What is new about hyperparathyroidism?

Eberhard Ritz
Heidelberg (Germany)
Incomplete insight into pathomechanisms triggering hyperparathyroidism

• Unfounded guidelines and
• unsatisfactory results of treatment
What triggers (secondary) hyperparathyroidism

- hyperphosphatemia → low ionised Ca++
Removal of one kidney → reduced fractional excretion of Pi (TRP)

the link between high Pi and high PTH
PTH mRNA – stabilised by binding of the cytoplasmic protein AUF to the nontranslated 3’region preventing degradation

Baseline serum phosphate predicts future need of parathyroidectomy

Pathogenesis of secondary hyperparathyroidism

Cunningham J., Kidn.Internat.(1999) 73, S59
What triggers (secondary) hyperparathyroidism

- hyperphosphatemia $\rightarrow$ low ionised $\text{Ca}^{++}$
- lack of $1,25(\text{OH})_2\text{D}_3$
Fraser D.R., Kodicek E.  
Unique biosynthesis of a biological active vitamin D metabolite  
Brickman A.S., Coburn J.W., Massry S.G., Norman A.W.

1,25 Dihydroxy-vitamin D3 in normal man and patients with renal failure

$1,25(\text{OH})_2\text{D}_3$ concentrations at different stages of CKD

Is excessive parathyroid hormone secretion the only abnormality of the parathyroids?
The main problem in secondary hyperparathyroidism – parathyroid hyperplasia and nodular hyperplasia

[Diagram showing the progression from hypertrophy, diffuse hyperplasia, early nodularity in diffuse hyperplasia, monoclonal proliferation of nodules, nodular hyperplasia, genetic abnormality, to a single nodular gland, with note: each nodule different chromosomal lesions]

Fukagawa, Kidn.Intern.(2006) 70:S3
Parathyroid proliferation:
(analogies to tumour growth)

- aggravated by high $P_i$, low $Ca^{++}$
- important signal:
  \[ \text{TNF}_{\alpha} \rightarrow \text{epidermal growth factor receptor (EGFR)} \]
- EGFR downstream signalling:
  - parathyroid hyperplasia
  - downregulation of vitamin D receptor, $Ca^{++}$ sensing receptor

[ blockade of downstream signalling prevents $P_i$ and $Ca^{++}$ mediated hyperplasia ]
Blockade of the EGF receptor abrogates and reverses effects of high P_i on #TGFα selfinduction (top) and #vitamin D receptor expression (bottom)

Dusso, Kidn.Internat.(2006) 70:S8
Parathyroid hyperplasia – analogies to tumor growth

Dusso, Kidn.Intern.(2006) 70:S8
In proliferating parathyroid:

downregulation of receptors for agents inhibiting parathyroid cell proliferation:

- **VDR (vitamin D receptor)**

- **Ca sensing receptor**
Reduced VDR expression in nodular parathyroid hyperplasia

Treatment with $1,25(\text{OH})_2\text{D}_3$ – lower glomerulosclerosis index in subtotally nephrectomised rats

Proliferation and calcification of aorta of uremic rats – calcimimetics vs calcitriol

<table>
<thead>
<tr>
<th></th>
<th>PCNA 1/mm²</th>
<th>Cbfa-1 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>subtotal nephrectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vehicle</td>
<td>0.14±0.29</td>
<td>11.9±18.1</td>
</tr>
<tr>
<td>calcimimetic</td>
<td>0.13±0.42</td>
<td>8.1±13.3</td>
</tr>
<tr>
<td>calcitriol</td>
<td>3.15±4.93</td>
<td>71.0±57.0</td>
</tr>
</tbody>
</table>

Koleganova, Kidn.Internat. (in press)
Survival of incident hemodialysis patients with and without active vitamin D treatment according to ethnicity.

Vit.D vs no vit D mortality:
- 16% in blacks and Hispanics
- 23% in whites (p<0.01)

Pathogenesis of secondary hyperparathyroidism

Cunningham J., Kidn.Internat.(1999) 73, S59
What triggers (secondary) hyperparathyroidism

- hyperphosphatemia $\rightarrow$ low ionised Ca$^{++}$
- not only lack of $1,25(OH)_2D_3$
- but also lack of $25(OH)D$ $\rightarrow$
  because of local production of $1,25(OH)_2D_3$ by 1-alpha hydroxylase in the parathyroid?
Vitamin D status of primates and humans

Vitamin D deficiency – high PTH concentration and risk of bone fractures

Potential explanations:

1. Parathyroid: 1,25D production

2. Osteoblast: Anabolic 1,25(OH)₂D₃ actions on bone
Prevalence of insufficient 25(OH) vitamin D$_3$ concentrations in the general population (NHANES)

<75 nmol/L = 30 ng/ml

High prevalence of low 25(OH)D3 concentrations in CKD 3 and 4

- “deficiency” < 10 ng/ml (< 25 nMol/L)
- “insufficiency” 10-30 ng/ml (25-75 nmol/L)

# sufficient concentrations (> 30 ng/ml) only in:

✓ 29% CKD 3 (eGFR 30-60 ml/min)
✓ 17% CKD 4 (eGFR 15-30 ml/min)

# sun exposure only modest increase:

17.9→21.2 ng/ml

LaClaire, Am.J.Kidn.Dis.(2005) 45:1026
Correlation: low 25(OH)D$_3$ - high iPTH

Expression of 1-α hydroxylase (and megalin) in parathyroids

In proximal tubule uptake of 25(OH)D via Megalin

Suppression of PTH secretion by 25(OH)D$_3$ and 1,25(OH)$_2$D$_3$ in bovine parathyroid cell cultures

What triggers (secondary) hyperparathyroidism

- hyperphosphatemia $\rightarrow$ low ionised Ca$^{++}$
- lack of $1,25(OH)_{2}D_{3}$
- lack of $25(OH)D$ $\rightarrow$
  local production of $1,25(OH)_{2}D_{3}$ ?
- ionised plasma Ca$^{++}$
Pathogenesis of secondary hyperparathyroidism

Cunningham J., Kidn.Internat.(1999) 73, S59
Calcium sensing receptor (CaR)

controls dimerization and normal receptor function

agonist binding
Caenorhabditis elegans
Olfactory sensing of Ca$^{++}$ by CaSr homologue

Ca\textsuperscript{++} sensing protein in plants

*(Arabidopsis guard cells)*

*Han, Nature (2003) 425, 196*
“Calcimimetics are a family of small organic molecules that allosterically modulate calcium receptors present on the surface of parathyroid cells and parafollicular cells of the thyroid glands to make them more sensitive to serum Ca\(^{2+}\) concentrations.”

“trick the parathyroid into believing it were in a hypercalcemic milieu”
Calcimimetic upregulates Ca-receptor in renal failure

Calcimimetics decrease PTH mRNA – posttranslational effect (AUF1) ~ high P_i
(model of adenine nephropathy)

Calcium sensing receptor is regulated by vitamin D, but not by calcium

\[ 1,25(OH)_2D_3 \text{ increases } \text{Ca}^{++} \text{sensitivity of PTH secretion in HD patients} \]

- 1. increased Ca\(^{++}\) sensitivity of parathyroid
- 2. reduced active intestinal Ca transport

Argument for calcimimetic plus active vitamin D?
What triggers (secondary) hyperparathyroidism

- hyperphosphatemia $\rightarrow$ low ionised Ca$^{++}$
- lack of $1,25(OH)_2D_3$
- lack of 25(OH)D $\rightarrow$
  local production of $1,25(OH)_2D_3$ ?
- ionised plasma Ca$^{++}$
- FGF23/klotho – new players
Pathogenesis of secondary hyperparathyroidism – not only a trio (rewrite the textbooks)

Cunningham J., Kidn.Internat.(1999) 73, S59
Evidence of **circulating factor**


# hyp mouse (genetic analogue of XLH) →
**kidney transplantation**

*normal to hyp*

*hyp to normal*

→ **phosphaturia**

→ **unchanged phosphate excretion**

⇒ **conclusion:**

*not intrinsic defect of tubular epithelial cells, but circulating factor*
Both FGF 23 and FRP 4 are phosphaturic

With decreasing GFR –
increasing FGF23
despite no early increase in S-phosphate


conclusion: FGF23 mitigates hyperphosphatemia, but accentuates calcitriol deficiency
Role of FGF 23 in renal failure

elevated FGF 23 concentrations in renal failure

Anti-GBM-glomerulonephritis as model of chronic renal failure

FGF 23 ↑↑
inversely correlated to $1,25\text{(OH)}_2\text{D}_3 \rightarrow$
FGF23 inhibits $1^\alpha$ hydroxylase

Shimada, 2003
Prevention of PTH increase by diminishing dietary phosphate in proportion to loss of GFR

60 days low $P_i$ diet in patients with moderate renal failure

# initially:
- impaired intestinal calcium absorption
- reduced calcemic response to PTH
- low serum ionized calcium
- elevated PTH

# after the diet $\rightarrow$ all parameters returned to normal

Prior to parathyroidectomy correlation PTH and FGF 23 concentrations

FGF23 predicts need of parathyroidectomy = refractory to conventional treatment

C-terminal and intact FGF23 predict renal survival

Fliser,
FGF23 predicts survival in dialysis patients

Can one modulate FGF 23?
FGF23 responds to P-restriction and supplementation in human volunteers

Calcitriol iv ➔

*PTH ↓,*

*FGF23 ↑↑*

30 dialysis patients

3 x week 0.5-1.0 µg calcitriol iv for 6 months

• PTH decreased (p<0.001)

• FGF23 gradually increased (p<0.027)

$\Delta$ FGF23 correlated to

total calcitriol dose \( (r^2 0.147; p<0.036) \)

_Nishi, Nephron Clin.PRACT. (2005) c94_
Scenario in CKD:
S-Pi kept normal by increased fractional excretion of Pi (FePi) via elevated FGF23 at the price of lowering calcitriol

FGF 23 –
beyond calcium-phosphate metabolism!
**klotho mouse**

The first documented mammalian model for human aging that manifests multiple aging-like phenotypes in a single individual.

- Short lifespan
- Growth retardation
- Infertility
- Premature thymic involution
- Skin atrophy
- Muscle atrophy
- Arteriosclerosis
- Osteoporosis
- Pulmonary emphysema
- Ectopic calcification
- Motor neuron degeneration
- Cognition impairment
- Hearing disorder
Overexpression of Klotho prolongs life expectancy

*klotho* gene is “aging suppressor gene”
Klotho

• Mouse :
klotho -/- ageing
klotho overexpression extension of lifespan

• Humans :
polymorphisms of klotho gene correlated with lifespan osteoporosis stroke coronary disease

klotho -/- and FGF23 -/- → common signalling pathway?

- hyperphosphatemia
- hypercalciuria
- increased $1,25(OH)2D3$
- increased $1\alpha$ hydroxylase

Tsujikawa, Mol.Endocrinol.(2003) 17:2393
LETTERS

Klotho converts canonical FGF receptor into a specific receptor for FGF23

Itaru Urakawa¹, Yuji Yamazaki¹, Takashi Shimada¹, Kousuke Iijima¹, Hisashi Hasegawa¹, Katsuya Okawa¹, Toshiro Fujita², Seiji Fukumoto² & Takeyoshi Yamashita¹
Is hyperparathyroidism and disturbed Ca,Pi metabolism fully explained by known factors?

Further systemic and/or local factors operative in uremic bone disease
PTH excess and 1,25(OH)2D3 deficiency do not fully explain bone disease

Subtotally NX and PTX rats, replacement doses of rat 1,34 PTH and 1,25(OH)2D3

<table>
<thead>
<tr>
<th></th>
<th>sham-op + solvent (n=8)</th>
<th>NX-PTX + solvent (n=8)</th>
<th>NX-PTX + PTH+1,25 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteoclasts (per mm²)</td>
<td>0.5 ± 0.3</td>
<td>0.28 ± 0.2</td>
<td>0.23 ± 0.2</td>
</tr>
<tr>
<td>osteoblast surface (ObS/BS%)</td>
<td>0.8 ± 1.2</td>
<td>0.54 ± 1.0</td>
<td>1.67 ± 2.4</td>
</tr>
<tr>
<td>Osteoid thickness (µm)</td>
<td>3.19 ± 3.3</td>
<td>7.7 ± 1.8</td>
<td>7.0 ± 3.6</td>
</tr>
<tr>
<td>bone volume (BV/TV%)</td>
<td>19.2 ± 9</td>
<td>19.3 ± 9.9</td>
<td>34.9 ± 7.9</td>
</tr>
</tbody>
</table>

Thank you for your attention
Wer von allem etwas gibt, wird allen etwas geben

(he who gives a bit of everything, will give something to everyone)

J.W. von Goethe
Faust
(Schauspieldirektor)
FGF23 increases 1(alpha) hydroxylase in parathyroid gland

A role of FGF23 in the genesis of hyperparathyroidism?

Fukagawa, Kidn.Intern. (2006) 70:S3
Relation between serum-phosphate and PTH – Spanish multicentre study

S-phosphate (mg/dl)

PTH (pg/ml)

Cannata J, personal communication
Alteration of Parathyroid Gland Function

Progressive loss of kidney function
- ↓ 1α-Hydroxylase
- ↓ VDR Expression
- ↓ CaSR Expression
- Partial 1,25(OH)D resistance

Normal → Diffuse → Early Nodular → Nodular Hyperplasia → Adenomatous Hyperplasia

Progression to Renal Failure

Guidance for Evaluating Elevated PTH Levels

• Is it due to excess PTH secretion?
  – regulated by calcium via CaSR
  – hypocalcemia

• Is it due to excess PTH gene transcription?
  – regulated by vitamin D
  – regulated by calcium
  – serum calcitriol (1,25(OH)₂D) levels
  – vitamin D nutrition (25(OH)D)
  – serum calcium concentration

• Is it due to parathyroid gland enlargement from tissue hyperplasia?
  – regulated by calcium via CaSR
  – phosphorus via TGFα and p21
What triggers (secondary) hyperparathyroidism

- hyperphosphatemia $\rightarrow$ low ionised Ca$^{++}$
- lack of 1,25(OH)$_2$D$_3$
- lack of 25(OH)D $\rightarrow$
  local production of 1,25(OH)$_2$D$_3$
- ionised plasma Ca$^{++}$
- klotho
Plasma 1,25(OH)$_2$D$_3$ – independent predictor of coronary calcium by EBCT

- 283 high risk subjects
- 1,25(OH)$_2$D$_3$ by radioimmunoassay, coronary Ca by EBCT
- 1,25(OH)$_2$D$_3$ inversely correlated to calcium mass ($r=-0.19; p<0.001$)

*Doherty, Circulation (1997) 96:1477*
Calcium sensing receptor is regulated by vitamin D, but not by calcium


$\text{1,25(OH)}_2\text{D}_3$ increases Ca$^{++}$sensitivity of PTH secretion in HD patients


- increased Ca$^{++}$sensitivity of parathyroid
- reduced active intestinal Ca transport
argument for calcimimetic plus active vitamin D?
Effect of calcitriol on parathyroid cell proliferation index in vitro

$[^3H]$Thymidine incorporation (% of basal value)

- $10^{-10}$
- $10^{-9}$
- $10^{-8}$
- $10^{-7}$

Calcitriol (M)

$p < 0.05$

$p < 0.005$

Naveh-Many, JCI (1995) 96: 1786
Progression of secondary HPT -

\[ \Rightarrow \text{progressively higher doses of vitamin D required} \]

(decrease of vitamin D receptors)

Tominaga, Curr Opin Nephrol Hypertens (1996)5:336
Correlation: serum phosphate and cardiovascular disease – patients without chronic kidney disease

Tonelli, Circulation (2005) 112: 2627
Baseline coronary calcification score predicts survival in incident dialysis patients

Block, Kidn.Internat.(2007) 71: 438
Sevelamer vs calcium carbonate – similar outcomes

Change of coronary calcium in dialysis patients – similar with statin and sevelamer: is it cholesterol or phosphate?

DOQI guidelines (iPTH 150-300 pg/ml) do not guarantee normal bone turnover

Treatment with nicotinamide lowers S-phosphate in hemodialysis patients

1,25(OH)\(_2\)D\(_3\) is an important regulator of serum FGF\(_{23}\)

Liu,
1,25(OH)2D3 is an important regulator of FGF23 synthesis by osteoblasts

Calcitriol in patients not yet on hemodialysis – change of parameters of Ca,P metabolism

Calcitriol reduces mortality in patients not yet on hemodialysis

1418 VA patients with CKD3 or 4 and hyperparathyroidism
1.9 year follow-up
26% lower risk of death
(95%CI 5-42; p=0.016)

FGF23 concentrations increase as GFR values decrease
