CARDIOVASCULAR DISEASE RELATED MORTALITY IN CKD: REVISITING THE ROLE OF VITAMIN D, CALCIMIMETICS, ALKALINE PHOSPHATASE, AND MINERALS

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Thank You so much. Mr Chairman, ladies and gentlemen,
CKD-MBD – a unifying concept or an unsolved puzzle?

- Bone Disorders, Mineral Abnormalities and Vascular Calcification are three closely interrelated conditions in patients with Chronic Kidney Disease.

during the next 15 minutes I will review the very complex issue, the most complex definition for sure in nephrology that is CKD-MBD. Although the components of CKD and MBD are very common and of potential clinical relevance and are very closely interrelated, it looks like a puzzle. Although we can identify most pieces of the puzzle, we cannot fit some of them especially those in the middle that are most clinically relevant.

Pathways of CKD-MBD

We have a clear pathway of CKD-MBD. Although we don’t have enough data we can identify the mineral abnormalities, we can identify calcification, renal osteodystrophy but we don’t have enough evidence to prove that – especially in the last part that is morbidity and mortality.
List of disorders related to CKD-MBD

1. Calcitriol deficiency
2. 25(OH)D deficiency
3. Hyperparathyroidism
4. Low PTH
5. Hyperphosphatasemia
6. Elevated FGF-23
7. High-turnover bone disease
8. Adynamic bone disease
9. Osteoporosis
10. Vascular calcification
11. Hyperphosphatemia
12. Hypophosphatemia
13. Hypercalcemia
14. Hypocalcemia
15. (Hypomagnesemia)

Two years ago doctor Kalantar-Zadeh identified a list of 14 disorders related to CKD-MBD. I won’t be able to review all of them but I will address the problem of the deficiency of vitamin D, both 25 and 1, 25, also the high PTH and low PTH conditions, hyperphosphatemia, hypophosphatemia, high calcium, low calcium and hyperphosphatasemia.

Prevalence of abnormal serum PTH, calcium and phosphorous levels increase with decline in kidney function

With the declining renal function, the prevalence of the abnormal serum PTH is increasing and this is one of the earliest abnormalities seen in our patients.
There is a close relation between increased PTH and low levels of both 25 and 1, 25 dehydroxy vitamin D. In fact, most patients in stage 3 or later of CKD have at least vitamin D insufficiency or even deficiency.

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Low vitamin D is a risk factor of cardiovascular events and mortality

There is a close relation between low vitamin D and cardiovascular events and mortality. It was shown not only in CKD but also in patients without renal impairment, as is shown on the slide these are the data from the Framingham Offspring study.

Slide 8
Vitamin D status in CKD affects both renal and patient survival

![Renal and patient survival curves by presence of 25D deficiency](image)


It was also nicely shown for patients with CKD that vitamin D status can affect both patient and renal survival.

Slide 9

Trade-off effect of therapeutic vitamin D on biochemical parameters of SHPT

But vitamin D as a drug is a double-edged sword because on the one hand it can decrease the level of PTH but on the other hand, it increases the levels of calcium and phosphate thereby may promote vascular calcifications. It’s difficult to assess the real role of vitamin D even if we take into account the other actions of vitamin D like its inflammatory, antioxidative or immunomodulatory effects.

Slide 10
Role of vitamin D in vascular calcification: bad guy or good guy (or both)?

Therefore, vitamin D is both a bad guy and a good guy and it depends on the dose. It can inhibit and promote vascular calcification depending on the dose.

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Are all vitamin D metabolites and analogues equal?

There are some vitamin D metabolites and vitamin analogues, also known as vitamin D receptor stimulators that are probably less hypercalcaemic and thereby it can explain the effect known from the retrospective studies, the most famous the one from Teng and co-workers, that paricalcitol, this is a synthetic analogue of vitamin D, can be linked to lower mortality than administration of calcitriol but the problem is that most of the studies were retrospective.

Slide 12
Disparate results from studies analyzing the associations between active vitamin D sterols and mortality

Both of the studies showed in fact, that there are associations between active vitamin D sterols and mortality, not all of them. In one of the studies it was found that after appropriate adjustment for comorbidities and baseline laboratory values this relation disappeared.

Vitamin D, cardiovascular disease and other effects in CKD – strength of evidence

In fact, we don’t have such strong evidence to support the role of vitamin D because we have many studies focused on biochemical endpoints, we have only a few looking at intermediate endpoints like bone histology or vascular calcification but we don’t have those looking at progression of CKD and especially on cardiovascular and all-cause mortality.
Effect of paricalcitol treatment on cardiac structure and function in CKD

The recent study recently published, the PRIMO studies showed that even with paricalcitol 2 µg/day the various indices of ventricular function were not changed with the 48th week of the therapy. Although the study looked at the surrogate endpoints, it was too small to look at the mortality.

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Effect of paricalcitol treatment on cardiac structure and function in CKD

Therefore, in the editorial to this article in JAMA Stefan Anker wrote that there are more questions than answers regarding the vitamin D role in CKD.

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The alternative is calcimimetics in fact, we have only one available for our patients, this is cinacalcet. This is the drug which is very specific in its action; it lowers PTH by increasing parathyroid hormone, parathyroid cell sensitivity to extracellular calcium.

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Cinacalcet and achievement of KDOQI treatment targets (phase 3 studies)

It was found, these are combined results from phase III studies, that it cannot not only lower serum PTH but also can lower indirectly serum calcium and serum phosphate.

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Rationale for the management of mineral abnormalities in CKD

Thereby giving a chance that we will be able to achieve the levels of serum PTH, serum calcium and serum phosphorous that are at the trough of the curves of the relation to mortality.

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Serum PTH and mortality in 16,173 HD patients between 2000-2004 – CORES Study (Latin America)

It has been nicely shown in many studies that there is some concentration of PTH that is linked to lowest mortality. It was shown in the CORES study, it was also shown in several other studies.

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Our current recommendations both by KDIGO and KDOQI recommend the value which is very close to the trough of this curve.

...In conclusion, patients whose serum iPTH, serum total calcium and serum phosphate values were within the KDOQI recommended targets experienced the lowest risk of mortality compared to those who were outside the respective target ranges...

Even with the latest Fresenius analysis of the relation between minerals and mortality
it was shown that even the older KDIGO guidelines better fit to the lowest mortality.

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Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with CKD: a meta-analysis

- 47 cohort studies (N=327,644 patients) met the inclusion criteria.
- Conclusion: The evidentiary basis for a strong, consistent, and independent association between serum levels of calcium and parathyroid hormone and the risk of death and cardiovascular events in chronic kidney disease is poor.
- There appears to be an association between higher serum levels of phosphorus and mortality in this population.

Palmer SC et al. JAMA 2011; 305: 1119-1127

There are several meta-analyses also and the largest one was published last year. It was found that although there was a strong relation between mortality and phosphate in patients with CKD, there was just a trend in case of calcium and no relation with PTH. So whether PTH is a good target for treatment, we don’t in fact know.

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We have several post-hoc analyses that showed that parathyroidectomy rates were reduced, the same was with fractures, CV hospitalisations but there was only a little effect on mortality.

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Cinacalcet and extraskeletal calcification: ADVANCE study

Subjects with Agatston CAC scores ≥30 were randomized to cinacalcet (30–180 mg/day) plus low-dose calcitriol or vitamin D analog (52 μg paricalcitol equivalent/dialysis), or flexible vitamin D therapy. 350 HD patients were randomized and 265 completed.

Primary Endpoint

- Percentage change from baseline in CAC score at week 52

Secondary Endpoints

- Absolute change in CAC score at week 52
- Absolute and percentage change from baseline in
  - Aortic calcification at week 52
  - Aortic valve calcification at week 52
  - Laboratory parameters at end of study (weeks 44 through 52)
- Proportion of patients achieving >15% CAC progression at week 52
- Safety

We also have a study looking at extra-skeletal calcifications. This study was important because it compared two strategies; one with cinacalcet with low dose of vitamin D and the other on with flexible vitamin D therapy.

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ADVANCE: Primary endpoint - Percent change in total CAC score

<table>
<thead>
<tr>
<th>Primary Analysis</th>
<th>Median % Change (P10, P90) in CAC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinacalcet (n=115)</td>
<td>Control group (n=119)</td>
<td>p-value</td>
</tr>
<tr>
<td>Agatston</td>
<td>24 (-22, 119)</td>
<td>31 (-9, 179)</td>
</tr>
<tr>
<td>Volume</td>
<td>22 (-12, 105)</td>
<td>30 (-6, 133)</td>
</tr>
</tbody>
</table>

Primary analysis based on a generalised Cochran-Mantel-Haenszel test on ranks

Adapted from Raggi P et al. Neprol Dial Transplant 2011;26:1327–1339

Although it was not shown for every kind of assessment of calcification,

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ADVANCE – secondary endpoints

it was a trend for a lower rate of calcifications when patients were treated with cinacalcet and with flexible vitamin D.

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Does cinacalcet treatment lower mortality in patients on HD?

So we all await the results of the largest trial in this field, so the EVOLVE trial

Cinalacalcet and CV outcomes: EVOLVE (results exp. Q4 2012)

Hypothesis
A treatment regimen for secondary HPT including cinacalcet reduces the risk of mortality and cardiovascular morbidity (MI, hospitalization for unstable angina, HF, PVE) compared to a treatment regimen without cinacalcet in subjects with CKD receiving maintenance hemodialysis

Primary endpoint
Time to the composite event comprising: all-cause mortality or non-fatal cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event)
Relation between serum alkaline phosphatase and risk of death in HD patients

- Association between the time-varying serum alkaline phosphatase values and the relative risk of death in 58 058 MHD patients over a 2-year interval using fixed covariate Cox modeling


It’s interesting but there is also a very nice and linear relation between serum alkaline phosphatase and the risk of death in hemodialysis patients. This relation is linear and the higher alkaline phosphatase can mean a higher risk of death. This is different in the case of PTH.

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Relation between serum alkaline phosphatase and risk of death in HD patients


If we compare these curves, in cases of PTH there is no linear relation that is the case with alkaline phosphatase.

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Plasma total vs bone alkaline phosphatase as markers of bone turnover: a histomorphometry study in 42 HD patients

In fact, alkaline phosphatase is a very good marker of bone turnover, it was found in several studies. This one is a small one but based on histomorphometry and it was found that total alkaline phosphatase and especially bone alkaline phosphatase is much more specific for bone turnover than PTH.

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Association of serum alkaline phosphatase with coronary artery calcification in HD patients

What are the explanations for the shape of this curve? Probably there is an association of serum alkaline phosphatase with coronary artery calcification.

In this study it was found that patients that were more calcified had also higher levels of serum alkaline phosphatase.

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Association of serum alkaline phosphatase with coronary artery calcification in HD patients

- Higher alkaline phosphatase has been linked to increased hydrolysis of pyrophosphate, a potent inhibitor of vascular calcification.


It was postulated that high alkaline phosphatase could be a result of increased hydrolysis of pyrophosphate, which is a potent inhibitor of vascular calcification.

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**Short-term mortality and serum alkaline phosphatase in HD patients (NECOSAD Study)**

Cumulative mortality curves for (A) all-cause mortality within 6 months, (B) cardiovascular (CV) mortality within 6 months, (C) all-cause mortality within 4 years, and (D) cardiovascular mortality within 4 years according to tertiles of bone alkaline phosphatase levels at baseline.


There is a strong relation between serum alkaline phosphatase and mortality. It was nicely shown in the NECOSAD study. It was shown for 6 month mortality and for 4 year mortality both for all-cause mortality and cardiovascular mortality.

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Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD

Multivariable-adjusted (B) log hazards (solid lines) and 95% CI (dashed lines) of all-cause mortality associated with baseline levels of serum ALP in Cox models

Kovesdy CP et al. Nephrol Dial Transplant 2010 25: 3003-3011

It was even shown in pre-dialysis patients, patients with impaired renal function but also in patients without renal function impairment in two large cohorts;

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Relation between alkaline phosphatase, phosphate, and mortality among survivors of myocardial infarction (CARE) and in a general population sample (NHANES III)

Risk of all-cause death by baseline level of phosphate (Phos) and/or AlkP

Risk of all-cause death by baseline level of AlkP in NHANES III participants

Findings from both CARE and the NHANES III were similar among individuals with and without evidence of kidney disease, defined by eGFR <60 ml/min

Tenelli M et al. Circulation. 2009;120:1784-1792

one amongst survivors of myocardial infarction the CARE study on the left and in the general population in the NHANES on the right.

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CME Slides Forum - M. Nowicki

We have known for a long time that vitamin D can lower alkaline phosphatase but we also have studies that show that cinacalcet can lower alkaline phosphatase in hemodialysis patients.

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Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with CKD: a meta-analysis

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- Conclusion: The evidentiary basis for a strong, consistent, and independent association between serum levels of calcium and parathyroid hormone and the risk of death and cardiovascular events in chronic kidney disease is poor.

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Palmer SC et al. JAMA 2011; 305: 1119-1127

Coming back to the meta-analysis I’ve already shown the strongest relation was between serum phosphate and mortality.

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No randomized trials have shown that selecting a particular phosphate binder will reduce the risk of clinically relevant outcomes.

Sevelamer and lanthanum are promising, but their superiority to calcium-containing agents has not been proved.

Furthermore, they are expensive and are associated with more adverse events.

So we expect that by treating patients with oral phosphate binders we can reduce mortality and cardiovascular events.

Mortality in kidney disease patients treated with phosphate binders: a randomized non-blinded study

Event-free survival from the composite end point of all-cause mortality and dialysis inception among patients treated either with sevelamer (dotted line) or calcium carbonate (continuous line).


We have some alternatives but so far no randomised trials have shown that a particular phosphate binder can reduce the risk of clinically relevant outcomes. There are some small studies. This study was carried out only in a group of about 200 patients. Treating the patients with non-calcium containing phosphate binders like sevelamer can be associated with lower mortality than when treating patients with calcium carbonate.
But in fact, critical evidence is missing because although the RIND study with sevelamer showed some advantage in terms of mortality, the larger DCOR study didn’t show an effect only in the post-hoc analysis in some groups of patients those who are treated for a longer time and remaining for a longer time on dialysis.

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Serum magnesium and mortality in HD patients – 51-month follow-up of 515 HD patients

The other mineral that is forgotten by nephrologists is serum magnesium. There are no large studies. But this study with a 51 month follow-up in 500 hemodialysis patients showed that patients with the highest serum magnesium can have lower mortality. In fact, magnesium is a very strong inhibitor of vascular calcification and an antagonist of calcium.
Conclusions

- Mineral abnormalities are common in CKD and have been related to mortality in multiple mostly retrospective or observational studies.
- Most observational data support the hypothesis that interventions directed at CKD-MBD have the potential to improve clinically relevant outcomes.
- These observations are currently the basis for patient care and for clinical practice guidelines.
- We urgently need randomized, placebo-controlled clinical trials to support our decision-making.

So just to conclude, mineral abnormalities are very common in CKD. They have been related in multiple studies to mortality but most studies were retrospective or observational. Most data from these observational studies support the hypothesis that those interventions that are directed at CKD-MBD can have a potential to improve clinically relevant outcomes. These observations are currently the basis of our patient care and for our clinical practice guidelines. But in fact what we need are large randomised placebo controlled clinical trials that can only support our decision making. Thank you.