Objectives

● 1. Mineral and hormonal disruption
   ➢ Ca, InP, PTH, vit-D, FGF23/Klotho
   ➢ Renal outcome
     ✓ Nutritional vit-D

✓ 2. Nutritional vit-D and Renal osteodystrophy
   ✓ Vit-D in high bone turnover
   ✓ Vit-D in low bone turnover

● 3. Nutritional vitamin-D in SHPT
   ➢ PTG: 1α-Hydroxylase/24-Hydroxylase/DBP
   ➢ Cholecalciferol for SHPT
Osteoblast dependent osteoclast development

Cholecalciferol → 25(OH)D₃
1α,25(OH)₂D₃

1α hydroxylase
1,25(OH)₂D₃ receptor

PTH
PGE₂

CFU-M
Macrophage progenitors

Osteoclast precursors

pre-osteoclasts

Osteoclasts

ATP

gp130

RANKL

Hematopoietic precursors
M-CSF

Osteoblasts

IL-6 (+sIL-6R)
IL-11
Oncostatin M
LIF

vit-D/PTH対が骨の細胞をつくるのはとても重要です
Treatment of postmenopausal osteoporosis with calcitriol or calcium

Calcitriol (0.25 micrograms twice a day) or Calcium (1 g of elemental calcium daily) can decrease vertebral fractures.

**Therapeutic dosage**

Calcitriol

Calcium

Effects of active vitamin D compounds in inhibiting bone resorption

BoneKEy Reports 3, Article number: 495 (2014)
JBMR 2017 Jul; 32(7): 1406-1420
Clastokines after vitamin D$_3$ treatment

Fig 1. TRAP stain analysis in osteoclast derived from RANKL-stimulated monocytes. Calcitriol inhibit clastogenesis effect of osteoclast precursor cells. Bar = 50 μm.

Fig 2. Wnt10b expression in osteoclasts. Osteoclasts were treated with different concentration of calcitriol and Wnt10b was significant increased as the dose dependent manner.

Fig 4. Confocal analysis of immunofluorescent labeling of Wnt10b (green) in calcitriol-treated osteoclast, Actin was labeled with Cy3 (red). Bar = 20 μm.
Overview of the Wnt signalling pathway in OB (Osteoblast)

Wnt 4, Wnt 5a, Wnt 10b, Wnt 16

CKD, VC, MP, GIOP

Antibodies

Indoxyl sulfate induces PTH resistance in CKD

1. Downregulation of PTH1R
2. Reduction in intracellular cAMP production
3. Competitive inhibition between PTH and PTH fragments to PTH1R
4. Increase in cellular oxidative stress
Bone Loss in CKD

Chronic Kidney Disease

Uremic Toxins $\uparrow$ (Indoxyl Sulphate)

IS/PCS

Vitamin D Deficiency

PTH $\uparrow$

Direct toxicity to OBs/OCs

Wnt Antagonist $\uparrow$ (SOST/DKK1)

Klotho deficiency
Aluminum intoxication
Metabolic Acidosis
Others

Low Bone Turnover
Bone Loss

Renal Function
More Worsen

PTH $\uparrow\uparrow\uparrow$

High Bone Turnover or Low Bone Turnover
Bone Loss

Progression of CKD

Lu et al. Clin Chim Acta 2018; 484: 197-206
Cytokines

TNF-α-induced osteoclastogenesis from WT or RANK deficient cells

J Exp Med
2005; 202: 589-595
Cytokines are key regulators of inflammatory osteolysis.
Cholecalciferol supplementation on systemic inflammation

25-OH-D₃ increase mineralization front (Osteoblast) and osteoclast in renal osteodystrophy.
Treatment with 25-OH-D$_3$ for 86 wks
endosteal fibrosis$\downarrow$ osteoid$\downarrow$
active bone (High turnover-SHPT)

Resorption of woven bone is necessary

Lamellar Bone

Woven Bone (SHPT)

吸収の編む骨 は良い骨を作る

高い循環率のosteopathyは変わる
Treatment with 25-OH-D$_3$ for 86 wks

mineral appositional rate $\uparrow$, osteoid mineralization $\uparrow$

inactive bone (Low turnover-ABD)

Adynamic Bone disorder

Rescue osteoblast viability is necessary

Non-anastamosing Trabeculae

Edited by Dr. Lu
Beneficial effects of vit-D on menopause

- Native vit-D
- Estrogen deficiency
- Bone loss
- Inflammation
- CV events

- RAAS
- eNO
- IL1, IL6
- IL4, Treg
- Osteoblast
- Osteoclast

References:
- Curr Opin Pharmacol 2017 Apr; 33: 1-5
- Methodist Debakey Cardiovasc J 2017; 13(1): 4-8
- Am J Physiol Regul Integr Comp Physiol 2013; 305: R459-R463

 высокооборотность остеопатії
Beneficial effects of vit-D on GIO

Low turnover

Glucocorticoids

- Apoptosis
- Autophagy

Osteoclast

- RhoA
- Rac1
- Life span

Osteocyte

- SOST
- DKK1, SFRP-1

Osteoblast

- RANKL
- OPG

Native vit-D

- ROS

Bone. 2017 Mar; 96: 29-37
Biomed Pharmacother. 2016 Dec; 84: 438-446
Horm Metab Res 2016; 48: 755-763
J Bone Miner Res. 2016; 31(10): 1787-1790
Expert Opin Pharmacother. 2016 Nov; 17(16): 2129-2133

## Derangements in bone turnover, mineralization and volume in ROD and in OP

<table>
<thead>
<tr>
<th>Classical definition</th>
<th>T</th>
<th>M</th>
<th>V</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal osteodystrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteitis fibrosa</td>
<td>High</td>
<td>Abnormal</td>
<td>High/normal/low</td>
<td>Increased bone remodeling with peritrabecular fibrosis. Increased number and activity of osteoclasts and osteoblasts</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Low</td>
<td>Abnormal</td>
<td>Normal/low</td>
<td>Defective mineralization of the organic matrix of bone</td>
</tr>
<tr>
<td>Adynamic bone disease</td>
<td>Low</td>
<td>Normal/abnormal</td>
<td>Normal/low</td>
<td>Low bone formation, low number of bone cells</td>
</tr>
<tr>
<td>Mixed uremic osteodystrophy</td>
<td>High-normal</td>
<td>Abnormal</td>
<td>Normal/low</td>
<td>Features of both osteitis fibrosa and osteomalacia</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High turnover OP</td>
<td>High</td>
<td>Normal</td>
<td>Low</td>
<td>Uncoupling of bone cells activity with prevailing resorption</td>
</tr>
<tr>
<td>Normal/low turnover OP</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Uncoupling of bone cells activity with prevailing low bone apposition</td>
</tr>
</tbody>
</table>

*ROD renal osteodystrophy, OP osteoporosis, T turnover, M mineralization, V volume*
Objectives

1. Mineral and hormonal disruption
   - Ca, InP, PTH, vit-D, FGF23/Klotho
   - Renal outcome
     - Nutritional vit-D

2. Nutritional vit-D and Renal osteodystrophy
   - Vit-D in high bone turnover
   - Vit-D in low bone turnover

3. Nutritional vitamin-D in SHPT
   - PTG: 1α-Hydroxylase/24-Hydroxylase/DBP
   - *Cholecalciferol* for SHPT
Parathyroid Tissue in Normal and CKD subjects
Enhanced innate vit-D necessary in high PTH

1α-hydroxylase/GAPDH mRNA expression ratio

外的なvit-Dは不十分にするために所有する必要がある

PTG

24-hydroxylase

PTH ↑ 導致
1α hydroxylase ↑ x10
24 hydroxylase ↓ <10%

J Clin Endocrinol Metab 2002; 87(6):2967–2972
J Clin Endocrinol Metab 2002; 87(12):5826–5829
CaR and VDR Expression Decrease as Parathyroid Gland Hyperplasia Progresses

Progression of PTG hyperplasia proceed the ↓ of VDR & CaSR


Revised by Dr. Lu
Oxyphil cell hyperplasia and proportion of oxyphil cells to total cells (O/T ratio) in parathyroid glands of uremic SHPT patients

Mild (A)                        Moderate (B)                        Severe (C)

Hyperplasia of oxyphil cells

Refractory hyperparathyroidism

J Proteomics. 2018 May; 179: 42-52
Part of differential abundance *proteins* in oxyphil and chief cell nodules

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
<th>Protein IPI</th>
<th>Oxyphil / Chief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid Hormone</td>
<td>PTH</td>
<td>IPI00000940</td>
<td>0.47</td>
</tr>
<tr>
<td>Vitamin D-Binding Protein Precursor</td>
<td>GC</td>
<td>IPI00742696</td>
<td>0.32</td>
</tr>
<tr>
<td>Extracellular Calcium-Sensing Receptor</td>
<td>CaSR</td>
<td>IPI00216479</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Downregulation of DBP in *oxyphil nodules* may reduce the *vitamin D transport*, therefore participate in calcitriol resistance.
Pathophysiology of secondary hyperparathyroidism in CKD
Revised by Dr. Lu

Progression of PTG hyperplasia proceeds the ↓ of VDR & CaSR

Acidosis
- Low calcium
- High phosphorus
- Low 1α,25(OH)₂D
- ↑ FGF23

Polyclonal proliferation
- Normal gland
- Diffuse hyperplasia
- Early nodularity

Monoclonal proliferation
- Nodular hyperplasia
- Single nodular gland

Oxyphil
- ↑
- ↓ VDR
- ↓ CaSR
- ↓ fGf R1/3c
- ↓ α-klotho

Oxyphil
- ↑↑
- ↓↓ VDR
- ↓↓ CaSR
- ↓↓ fGf R1/3c
- ↓↓ α-klotho

DBP ↓
1α-OHase ↑
24-OHase ↓

1α-OHase ↑↑ x10
24-OHase ↓↓ x1/10
Direct upregulation of parathyroid CaSR and VDR by calcimimetics in uremic rats

Add on Effects: VDRA

Calcimimetics directly increase CaSR and VDR expression by hyperplastic parathyroid glands.
Cinacalcet on parathyroid cell proliferation in 5/6 Nx rats

![Graph showing number of PCNA-positive cells/mm² for different conditions.](image)

- **5/6 Nx** + cinacalcet (mg/kg) 1, 5, 10, Sham + cinacalcet (mg/kg) 10
- **Control**

What’s the role of nutritional vit-D?

CaR and VDR Expression Decrease as Parathyroid Gland Hyperplasia Progresses

Chronic Kidney Disease

Progression of Hyperplasia

Vit-D hunger in PTG of SHPT

1α-hydroxylase ~ x 10
24-hydroxylase ~ x 1/10

Cholecalciferol

25(OH)D

Calcifediol

Edited by Dr. Lu, 2015 Dec
Means for different variables before and after 12 weeks on treatment with cholecalciferol (8,000 IU/day) or placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cholecalciferol</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
<td>Baseline</td>
</tr>
<tr>
<td>25(OH)D (nmol/L)</td>
<td>57.5 ± 22</td>
<td>161.6 ± 49</td>
<td>56.8 ± 22</td>
</tr>
<tr>
<td>iPTH (pmol/L)</td>
<td>10.9 ± 5</td>
<td>10.5 ± 5</td>
<td>13.1 ± 9</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.24 ± 0.14</td>
<td>2.23 ± 0.13</td>
<td>2.27 ± 0.12</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.2 ± 0.28</td>
<td>1.3 ± 0.28</td>
<td>1.2 ± 0.27</td>
</tr>
<tr>
<td>1,25(OH)D (pmol/L)</td>
<td>64 ± 43</td>
<td>102 ± 54</td>
<td>64 ± 40</td>
</tr>
<tr>
<td>FGF23 (pg/mL)</td>
<td>132 ± 115</td>
<td>160 ± 131</td>
<td>138 ± 87</td>
</tr>
<tr>
<td>Urinary phosphate (mmol/L)</td>
<td>14.7 ± 9.6</td>
<td>15.8 ± 9.3</td>
<td>16.3 ± 7.8</td>
</tr>
<tr>
<td>Hand grip strength (kg)</td>
<td>26.5 ± 11</td>
<td>27.7 ± 12</td>
<td>33.2 ± 13</td>
</tr>
<tr>
<td>Fatigue score, total</td>
<td>14.7 ± 5</td>
<td>12.3 ± 5</td>
<td>13.7 ± 4</td>
</tr>
<tr>
<td>Physical</td>
<td>9.6 ± 4</td>
<td>8 ± 4</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Mental</td>
<td>5 ± 2</td>
<td>4.2 ± 2</td>
<td>4.7 ± 2</td>
</tr>
<tr>
<td>VAS (mm)</td>
<td>42.6 ± 26</td>
<td>36.0 ± 23</td>
<td>38.8 ± 25</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. P denotes difference in mean change between groups based on ANCOVA with baseline value as covariate. VAS, visual analogue scale.

High doses of cholecalciferol alleviate the progression of hyperparathyroidism in patients with CKD Stages 3-4: results of a 12-week double-blind, randomized, controlled study.
## Combination therapy

The effect of lowering serum parathyroid hormone

Native + Active vit-D, n=60

![Graph showing the effect of lowering serum parathyroid hormone](chart.png)

**Primary Outcome** | 4th Week | 8th Week | 12th Week | 16th Week
--- | --- | --- | --- | ---
\(i\)PTH \(\leq 300\) pg/mL | \(n/30\) (%) | \(n/30\) (%) | \(n/30\) (%) | \(n/30\) (%)  
Paricalcitol | 2/30 (6.7) | 7/30 (23) | 12/30 (40) | 15/30 (50)  
Paricalcitol + Cholecalciferol | 2/30 (6.7) | 7/30 (23) | 18/30 (60) | 23/30 (76.7)  
\(p = 1.000\) | \(p = 1.000\) | \(p = 0.121\) | \(p = 0.032\)

Lu et al. Nutrients 2016; 8: 708
Cholecalciferol Decreased Serum PTH, Increased Vitamin-D and Cathelicidin Levels in Paricalcitol Treated SHPT of HD Patients

Lu et al. Nutrients 2016; 8: 708
Calcimimetics

Calcium sensing

1-OHase

50%

1,25(OH)$_2$D$_3$

Decreased parathyroid hormone

$\downarrow$PTH

Edited by Dr. Lu, 2015 Dec
Cholecalciferol Additively Reduces Serum Parathyroid Hormone Levels in Severe SHPT Treated with Calcitriol and Cinacalcet in HD Patients

Lu et al. Nutrients 2018; 10(2): 196
<table>
<thead>
<tr>
<th>Week</th>
<th>Cholecalciferol (μg/week)</th>
<th>Placebo (μg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4th week</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>8th week</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>12th week</td>
<td>2.67</td>
<td>3</td>
</tr>
<tr>
<td>16th week</td>
<td>2.22</td>
<td>2.79</td>
</tr>
<tr>
<td>20th week</td>
<td>1.44</td>
<td>2.57</td>
</tr>
<tr>
<td>24th week</td>
<td>0.56</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Mean dose of intravenous calcitriol (μg/week) during the course of treatment

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>12th Week</th>
<th>16th Week</th>
<th>20th Week</th>
<th>24th Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH ≤ 300 pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCC (n = 27)</td>
<td>3/27 (11.1%)</td>
<td>8/27 (29.6%)</td>
<td>15/27 (55.6%)</td>
<td>22/27 (81.5%)</td>
</tr>
<tr>
<td>CCP (n = 28)</td>
<td>2/28 (7.1%)</td>
<td>3/28 (10.7%)</td>
<td>4/28 (14.3%)</td>
<td>7/28 (25%)</td>
</tr>
<tr>
<td>p</td>
<td>1.000</td>
<td>0.270</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>12th Week</th>
<th>16th Week</th>
<th>20th Week</th>
<th>24th Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D₃ ≥ 30 ng/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCC (n = 27)</td>
<td>21/27 (77.8%)</td>
<td></td>
<td></td>
<td>24/27 (88.9%)</td>
</tr>
<tr>
<td>CCP (n = 28)</td>
<td>2/28 (7.1%)</td>
<td></td>
<td></td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td></td>
<td></td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

| ↑ FN-BMD > 10% |           |           |           |           |
| CCC (n = 27)   |           |           | 13/27 (40%) |           |
| CCP (n = 28)   |           | 5/28 (6.7%) |           | p = 0.150  |
Bone loss (BL) & Vascular Calcification (VC) in CKD

- **Early CKD**
  - Uremic Toxins
    - IS, PCS
  - Kidney Wnt inhibitor
    - DKK1
  - Supress OB & OC
  - Decrease BF & BR
  - Low bone turnover
  - Altered bone architecture

- **Bone loss**: Quality
  - Low PTH
    - RANKL ↓
    - Wnt ↓↓
    - Bone formation ↓↓↓
    - Bone resorption ↓↓
  - High PTH
    - RANKL ↑↑
    - Wnt ↑
    - Bone formation ↑↑
    - Bone resorption ↑↑↑

- **Bone loss**: Quantity
  - Add on

- **Progress CKD**
  - Hypogonadism
  - Hyponatremia
  - Metabolic acidosis
  - AGE, FGF23

- **Uremic Osteoporosis** (Decrease elasticity)
  - CKD-MBD
  - ROD (renal osteodystrophy)
  - (TMV changes)

- **Bone loss**: Quality + Quantity
  - Low turn over bone disorder
    - RANKL ↓
    - Wnt ↓↓
    - Bone formation ↓↓↓
    - Bone resorption ↓↓
  - High turn over bone disorder
    - RANKL ↑↑
    - Wnt ↑
    - Bone formation ↑↑
    - Bone resorption ↑↑↑

- **Bone loss**: Quality + Quantity
  - DKK1, SOST, sFRP
  - SC, VC
  - media > intima VC, SC
  - media > intima VC, SC

**Lu et al. Bone 2016; 87 : 57–70**
Native vitamin D and bone turnover disorders

Lu, et al.
Clinica Chimica Acta
2016 Jan; 453: 1-12
Therapeutic role of cholecalciferol in CKD: A multidisciplinary-based opinion

25(OH) vitamin D <30 ng/mL

Cholecalciferol “starting” dose of ≥1000-2000 IU/day

Target
- 25(OH) vitamin D: 30 ng/mL
- Normal PTH
- Proteinuria: <0.5 g/24h
- Hb 11-12 g/dl with low dose EPO

Add active Vit D if target not reached
Conclusions

◆ Sunlight exposure and food can’t provide adequate vit-D
◆ CKD, DM, IS/PCS: Contribute to low vit-D levels
◆ Vit-D in *PTG* of SHPT
  - Vit-D hunger: ↓ 1α-OHase, ↑ 24-OHase
  - Vit-D resistance: ↓ VDR, ↓ DBP, ↓ FGF-r1
◆ Critical to prevent the progress of PTG hyperplasia in CKD
◆ Possible beneficial of *vit-D combination therapy* for SHPT
  - More efficient ↓ PTH
  - ↓ VDRA dosage & VDRA related drawbacks
  - Synergistic actions with calcimimetics
  - Improve bone health (both high and low bone turnover)
  - Alleviate vascular calcification
  - No/minimal effects on intestinal absorption of Ca/Pi
  - Attenuate inflammatory cytokines/status

Beneficial role of nutritional vitamin-D in the treatment of SHPT
Thanks for your attentions.