Treatment Options for Chronic Kidney Disease: Metabolic Bone Disease

Goce Spasovski, R. Macedonia

Budapest, August 29, 2011
Session Objectives

- Definition of the problem of CKD-MBD
- Clinical relevance and consequences
  - increased morbidity and mortality
- Current therapeutical options-modification
  - Calcium and phosphate levels (bone)
  - Calcifications (vessels)
  - CVDs (outcome)
  - phosphate binders

New Strategies in Treatment of Mineral and Bone Disorders and Associated Cardiovascular Disease in Patients with Chronic Kidney Disease

Goce Spasovski*
Mineral & Bone Disorder (MBD)
Systemic Complication in CKD

- Mineral
- Hormonal
- Bone abnormalities,
- Vascular calcifications
- Soft tissue calcifications

CVD, fractures, mortality
Pathophysiology of CKD - MBD

PARATHYROID GLAND

BONE resorption

200 mg/day Resorption
150 mg/day Formation

200 mg/day

1,25(OH)2D3↓

Ca ++ PTH↑

PO4↓

Ca ++ PTH↑

PO4↓

800 mg/day Absorption

1200 mg Daily food

PO4↓ abs. 800 mg

400 mg Faecal excretion

INTESTINE

BLOOD

150 mg/day

KIDNEY (RENAI FAILURE)

Vascular calcification

Ca reabs.↑

α hydroxylase↑

PARATHYROID GLAND

BLOOD

FOOD

FGF-23 Regulation of Phosphorous Homeostasis

- **Bone**: 
  - ↑Serum Phosphorous

- **Kidney**: 
  - ↓P reabsorption
  - ↑P excretion in urine
  - ↓1,25(OH)$_2$D$_3$

Adapted from Stubbs J, et al. *Semin Dial. 2007;20:302-308*
Changes in FGF-23 Levels With Decline in Kidney Function

Changes in PTH and 1,25(OH)$_2$D$_3$ Levels With Decline in Kidney Function

Median Values of Serum 1,25(OH)$_2$D$_3$ and iPTH by GFR

- CKD 2
- CKD 3
- CKD 4 & 5

GFR (mL/min)

iPTH (pg/mL)

1,25(OH)$_2$D$_3$ (pg/mL)

N = 1,814

iPTH = intact PTH; GFR = glomerular filtration rate.
Mineral Metabolism and Mortality Risk in the DOPPS

Disorders of mineral metabolism are associated with increased mortality

<table>
<thead>
<tr>
<th>Component</th>
<th>K/DOQI Guidelines</th>
</tr>
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<tbody>
<tr>
<td>P</td>
<td>3.5 – 5.5 mg/dL (1.1 – 1.8 mmol/l)</td>
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*National Kidney Foundation K/DOQI (Kidney Disease Outcome Initiative)

The K/DOQI guidelines have become widely accepted and are basis of many national treatment guidelines in Eastern Europe
Mortality Risk Varies According to Number of Laboratory Targets* Achieved Concurrently

\[ iPTH & Ca \] & \[ iPTH & P \] & \[ Ca & P \] & \[ P \] & \[ iPTH \] & \[ Ca \] & \[ None \]  
<table>
<thead>
<tr>
<th>Relative Hazard of Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 22,937</td>
</tr>
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</table>

Bone as primary reservoir of calcium & phosphorus

<table>
<thead>
<tr>
<th></th>
<th>% of total body Ca</th>
<th>% of total body PO₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>99 %</td>
<td>29 %</td>
</tr>
<tr>
<td>Intracellular</td>
<td>0.9 %</td>
<td>70 % (exch.)</td>
</tr>
<tr>
<td>Interstitial</td>
<td>0.075 %</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.025 %</td>
<td>0.9 %</td>
</tr>
</tbody>
</table>

Consequences of Elevated Serum Phosphorus

Pi → ↑ PTH Secretion → Parathyroid Cell Growth → HPTH → Treatment → ABD → ↑ Morbidity & Mortality

Ca++ ↓ → PTH resistance
Calcitriol ↓ → Calcitriol resistance

Increased Ca×P & risk of metastatic calcifications

Bone biopsy as a diagnostic tool in the assessment of renal osteodystrophy

G.B. SPASOVSKI

Department of Nephrology, Clinical Center Skopje, University of Skopje - Macedonia
Bone Histology in ROD

- Osteitis Fibrosa
- Mixed lesion
- Adynamic bone disease
- Osteomalacia
Changing Spectrum of ROD

• Earliest reports
  • HPTH – most prevalent, followed by OM
    • Insufficient treatment of sHPTH
    • Vitamin D deficiency
    • Al intoxication

• Last two decades
  • ABD
    • Older age of the patients
    • Diabetes
  • Calcium containing phosphate binder
  • Vitamin D treatment
  • High calcium dialysate concentration
Adynamic Bone Disease - bone and beyond

![Graph showing the evolution of ROD distribution pattern over time]

**Evolution of ROD distribution pattern over time**

- Mixed lesions
- Osteitis fibrosa
- ABD
- Osteomalacia

Spectrum of Renal Bone Disease in patients with end-stage renal bone disease not yet in dialysis

- Normal bone: 38%
- Adynamic bone: 23%
- Osteomalacia: 12%
- Mixed lesion: 18%
- Hyperpara: 9%

Prospective, Non-randomized, Macedonian Population
N = 84 patients
Histomorphometric criteria according to:
Salusky et al., Kidney Int., 33, 1988
Parfitt et al., Calcif Tissue Int 42, 1988
Physiopathology of Adynamic Bone

Down regulation of PTH receptor
Insufficient PTH levels
Osteoblastic dysfunction

Relative hypoparathyroidism

Decreased BFR

Better Pi control
Diabetes
Older age
Malnourishment
Ca receptor expression

Extracellular Ca++

Ca load: Ca based binders
HD & CAPD dialysis fluid Ca conc.

Vit.D treatment
VDR poly-morphism
VDR expression

Diabetes
Older age
Male gender
Uremic toxins
Growth factors
Al + Fe↓
Vit.D treatment

Al + Fe↓
Mg++

Vit.D treatm.
Clinical Relevance and Consequences

Association in CKD patients between:

**MBD (abnormal mineral metabolism & bone health)**

&

Fractures - decreased quality of life

**VC** - most important cause of morbidity

**CVD** - significant mortality

Bone health and vascular calcification relationship in chronic kidney disease
Spasovski G. *Int Urol Nephrol* 2007;39:1209–1216
CKD - MBD: Bone lose & fracture

United States Renal Data System data (300,000 patients)
- The relative risk for hip fracture in dialysed patients is 4.4 times (men and women) that of age-matched controls.

Disordered bone remodelling can induce vascular calcification.

High bone turnover leads to release of Ca + P from bone. Low bone turnover hinders their emplacement in bone. Result is cardiovascular and soft tissue calcification.

Arterial Calcifications and Bone Histomorphometry in ESRD

*Determined by ultrasonography


n = 58
VSMCs can Transdifferentiate into Osteoblasts

CKD - MBD: Vascular calcifications

- More rapid rate of progression (Tamashiro M et al., AJKD, 2001, 38:64-9)
Arterial calcification increases mortality risk

Presence and extent of vascular calcifications predict cardiovascular and all-cause mortality in dialysis patients.

Prospective trial in 110 dialysis patients assessing cardiovascular (CV) calcifications, mean follow up 53 months. Endpoints: All cause and CV mortality using univariate and multivariate survival analysis. Blacher et al. Hypertension 2001;38:938–942
Patients with cardiovascular calcifications had a higher mortality risk than non-calcified patients.

Follow up of a randomized, prospective, open label, multicenter study over a median of 44 months (RIND). 127 patients randomized to either sevelamer or Ca. Prespecified secondary endpoint. Block GA et al. *Kidney Int* 2007;71:438-441
Increased CVD Morbidity & Mortality

CVD = cardiovascular disease
GP = general population

Foley FN et al. AJKD 1998;32:S112-S119
Increased serum phosphorus negatively impacts the mortality of CKD patients not on dialysis.

The association between higher phosphate levels and mortality risk was present among patients with absolute serum phosphate levels in the high-normal range.

Management of Hyperphosphatemia

Serum phosphorus not sufficiently controlled through dialysis and diet
Almost all dialysis patients need phosphate binders

1. Dietary phosphorus restriction
2. Dialysis
3. Phosphate binders

New Strategies in Treatment of MBD and Associated Cardiovascular Disease in Patients with CKD
NKF - K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.
K/DOQI* guidelines for Bone Metabolism and Disease / Dislipidemia in Chronic Kidney Disease

<table>
<thead>
<tr>
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<tr>
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*National Kidney Foundation K/DOQI (Kidney Disease Outcome Initiative)

The K/DOQI guidelines have become widely accepted and are basis of many national treatment guidelines in Eastern Europe.

K/DOQI* guidelines for Bone Metabolism and Disease in Chronic Kidney Disease

If your patient has...

- Elevated phosphorus level
  - > 5.5 mg/dL (> 1.8 mmol/l)

and

- Hypercalcaemia
  - > 10.2 mg/dL (> 2.7 mmol/l)

- Low PTH level
  - < 150 pg/mL on 2 consecutive measurements

- Severe calcifications
  - (vascular and/or soft tissue)

Choose as primary therapy...

- Non Ca based
- Calcium based binder
  - ≤ 1500 mg elemental calcium per day
- Non Ca based

Sevelamer remains first line treatment option (Lanthanum, MCI 196)
Ca based binders contraindicated in low PTH, high Ca, severe calcifications

Calcium restriction in KDIGO

Calcification: 51% - 83%¹,²,³
Persistently Low PTH: 57%²
Hypercalcemia: 16% - 54%²,³,⁴
ABD: 5% - 40% CKD 3/4⁶

Recommended for Calcium Restriction

References:
⁵Andress D. Kidney Int. 2008;73:1345-1354
⁶KDIGO. Kidney Int. 2009; 76 (Suppl 113):S1-S130
Mineral Metabolism and Mortality Risk in the DOPPS

Hyperphosphatemia is the most frequent abnormality.

Around 90% of dialysis patients on phosphate binders, still 35% out of KDOQI targets.

Types of Phosphate Binders

- **Calcium-based**
  - Calcium carbonate and acetate (Mg)—effective at binding dietary phosphate, but associated with vascular-soft tissue calcification

- **Metal-based** - (non-calcium)
  - Aluminium—effective at binding dietary phosphate, but long-term toxicity shown
  - Lanthanum—systemically absorbed; bone deposition (no toxicity) has been demonstrated

- **Renagel® (sevelamer) — (non-calcium)**
  - Calcium-free, metal-free phosphate binder. The only non-absorbed phosphate binder. Does not expose patients to increased risk of vascular and soft tissue calcification

- **MCI-196 — (non-calcium)**
  - Calcium & metal-free non-absorbed phosphate binder. Efficient and safe treatment, no risk of soft and VC

Mineral Metabolism and Mortality Risk in the DOPPS

Disorders of mineral metabolism are associated with increased mortality

Vascular events in healthy older women on calcium supplementation


Myocardial infarction and the composite endpoint occurred more frequently in the calcium group
## Risk Factors Associated With Cardiac Calcification in Young Dialysis Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>coronary calcification (n=14)</th>
<th>no calcification (n=25)</th>
<th>( P ) - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca from calcium binders (mg/day)</td>
<td>6456 ± 4278</td>
<td>3325 ± 1490</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum Ca (mmol/L)</td>
<td>2.4 ± 0.2</td>
<td>2.28 ± 0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum P (mmol/L)</td>
<td>2.2 ± 0.3</td>
<td>2.0 ± 0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Ca ( \times ) P (mmol(^2)/L(^2))</td>
<td>5.2 ± 0.9</td>
<td>4.5 ± 1.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 ± 3</td>
<td>15 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean duration of dialysis (years)</td>
<td>14 ± 5</td>
<td>4 ± 4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- 39 HD patients 7 – 30 years
- 60 controls 20-30 years
- EBT scans at baseline and after 18-24 months

NEW THERAPEUTIC APPROACH

PREVENTION OF COMPLICATIONS OF THERAPY

OF HYPERPHOSPHATEMIA & MBD & ROD & VC IN CKD PATIENTS
Reducing Calcium Load With a Calcium-free Phosphate Binder

**Phosphate binder:** 3-5 g/day (20-30% resorption) ≈ 1300 mg/day

**Dialysate:** 1.25 mEq/L - net influx ≈ 100-150 mg calcium / HD

**Diet:** intake ≈ 600 mg calcium per day


Data on file, Genzyme Corporation

Mortality effect of coronary calcification and phosphate binder choice

Follow up of a randomized, prospective, open label, multicenter study over a median of 44 months (RIND). 127 patients randomized to either sevelamer or Ca. Prespecified secondary endpoint. Block GA et al. Kidney Int 2007;71:438-441

Treatment with sevelamer was associated with a significant survival benefit. There were 11 deaths in the sevelamer and 23 in the Calcium group.

<table>
<thead>
<tr>
<th>Months</th>
<th>Calcium</th>
<th>Renagel</th>
<th>P=0.016</th>
</tr>
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<tbody>
<tr>
<td>0-6</td>
<td>67</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>63</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>12-18</td>
<td>60</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>55</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>24-30</td>
<td>45</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>30-36</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>36-42</td>
<td>5</td>
<td>4</td>
<td></td>
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<tr>
<td>42-48</td>
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<tr>
<td>48-54</td>
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<td></td>
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<tr>
<td>54-60</td>
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<td></td>
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<tr>
<td>60-66</td>
<td></td>
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</tr>
</tbody>
</table>

No. at Risk

Calcium: 67, 63, 60, 55, 45, 22, 5
Renagel: 60, 57, 57, 51, 47, 25, 4
Results of the DCOR trial were inconclusive for the primary end-point of all-cause mortality across the entire patient cohort (RR 0.91; p = 0.3)

DCOR: Mortality risk reduction with Renagel®

A mortality benefit for patients treated with Renagel® was shown in subgroups:
Patients older than 65 (predefined) and patients on study for more than 2 years

### Hospitalisation rate by binder choice

<table>
<thead>
<tr>
<th>Rate per patient-year</th>
<th>Sevelamer</th>
<th>Calcium</th>
<th>HR*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hospitalisations</td>
<td>0.96</td>
<td>0.97</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Multiple hospitalisations</td>
<td>1.70</td>
<td>1.91</td>
<td>0.89</td>
<td>0.02</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>12.3</td>
<td>13.9</td>
<td>0.88</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Almost every patient was hospitalised once per year. Renagel® treated patients were hospitalized less frequently and spent less time in the hospital.


*Adjusted for demographic variables and prestudy cardiovascular comorbidity*
Calcium-treated subjects had decreased bone density

The lower time averaged PTH achieved in calcium-treated subjects is a likely explanation for the changes observed in bone attenuation.

Post-hoc analysis of a randomized, prospective, open label, multicenter study over one year (Treat to Goal) evaluating EBCT scans of vertebrae.

Raggi P et al. J Bone Miner Res. 2005;20:764-72. *p=0.01 Sevelamer vs. Calcium, †ns
Effects of Sevelamer Hydrochloride and Calcium Carbonate on ROD in HD Patients

Patients with either low bone turnover at baseline and those evolving toward low bone turnover at follow-up in both study groups

Evolution of renal bone disease of all patients after one year of treatment with either lanthanum or calcium carbonate

Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year treatment with lanthanum carbonate and after two years of follow up.

Bone lanthanum concentrations of patients receiving lanthanum carbonate (solid circle) and calcium carbonate treatment (open circle) for 12 months, followed by 2 years of treatment with calcium carbonate.

There is a slow release of lanthanum from its bone deposits 2 years after the discontinuation of the treatment and no association with aluminium-like bone toxicity.

Effects of Treatment of Renal Osteodystrophy on Bone Histology

Baseline 1 year 2 years

Higher activation frequency (bone turnover) in patients who were treated with lanthanum carbonate after 1 year.

Higher bone volume (tissue volume) in patients who were treated with lanthanum carbonate after 2 years.

Analysis of survival in a 2-year comparative study of lanthanum carbonate vs. standard therapy

Figure 1. Survival probability: lanthanum carbonate versus standard therapy. LC, lanthanum carbonate; Standard, standard therapy.

Figure 2. Survival probability in patients aged >65 years: lanthanum carbonate versus standard therapy. LC, lanthanum carbonate; Standard, standard therapy.

New Strategies in Treatment of MBD and Associated CVD in Patients with CKD

Spasovski G, Recent Patents on Cardiovascular Drug Discovery, 2008; 3(3):222-8

- **Cost-effectiveness** - *Good value for money!*


  *Lack of outcome data favorable enough to justify widespread utilisation*


  The yearly cost of implementation of the K/DOQI guidelines for 416 pts. at this center (University of Ottawa) was estimated at $500,605 (American dollars). Given the significant cost, widespread adoption of the K/DOQI CPGs for Bone Metabolism and Disease should await the publication of compelling data demonstrating significant improved outcomes in patients treated with sevelamer.
Economic evaluation of sevelamer in patients with end-stage renal disease

Braden Manns¹,²,³, Scott Klarenbach³,⁴, Helen Lee¹, Bruce Culleton², Fiona Shrive¹ and Marcello Tonelli³,⁴,⁵,⁶

Conclusions. The cost per QALY gained for treating all dialysis patients with sevelamer exceeds what would usually be considered good value for the money. While the high cost per QALY was in part due to the inclusion of the costs of dialysis and transplant in the analysis, the cost per QALY gained remained relatively unattractive even when these costs were excluded. Although a lower cost per QALY gained is realized when only patients older than 65 years are treated, this strategy remains economically unattractive, particularly given the uncertainty of clinical benefit in this group.
Type of treatment for hyperphosphataemia and related outcomes

The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis

Sophie A. Jamal¹, David Fitchett², Charmaine E. Lok³, David C. Mendelssohn⁴ and Ross T. Tsuyuki⁵

**Background.** The effects of calcium compared with non-calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification in patients with chronic kidney disease (CKD) are unknown.

**Methods.** To address this question, we conducted a systematic review. We electronically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. We identified 160 potential studies and included 8 randomized trials. Eligible studies, determined by consensus using predefined criteria, were reviewed, and data were extracted onto a standard form.

**Conclusion.** Despite the trends observed, we did not find a statistically significant difference in cardiovascular mortality and coronary artery calcification in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders. However, the data are limited by the small number of studies and the confidence intervals do not exclude a potentially important beneficial effect. Therefore, further randomized trials are required.
A Review of Sevelamer Hydrochloride in End-Stage Renal Disease Patients on Dialysis

Goce Spasovski

Department of Nephrology, University of Skopje, Skopje, R. Macedonia. Corresponding author email: gspas@sonet.com.mk

Although KDOQI and KDIGO published CKD—MBD guidelines has clearly stated where calcium-based phosphate binders should not be used in D patients (hypercalcemia and low PTH) and where non-calcium-containing phosphate binders are preferred (patients with severe vascular and/or other soft tissue calcifications), the greatest controversy and disagreements within the nephrological community still exists upon the cost-effectiveness of non-calcium binder (sevelamer) use. Indeed, despite the evidence and recognised trend towards both a decrease in VC and CVD associated with sevelamer use, it is still an ongoing matter of debate. The magnitude of this controversy is increased when the issue of advanced medical and/or budgetary evaluation related to the implementation of clinical guidelines for CKD—MBD treatment is considered. Despite advocated use of sevelamer across a range of common clinical scenarios in CKD, its widespread utilization is challenged as exceeding what would usually be considered good value for money. If so, it is questionable whether the recommendations and suggestions from the guidelines should be followed, and further, do we need guidelines and innovative drugs for treatment of hyperphosphatemia? While awaiting the answer, as clinicians we should proceed with a treatment to “do no harm”, trying to at least limit the calcium exposure of our dialysis patients.
Cost-effective Reduction of Calcium Load and possible treatment of ABD as most prevalent ROD type

“Individualized program”

Dose reduction of the calcium phosphate binders 1-2 gr/day

Low-calcium dialysis bath 1.25 mmol/l
Lowered Dialysate Calcium in PD: Increased PTH and Bone Formation.
Haris A et al. Kidney Int 2006; 70(5):931-7

<table>
<thead>
<tr>
<th></th>
<th>Control Ca</th>
<th>Low Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>tCa (mM)</td>
<td>2.19 ± 0.08</td>
<td>2.18 ± 0.03</td>
</tr>
<tr>
<td>iCa (mM)</td>
<td>1.18 ± 0.01</td>
<td>1.15 ± 0.02</td>
</tr>
<tr>
<td>PO₄ (mM)</td>
<td>1.70 ± 0.12</td>
<td>1.72 ± 0.13</td>
</tr>
<tr>
<td>Mg (mM)</td>
<td>1.24 ± 0.06</td>
<td>1.22 ± 0.03</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>87.3 ± 11.4</td>
<td>76.5 ± 8.9</td>
</tr>
<tr>
<td>PTH (pM)</td>
<td>7.3 ± 1.6</td>
<td>9.4 ± 1.5</td>
</tr>
</tbody>
</table>

n = 9
n = 14
## Improvement of Bone and Mineral Parameters Related to ABD by Diminishing Dialysate Calcium

### Treatment of ABD with LCD and HCD

<table>
<thead>
<tr>
<th>Pre HD param.</th>
<th>LCD</th>
<th>HCD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>tCa</strong></td>
<td>2.44 ± 0.20</td>
<td>2.32 ± 0.19&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>tCa</strong></td>
<td>2.41 ± 0.19</td>
<td>2.34 ± 0.17</td>
</tr>
<tr>
<td>Post HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>iCa</strong></td>
<td>1.10 ± 0.09</td>
<td>0.97 ± 0.12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>iCa</strong></td>
<td>1.09 ± 0.08</td>
<td>0.91 ± 0.14&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>1.50 ± 0.51</td>
<td>1.58 ± 0.46</td>
</tr>
<tr>
<td><strong>Ca x P</strong></td>
<td>3.68 ± 1.35</td>
<td>3.52 ± 1.21</td>
</tr>
<tr>
<td><strong>iPTH</strong></td>
<td>38.6 ± 22.9</td>
<td>61.4 ± 43.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>pg/ml*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TAP</strong></td>
<td>59.5 ± 18.7</td>
<td>75.9 ± 26.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>U/L*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BAP</strong></td>
<td>23.4 ± 7.3</td>
<td>24.1 ± 15.9</td>
</tr>
<tr>
<td>U/L*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Vitamin K₂ Improves Bone Metabolism in HD pts. with a Low PTH**

40 HD pts with low intact PTH levels (<100 pg/ml) randomised into a vitamin K₂ group receiving oral menatetrenone (45 mg/day) for 1 year and a control group without vitamin K₂.

<table>
<thead>
<tr>
<th>Group</th>
<th>B-ALP (U/l)</th>
<th>intact-Osteocalcin (ng/ml)</th>
<th>NTX (nmol BCE/l)</th>
<th>intact-PTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
<td>3 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Vitamin K₂</td>
<td>18.3±5.5</td>
<td>17.9±6.0</td>
<td>22.1±10.9</td>
<td>25.9±14.1*</td>
</tr>
<tr>
<td>Control</td>
<td>19.3±7.6</td>
<td>20.5±10.3</td>
<td>20.4±8.8</td>
<td>20.6±8.6</td>
</tr>
<tr>
<td>Control</td>
<td>46.7±29.6</td>
<td>44.5±</td>
<td>43.8±</td>
<td>47.4±28.4</td>
</tr>
</tbody>
</table>
### K/DOQI* guidelines for Bone Metabolism and Disease / Dislipidemia in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>K/DOQI Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>3.5 – 5.5 mg/dL (1.1 – 1.8 mmol/l)</td>
</tr>
<tr>
<td>Ca x P</td>
<td>&lt; 55 mg²/dL² (&lt; 4.4 mmol²/l²)</td>
</tr>
<tr>
<td>PTH</td>
<td>150 – 300 pg/mL</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt; 100 mg/dL (&lt; 2.56 mmol/l)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt; 200 mg/dL (&lt; 5.12 mmol/l)</td>
</tr>
</tbody>
</table>

*National Kidney Foundation K/DOQI (Kidney Disease Outcome Initiative)

The K/DOQI guidelines have become widely accepted and are basis of many national treatment guidelines in Eastern Europe

---

Impact of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in a Large Dialysis Network

Ron Wald, MDCM, Francesca Tentori, MD, Hocine Tighiouart, MS, Philip G. Zager, MD, and Dana C. Miskulin, MD

Am J Kidney Dis 49:257-266. © 2007

Application of NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease: changes of clinical practices and their effects on outcomes and quality standards in three haemodialysis units

M. Dolores Arenas¹, Fernando Alvarez-Ude², M. Teresa Gil¹, Antonio Soriano¹, Juan José Egea¹, Isabel Millán¹, M. Luisa Amoedo¹, Salomé Muray¹ and M. Antonia Carretón¹


ACHIEVEMENTS IN CKD-MBD GUIDELINES TARGETS - IS THERE A PROGRESS IN THE IMPLEMENTATION PRACTICE

Spasovski G¹, Zdravkovska V², Zabzum M³, Antarorov R⁴, Ivanovski K⁵, Janakievska P⁶, Neskovski J⁷, Karceva-Sarajlia E⁸, Panova B⁹, Petrovska T¹⁰, Zulbeari L¹¹, Masin-Spasovska J¹, Taleska-Matovska N³, Gelev S¹

Implementation of CKD-MBD guidelines - IUN 2011.doc
K/DOQI guidelines achieved parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Guidelines</th>
<th>After Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.40 ± 0.66</td>
<td>9.33 ± 0.64</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.49 ± 1.35</td>
<td>5.34 ± 1.28</td>
</tr>
<tr>
<td>Ca × P product (mg²/dL²)</td>
<td>51.51 ± 12.73</td>
<td>49.74 ± 12.12</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>259.41 ± 248.31</td>
<td>241.48 ± 214.95</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Serum PTH (pg/ml)</th>
<th>Mean ± SD</th>
<th>% of patients between 150 and 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-K/DOQI (2003)</td>
<td>201.4 ± 43.1</td>
<td>25.6</td>
</tr>
<tr>
<td>Post-K/DOQI (2004)</td>
<td>311.8 ± 64.5</td>
<td>18.7</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum calcium (mg/dl)</th>
<th>Mean ± SD</th>
<th>% of patients between 8.4 and 9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-K/DOQI (2003)</td>
<td>9.7 ± 0.3</td>
<td>38.7</td>
</tr>
<tr>
<td>Post-K/DOQI (2004)</td>
<td>9.4 ± 0.2</td>
<td>46.6</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum phosphate (mg/dl)</th>
<th>Mean ± SD</th>
<th>% of patients between 3.5 and 5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-K/DOQI (2003)</td>
<td>4.8 ± 0.2</td>
<td>56.9</td>
</tr>
<tr>
<td>Post-K/DOQI (2004)</td>
<td>4.9 ± 0.3</td>
<td>56.2</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>2009</th>
<th>2005</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca (mM/L)</td>
<td>2.30±0.24</td>
<td>2.36±0.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ca (2.1 - 2.6)</td>
<td>79.0</td>
<td>67.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P (mM/L)</td>
<td>1.49±0.41</td>
<td>1.64±0.61</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P (1.1 - 1.8)</td>
<td>64.9</td>
<td>59</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ca x P</td>
<td>3.44±1.05</td>
<td>3.79±1.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ca x P (&lt;4.4 mM²/L²)</td>
<td>80.6</td>
<td>71.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>PTH</td>
<td>323.3±363.8</td>
<td>437.3±611.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PTH (150 - 300 pg/ml)</td>
<td>35.1</td>
<td>17.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
### Treatment options

#### Intravenous vitamin D preparations (%)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>12.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>44.1</td>
<td>48.2</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>35.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Never used</td>
<td>36.8</td>
<td>40.1</td>
</tr>
</tbody>
</table>

#### Phosphate binders (%)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>30.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>51.9</td>
<td>50.7</td>
</tr>
<tr>
<td>Aluminum based</td>
<td>7.0</td>
<td>5.7</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>38.6</td>
<td>43.5</td>
</tr>
<tr>
<td>Cinacalcet (%)</td>
<td>0</td>
<td>6.3</td>
</tr>
</tbody>
</table>

**Dialysate calcium (mEq/L)**

- Pre-K/DOQI (2003): $2.57 \pm 0.28$
- Post-K/DOQI (2004): $2.58 \pm 0.28$

#### Phosphate binders

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-containing (mg Ca/day)</td>
<td>$891.9 \pm 665.5$</td>
<td>$565.5 \pm 550.0$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sevelamer (800mg tablets/day)</td>
<td>$4.8 \pm 4.4$</td>
<td>$7.5 \pm 4.6$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium in dialysate (mEq/L)</td>
<td>27.2</td>
<td>50.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of patients with Ca 2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2009</th>
<th>2005</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca dialysate (mM/L)</td>
<td>$1.64 \pm 0.14$</td>
<td>$1.72 \pm 0.12$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ca dialysate 1.25</td>
<td>3.7</td>
<td>6.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ca dialysate 1.5</td>
<td>38.6</td>
<td>29.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ca dialysate 1.75</td>
<td>57.7</td>
<td>64.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Calcium carbonate (g/day)</td>
<td>$2.77 \pm 1.71$</td>
<td>$3.06 \pm 1.54$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>90.3</td>
<td>95.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Vitamin D (meg/week)</td>
<td>$0.63 \pm 0.85$</td>
<td>$0.98 \pm 0.94$</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Conclusion from the KDOQI based studies

- The individualisation of the CKD-MBD management may be successful even in the absence of modern new treatment possibilities.

- Nephrologists should ask for advanced treatment options in accordance with the guidelines at least for a small subset of patients where current standard therapy does not work.

- Implementation process should be continuous and self-monitored at least through surveys.

- Judicious treatment could be a better option than overzealous treatment in order to “do no harm” for the patients’ health.
Modification of current therapeutic options in pts. with low PTH - ABD

- **Avoid hypoparathyroidism 🧐**
- Avoid high-dose vitamin D
- Avoid high-dose oral calcium
- Avoid high-Calcium dialysate
- **Use low-Ca dialysate !**
- **Use Vit. K₂ !**
Summary: Treatment of MBD in CKD

- An aggressive treatment of hyperphosphatemia with Ca based P-binders might lead towards an opposite effect:
  - hypoparathyroidism, hypercalcemia, calcifications

- An individualised treatment and prevention of complications of therapy preserving bone and vascular health:
  - Calcium phosphate binders (as less as possible / 1-2 g/day)
  - Low-calcium dialysis bath (1.25 mmol/l)
  - Vitamin K₂
  - Non Ca-based P binders in pts at risk for fractures & VC & CVD
  - Calcimimetics & Vit.D analogs - no other armamentarium is available
Treat the Hyperphosphatemia & Bones in order to save blood vessels & the Heart!