Improving sHPT Treatment for Better Patient Outcomes

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Honoraries: Abbvie, Amgen, Ineos Healthcare, Fresenius, Genzyme/Sanofi, Hexal and Medice
sHPT: From Evidence back to Eminence?

Post- EVOLVE era

... fighting with the problem that we have only few high grade randomised studies with clinically relevant endpoints, and therefore – as 2009 – much will remain eminence based and not evidence based.
Background: Treatment of sHPT in dialysis patients is in motion

The mission

The tools

The results

and consequences

....
Multiplicity of hormonal disturbances early in CKD

\[\text{iPTH (pg/mL)} \quad 1,25\text{D (pg/mL)} \quad 25\text{D (ng/mL)}\]

*measured as 1,25D₃

\[\text{eGFR interval (mL/min/1.73 m}^2\text{)}\]

\[\geq 80 \quad 79–70 \quad 69–60 \quad 59–50 \quad 49–40 \quad 39–30 \quad 29–20 \quad <20\]

\[n=61 \quad n=117 \quad n=230 \quad n=396 \quad n=355 \quad n=358 \quad n=204 \quad n=93\]

\[†p<0.001\]

The facts: Increased risk of cardiovascular events early in CKD 3–4

Myocardial infarction

n=11,340 of 1,268,029 participants Alberta, Canada, eGFR 15–59.9 mL/min/1.73 m²

All-cause mortality

Especially pronounced at eGFR <45 mL/min/1.73 m²

The facts: Mortality is dramatically increased in dialysis patients

Cardiovascular risk factors are different in CKD

Classical risk factors
- Hypertension
- Hyperlipoproteinaemia
- Diabetes mellitus
- Smoking
- LV hypertrophy

Renal risk factors
- Hyperphosphatemia
- Calcium load
- sHPT
- Anaemia
- Micro inflammation
- Oxidative stress
- Malnutrition
- Acidosis
What can we change?

18% total mortality is related to CKD-MBD

*15–20% in general population


USRDS annual report at http://www.usrds.org/atlas.aspx
Regulation of serum–calcium–phosphate–PTH–homeostasis

Where do we start?
What should we be concentrating on?

• Phosphate (P)
• Calcium (Ca)
• Parathyroid hormone (PTH)
• Bone alkaline phosphatase (bAP)
• Bone morphology
Parameters:
Lowering of phosphate targets

• KDOQI 2002:
  1,13 – 1,78 mmol/L
  (3,5 – 4,5 mg/dL)

• KDIGO 2009:
• Reduce towards the normal range
Parameters:
Lowering of calcium targets, KDOQI 2002

- **6.2** ... calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L])

- **6.4** Total elemental calcium intake (including both dietary calcium intake and calcium-based phosphate binders) should not exceed 2,000 mg/day
Change in calcium targets 2002 — however, not without a long hard debate ...
• 1,500 mg elementary calcium daily led to a positive balance, which was increased by vitamin D

• As the calcium level cannot increase indefinitely, calcium must be deposited outside of the bone

Calcium distribution model

Calcium homeostasis (without perspiration)
Calcium balance in CKD 5

Neutral balance on vit D: 1,000 mg Ca/day

with active vit D

without active vit D

Calcium balance in CKD III/IV

- 6 children in CKD III/IV (Ø eGFR 29 mL/min/1.73m² BSA) on 2 calcium-containing diets (800 mg and 2000 mg/day) over 9 days.
- 48 hour urine collection, daily blood measurements in the morning.
- Faecal estimations on basis of neutral phosphate balance.
- No increase in calcium excretion in the urine

Spiegel DM, Moore RH. Positive Calcium Balance in CKD, ASN 2010, Denver/USA, TH-PO162
Medium sized arterial rings from patients in CKD 3-5D were cultivated in 4 mediums:

- Controls (Phos 1.0 m.mol/L + Ca 1.8 mmol/L)
- ↑ Phos (Phos 2.0 mmol/L + Ca 1.8 mmol/L)
- ↑ ↑ Phos (Phos 3.0 mmol/L + Ca 1.8 mmol/L)
- ↑ Phos und ↑ Ca (Phos 2.0 mmol/L + Ca 2.7 mmol/L)
- Examinations after 7, 14 and 21 days.

*Protein deficient nutritional solution*

Vessel calcification: Combination of phosphate and calcium worsens the situation

Significant less calcification in vessels from patients without CKD

Ca-loading tin the vessel wall (µg/µL)

- Normal: n = 6
- Pre-dialysis: n = 10
- Dialysis: n = 20

Ca x P = 5.4 mmol^2/l^2

Meaning of protective factors in CKD 5D

Loss of vessel wall smooth muscle cells via necrosis and apoptosis.

Cristaline apatite is normally transported out of the cells. However, calcification initiates if Matrix Gla Protein and Fetuin-A are deficient.

Even normal Ca-Phos-levels precipitate without these factors

Serum calcium is unreliable predicting calcium load

• n = 42 haemodialysis patients for 1 week

• Total group
  Serum calcium and calcium intake very poor correlation:
  \( r=0.14, \ p=0.39 \)

In everyday routine, we are blind to the calcium damage we are causing.

• PTH < 300 pg/mL:
  Corrected serum calcium and calcium poor correlation:
  \( r=0.38, \ p=0.1 \) (=correct estimation in 1 in 7 patients)
**Parameters:**

**Parathyroid hormone (PTH)**

**K/DOQI 2002**

- PTH levels <65 pg/mL: Normal bone or low turnover
- PTH levels >450 pg/mL: High turnover
- Levels in between did not have good predictive value
- Overall bone turnover could not be predicted in 30% of HD and 50% of PD patients

**KDIGO 2009**

- iPTH levels between two to nine times the upper normal limit for the assay

http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p6_comp_g10.htm
Forgotten parameters:
Bone alkaline phosphatase (bAP)

K/DOQI 2002
• High bAP: High bone turnover
• Low bAP: Adynamic bone disease.
• High bAP + high PTH increased sensitivity for diagnosis of high turnover
• Low bAP + low PTH increased sensitivity for diagnosis of low turnover lesions

KDIGO 2009
• Serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B)
Avoided Parameters:
Bone morphology

K/DOQI and KDIGO:

- Classification of renal osteodystrophy.
- Association of hypodynamic bone disease, prior to treatment with bisphonates.
So what should we be concentrating on for optimal results?

Isolated measurements of one parameter are not the whole story (EVOLVE)

It’s the mix

CKD-MBD is not just one parameter: Ca, P and PTH are associated with mortality

- n=7,970 European haemodialysis patients
- 21 months

Calcium

Resembles K/DOQI 2002

AP is also associated with CKD mortality

- n=1,158
- CKD 1–5
- Salem Veterans Affairs Medical Center
- 1990–2007
- +2 year follow up

Vitamin D levels are associated with mortality

Prospective observation of 444 patients with eGFR <60 mL/min/1.73 m², median follow-up 9.4 years

The tools
Therapeutic tools of sHPT: Vitamin D, selective VDRA and calcimimetics

VDRA = Vitamin D Receptor Activator

The tools of sHPT: VDR activators reduce mortality in incident dialysis patients


Total mortality

Cardiovascular mortality

n = 825 HD
90 day mortality
Nested case control

*p<0.05; R = reference

Odds Ratio

25D levels (ng/mL)

1,25D (calcitriol) levels (pg/mL)
**Therapeutic tools of sHPT:**
Selective VDRA, vitamin D

<table>
<thead>
<tr>
<th>Biological effect</th>
<th>Paricalcitol vs Calcitriol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH-suppression</td>
<td>1 : 3</td>
</tr>
<tr>
<td>Increase in serum calcium</td>
<td>1 : 10</td>
</tr>
<tr>
<td>Increase in serum phosphate</td>
<td>1 : 10</td>
</tr>
</tbody>
</table>

*Paricalcitol has a ~3-fold increased selectivity regarding PTH suppression (selective VDRA)*

14% less calcium absorption on selective VDRA compared with calcitriol

Double blind, randomised, double-dummy, crossover

Efficacy of controlling PTH:
unspecific active vitamin D?

- 0.5 µg oral calcitriol daily
- n=30, randomised, double-blind, CKD 3–5
- Study duration 8 months
- PTH reduction from 1.33 µg/L to 0.98 µg/L; p<0.01
- AP reduction from 201 U/L to 155 U/L; p<0.05

- However, serum calcium increased from 2.3 mmol/L to 2.5 mmol/L; p<0.01

### Efficacy of controlling PTH: unspecific 1-alpha-OH-vitamin D?

<table>
<thead>
<tr>
<th></th>
<th>'Responders' (n=18)</th>
<th>'Nonresponders' (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day 0</td>
<td>day 56</td>
</tr>
<tr>
<td>Intact PTH, pmol/l</td>
<td>23.1 ± 6.7</td>
<td>8.0 ± 4.3**</td>
</tr>
<tr>
<td>COOH-terminal iPTH, pmol/l</td>
<td>287.7 ± 38.0</td>
<td>187.2 ± 33.0***</td>
</tr>
<tr>
<td>Serum Ca(^2+), mmol/l</td>
<td>1.2 ± 0.02</td>
<td>1.3 ± 0.02***</td>
</tr>
<tr>
<td>Serum Ca, mmol/l</td>
<td>2.3 ± 0.05</td>
<td>2.6 ± 0.07***</td>
</tr>
<tr>
<td>Serum 1,25(OH)(_2)D(_3), pg/ml</td>
<td>9.1 ± 0.6</td>
<td>16.4 ± 1.9***</td>
</tr>
<tr>
<td>Serum 25(OH)D(_3), ng/ml</td>
<td>16.3 ± 3.2</td>
<td>16.4 ± 3.0</td>
</tr>
<tr>
<td>Serum inorganic phosphate, mmol/l</td>
<td>1.9 ± 0.1</td>
<td>2.23 ± 0.2</td>
</tr>
<tr>
<td>Serum albumin, μmol/l</td>
<td>561 ± 18</td>
<td>565 ± 17</td>
</tr>
<tr>
<td>Serum alkaline phosphatase, arbitrary units/l</td>
<td>273 ± 45</td>
<td>229 ± 40*</td>
</tr>
<tr>
<td>Serum Mg, mmol/l</td>
<td>1.38 ± 0.05</td>
<td>1.43 ± 0.07</td>
</tr>
<tr>
<td>Serum aluminum, mmol/l</td>
<td>1.05 ± 0.27</td>
<td>0.76 ± 0.15</td>
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</tbody>
</table>

*\(p<0.05; **p<0.003; ***p<0.001.\)

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PTH control: calcitriol versus paricalcitol

n=263 haemodialysis patients, randomised

Calcitriol 0.01 µg/kg
Paricalcitol 0.04 µg/kg

Very similar serum calcium levels

Calcification: Calcitriol (CTR) versus paricalcitol (PCT)

Aortic rings from 66 subtotal nephrectomised (5/6) rats (in vivo) and human vascular smooth muscle cells (in vitro).

Cultured for 9 days with Phos 3.3 mmol/L + TNF-α

Ratio PCT 4:1 CTR 240:80 ng/kg

Calcification: Calcitriol (CTR) versus paricalcitol (PCT)

Aortic rings from 66 subtotal nephrectomised (5/6) rats (in vivo) and human vascular smooth muscle cells (in vitro).

Cultured for 9 days with Lipo-polysaccharides

Ratio PCT 4:1 CTR
240:80 ng/kg

Calcification:
Calcitriol (CTR) versus paricalcitol (PCT)

Left:
Phos 3.3 mmol/L + TNF-α
CTR
PCT
Ratio PCT 4:1 CTR
240:80 ng/kg

Right:
Lipopolysaccharides
CTR
PCT

**Therapeutic tools of sHPT:**
Active vitamin D and calcimimetics

- These effects explain why cinacalcet is not advisable in non-CKD 5d patients

<table>
<thead>
<tr>
<th>Table 1. Comparison of Changes in Relevant Serum and Urine Measurements Upon Administration of Cinacalcet Versus Activated Vitamin D Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cinacalcet</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serum calcium</td>
</tr>
<tr>
<td>Serum phosphorus</td>
</tr>
<tr>
<td>Serum PTH</td>
</tr>
<tr>
<td>Serum FGF-23</td>
</tr>
<tr>
<td>Serum calcitriol</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
</tr>
<tr>
<td>Urine calcium</td>
</tr>
<tr>
<td>Urine phosphorus</td>
</tr>
</tbody>
</table>
**Tools:** Selective VDRAs are not identical to calcimetics regarding phosphatoninins

- Phosphatonins: PTH and FGF23 + Klotho

- PTH + FGF23 increase phosphaturia (good guys).

- Yes, both VDRA and calcium sensitizers suppress PTH.

- *But calcium sensitizers also suppress FGF23 – whereas VDRAs augment FGF23.*
And we are still exploring FGF23 ...

- FGF23 is the first parameter to increase in the course of CKD
- FGF23 can lead to myocardial hypertrophy and thus increase mortality
- Feedback loops:
  - FGF23 suppresses calcitriol
  - Calcitriol stimulates FGF23
  - Calcitriol stimulates Klotho
  - FGF23 subdues Klotho
  - PTH stimulates FGF23

And as more results come in, we shall improve are therapies.

The clinical results
Results:
sHPT treatment combination options

Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the
treatment of secondary hyperparathyroidism in patients receiving
haemodialysis: results of the IMPACT SHPT study

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**IMPACT:**

iPTH course

n = 211 randomised HD patients

**Serum Calcium**
- Paricalcitol / Cinacalcet
- IV: +0.16 / −0.23 mmol/l
- Oral: 0.10 / −0.23 mmol/l

**Serum phosphate**
- Paricalcitol / Cinacalcet
- IV: +0.01 / −0.01 mmol/L
- Oral: +0.23 / +0.01 mmol/L

## IMPACT: Doses

<table>
<thead>
<tr>
<th>Mean doses / 28 weeks</th>
<th>IV stratum</th>
<th>Oral stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paricalcitol</td>
<td>6.5 µg IV</td>
<td>5.7 µg oral</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>49.1 mg oral</td>
<td>33.7 mg oral</td>
</tr>
</tbody>
</table>

IMPACT:
Primary endpoint iPTH reduction

IMPACT:
Secondary endpoint – Quality of Life

Poster FR-PO1664, ASN Congress, Philadelphia
Therapeutic tools of sHPT: Parathyroidectomy

n=150 HD patients
Retrospective data bank
1993–2009
Emory University, Atlanta vs USRDS

Aim: intraoperative PTH 100 pg/mL

Mean Post-op PTH = 301.2 ± 285.7 pg/ml
Therapeutic tools of sHPT: Parathyroidectomy

Cumulative total survival

Therapeutic tools of sHPT: Parathyroidectomy

Cumulative cardiovascular survival

Therapeutic tools of sHPT: “High level” parathyroidectomy

The vast majority do not have access to such specialized techniques

Therapeutic tools of sHPT: Standard total parathyroidectomy +/- auto-implant (AI)

Systematic removal of at least four glands (TP) – AI in 20 patients:

- Immediate normalization of iPTH level in 11/20 TP cases
- Hypoparathyroidism in 4/20
- Persistent HPT in 5/20
- One year: Slight increase in hypoparathyroidism and 1/20 (5%) recurrence of the disease

One-year TP + AI results showed a similar percentage of euparathyroidism, however a higher longterm recurrence rate in 4/20 (20%).

Thus, parathyroidectomy is only a last resort
Therapy algorithm for PTH correction

CKD 3–5 (nondialysis)
- Parathyroidectomy
- Paricalcitol (replacing act. vit. D)
- Low dose active vitamin D
- Phosphate binder
- Nutrition, native vitamin D

CKD 5(D)
- Parathyroidectomy
- Paricalcitol (replacing act. vit. D) / cinacalcet
- Low dose active vitamin D
- Phosphate binder
- Nutrition, native vitamin D, dialysis
Paricalcitol associated with improved survival

1999-2004

Dialysis Clinic Inc.
- non profit organisation

Calcitriol n= 3212
Paricalcitol n= 2087

Tentori F et al. Kidney Int. 2006;70(10): 1858-1865
Reduction in haemodialysis mortality is a multimodal success
Yes, we do not have THE definitive study...

... especially as our definitions of good and bad are in flux due to the complexity of body responses.

But we have gained insights that were not imaginable just 12 years ago.
CKD-MBD – this story will continue…

Thank you for your attention!