Core slide content from the ERA-EDTA CKD-MBD Working Group CME in Amsterdam, 2014
First ERA-EDTA CME course of our CKD-MBD WG

Our first CME course (number 17 of the official program) aimed at updating the most recent acknowledgements and critical concepts in the field of CKD-MBD

As you can see from the pictures (technically poor, indeed) the room meeting was crowded with an estimated number of attendees of 350.

Importantly, presentations were interactive, with questions (and electronic answers) raised at the beginning and end of the presentations. This resulted in increased interest and attention from the audience.

We report here the official program and few slides from the individual presentations.
CME COURSE 17

E104-107  15.30 - 17.30

CKD-MBD
(Working Group on Chronic Kidney Disease – Mineral and Bone Disorders)

CKD-MBD: Update 2014

Chairs: Mario Cozzolino, Milan, Italy
       Marc Vervloet, Amsterdam, The Netherlands

Biomarkers in CKD-MBD: what’s new on the horizon
Pieter Evenepoel, Leuven, Belgium

News from the bone in CKD
Sandro Mazzaferro, Rome, Italy

Native vitamin D: to supplement or not?
Pablo Urena-Torres, Paris, France

Treatment of secondary hyperparathyroidism in 2014
David Goldsmith, London, UK
Biomarkers in CKD-MBD. What’s new on the horizon.
Pieter Evenepoel, Leuven, Belgium

Promising diagnostic tools include fibroblast growth factor 23, klotho and sclerostin.
- FGF23 proved to be a very robust risk-prediction biomarker of poor renal and cardiovascular outcomes. FGF23 not only is marker but also a mediator of cardiovascular disease as it may trigger left ventricular hypertrophy.
- Sclerostin, an inhibitor of canonical β/Wnt signaling, may be involved in bone and vascular pathobiology. Sclerostin levels in CKD patients are increased and high circulating levels in these patients have been associated with low bone turnover disease and improved survival. Sclerostin probably may play a crucial role in the bone vascular axis.
- Klotho protein, the product of the anti-ageing gene Klotho, exists in two forms, transmembrane and soluble. Soluble klotho is a pleiotropic humoral factor exerting multiple renal and extrarenal effects. Soluble klotho levels decrease along with the progression of CKD paralleling the decreased expression of the transmembrane form. Low sKlotho levels associate with poor renal outcome, but data are limited, preliminary and controversial.
- In conclusion, FGF23, sclerostin and sKlotho are promising biomarkers, but several hurdles have to be passed before these biomarkers can enter clinical practice, including preanalytical (stability, biological variability...) and analytical (interassay variability...) issues.
**Biomarker**

- Urine/blood

**Novel biomarkers on the horizon:**
- FGF23
- sKlotho
- Sclerostin

**Promising, not ready for clinical prime time**

**Imaging techniques**
- DEXA - (HR-)pQCT
- XR – CT
- US
- MRI

**Functional tests**
- PWV

**Histopathology**
- Bone histomorphometry
News from the bone in CKD.
Sandro Mazzaferro, Rome, Italy

Bone strength, resulting from bone density and quality, was the subject of this presentation.

- The practical significance of the new TMV classification of renal osteodystrophy (suggested by KDIGO in 2009) was considered. The seminal paper by Malluche H. (J Bone Min Res 2011), including 630 bone biopsies of dialysis patients from Europe and USA, allowed to verify: high prevalence of low turnover especially in white patients; almost complete absence of Mineralization defects; high prevalence of increased trabecular bone volume especially in black patients; increased porosity of cortical bone in both races. Race, age, dialysis duration and serum levels of P, Ca, AP and PTH are the suggested potentially useful markers.

- As for bone quality, either low turnover or high turnover may have negative effects.

- The subject of bone strength in renal patients is clearly important given the high prevalence of fractures in these patients.

- Bone biopsy is the gold standard but rarely employed

- More sophisticated diagnostic tools (like HRpQCT, MRI etc) should be tested in their clinical reliability in renal patients
Bone strength = the capacity of bone to resist mechanical stresses

Bone Strength = Bone Density + Bone Quality

Bone Density = BMD

I. Turnover
II. Mineralization
III. Architecture (T and C Volume)
IV. Material properties

DXA = Limited utility in CKD

Bone biopsy = rarely obtained in CKD patients
How can we assess Bone strength in CKD?

- **Bone Biopsy** (gold standard, rarely performed)
- **Biochemical markers** (limited reliability)
- **DXA** (2D assessment of a 3D structure, ineffective discrimination between cortical and trabecular bone)
- **pQCT** (discriminates cortical and trabecular Volumes)
- **HR-pQCT** (more powerful analysis of microarchitecture than pQCT)
- **Trabecular Bone Score** (derived from DXA, a microarchitecture index indicative of TbN and TbS)
- **MRI** [evaluates mechanical (stiffness and fracture load) and structural (BV/TV; TbTh; CtTh) parameters]
- **Nuclear Bone Scan** (used to estimate bone formation rate. High radiation dose)
Conclusions

• Bone lesion in CKD are:
  – Changing with time (changes in therapies?)
  – Different according to race
• The new TMV classification seems to be promising and useful for clinical considerations and points to the importance of bone quality
• Bone TO is only one aspect of bone mechanical and metabolic competence;
• Bone TO abnormalities are expected to modify bone quality;
• It is reasonable to hypothesize that therapies for ROD would be more adequately addressed if based on bone biopsy data
• Biomechanical properties of bone are relevant for fractures and pain
• Importantly, we should not forget that also bone endocrine function may be affected by ROD.
Native Vitamin D: To supplement or not?

Pablo Urena Torres, Paris, France

Subject of this presentation was the clinical use of native vitamin D in CKD.

- Low circulating vitamin D levels associate with increased serum PTH and a variety of non-skeletal alterations, including hypertension, cardiovascular diseases, proteinuria, diabetes, multiple sclerosis, cancer, and immune system dysfunction.

- Circulating 25(OH)D are used to estimate vitamin D storage in the body, with values < 10 ng/mL widely recognized as indicative of deficiency because of its association with muscle weakness, bone pain, fractures, and high PTH. However, the definitions of normality and insufficiency remain controversial.

- The KDIGO recommended monitoring 25(OH)D levels in CKD stages 3–5D patients and adopting treatment strategies similar to those for the general population.

- More than 50% of CKD patients are vitamin D deficient (< 15 ng/ml) due to several contributing factors.

- Native vitamin D supplementation has regained a great interest, also because of the hypothesis that extra-renal 1a-hydroxylase activities could contribute to the beneficial, paracrine, pleiotropic actions of locally produced calcitriol.

- Supplementation with native vitamin D usually improves many of mineral and bone disorders, including decreasing circulating levels of PTH, bone-specific alkaline phosphatase, and histological signs of osteitis fibrosa.

- However, scientific evidences demonstrating the beneficial effect of native vitamin D supplementation on non-classical organs are still inconsistent and need to be confirmed by large randomized clinical trials, which are actually ongoing.

- Native vitamin D supplementation is of easy usage with long-term dosing intervals, of low costs (compared to other anti-hyperparathyroidism therapies), and little need for follow-up monitoring. It is also of a relative wide safety margins since the rare cases of hypercalcemia and hyperphosphatemia seen after native vitamin D supplementation.
Both, Circulating 25(OH)D and 1,25(OH)2D Levels Decrease in CKD patients

Factors Associated with an Increased Risk of Vitamin D Deficiency

<table>
<thead>
<tr>
<th>Vitamine D determinant</th>
<th>OR</th>
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<tbody>
<tr>
<td>Black</td>
<td>1.59</td>
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<tr>
<td>Systolic BP 130-159</td>
<td>1.21</td>
</tr>
<tr>
<td>Systolic BP &gt;=160</td>
<td>1.62</td>
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<tr>
<td>DM</td>
<td>1.67</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.24</td>
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<tr>
<td>Obese</td>
<td>1.54</td>
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<tr>
<td>ACR &gt;30(mg/mmol)</td>
<td>1.38</td>
</tr>
<tr>
<td>Albumin &lt;35 (g/l)</td>
<td>1.59</td>
</tr>
<tr>
<td>Winter</td>
<td>1.39</td>
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<tr>
<td>MRC stage 5</td>
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<td>MRC stage 4</td>
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<tr>
<td>MRC stage 3b</td>
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<tr>
<td>MRC stage 3a</td>
<td>1.44</td>
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Adjusted by age, gender, and site

In addition
- Decreased liver conversion of vitamin D to 25(OH)D
- Accelerated catabolism of 25OHD by 24-hydroxylase (CYP24A1), in part because of high FGF23

Diseases Associated with Low Vitamin D
(non classical actions)

1- Cardiovascular diseases (arterial hypertension, stroke, myocardial infarction, heart failure, sudden cardiac death, and mortality of cardiovascular origin.

2- Diabetes Mellitus, insulin resistance, obesity

3- Progression of chronic renal disease and proteinuria

4- Immune system dysfunction

5- Infection disease (tuberculosis, AIDS, etc)

6- Cancers (breast, colorectal, skin, lymphoma, prostate)

7- Neurological diseases (Alzheimer, amyotrophic lateral sclerosis)

8- Pregnancy (hypocalcemia and rickets in newborn)
Vitamin D and Mortality in Chronic Kidney Disease

Figure 2. Forest plot and summary relative risk (RR) for the association of 25-hydroxyvitamin D (25[OH]D) level and mortality in patients with chronic kidney disease. The size of the box is proportional to the weight of the study (1/variance of the estimate). Abbreviations: 4D, Die Deutsche Diabetes Dialyse Studie; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis.
Conclusions

1- Vitamin D is a complex hormonal system involved in the regulation of mineral and bone metabolism as well as a multitude of other systems (cardiovascular, immune, endocrine, muscular, nervous, etc)

2- Thirty to 50 % of CKD patients have vitamin D deficiency and/or insufficiency

3- Vitamin D deficiency in CKD is associated with an increased risk of secondary hyperparathyroidism, low calcitriol, and low ionized calcium

4- Vitamin D supplementation is easy, non expensive, well tolerated, and efficient in controlling serum PTH levels

5- The clinical benefits of 25OHD supplementation in CKD remain unproven: long-term RCTs will provide the answer
Treatment of Secondary Hyperparathyroidism in 2014.
David Goldsmith, London, UK

• Secondary hyperparathyroidism has definitely changed its picture.
• Hyperphosphatemia is still a major causative factor, but new paradigms are suggested for its management.
• Bone health, with its mechanical competence and endocrine functions, is now considered of principal importance. Bone disorders increase not only the risk of fractures, but also of cardiovascular disease (both responsible for increased mortality).
• Evidence that current therapeutic efforts are significantly affecting the outcome of renal patients are still limited, for several reasons.
• New efforts in terms of basic research and clinical observations are warranted.
# Phosphate + FGF23: Paradigm Shift

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Current paradigm</th>
<th>Proposed paradigm</th>
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<tbody>
<tr>
<td>Rationale</td>
<td>High levels of serum phosphate promote vascular calcification and cardiovascular events</td>
<td>High levels of urinary phosphate injure renal tubules and induce renal fibrosis</td>
</tr>
<tr>
<td>Goal</td>
<td>To decrease serum phosphate level</td>
<td>To decrease serum FGF-23 level</td>
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<td>Indication</td>
<td>End-stage renal disease with hyperphosphataemia (~0.3% of patients with CKD)</td>
<td>Stage 2–5 CKD with high FGF-23 levels (~35% of patients with CKD)</td>
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</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23.

Kuro-o, M. *Nat. Rev. Nephrol.* advance online publication 18 June 2013; doi:10.1038/nrneph.2013.111
Bone Fractures & Death

Mortality and hospitalization rates 2–9 times higher

Tentori F et al., Kidney Int 201
Conclusions – what do we still LACK?

- Evidence that by manipulating serum phosphate, calcium, PTH or vitamin D concentrations, there is ANY survival advantage for CKD or dialysis patients

- No guideline progression unless high-quality fresh evidence on hard outcomes

- More academic and research interest in
  - (a) better biomarkers of bone (volume, strength, turnover)
  - (b) better imaging techniques to interrogate bone (micro qCT, MRI, PET)