KDIGO CONTROVERSIES CONFERENCE ON CHRONIC KIDNEY DISEASE-MINERAL AND BONE DISORDER: PROGRESS AND KNOWLEDGE GAPS TOWARDS PERSONALIZING CKD-MBD CARE

Rod and Osteoporosis in CKD

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Disclosures

- Research Grant: Kiowa Kirin
- Education Grant: Jansen, Merck
ROD and Osteoporosis in CKD

• Osteoporosis in CKD: is it different from the general population? which drugs should we use, for whom and when?
• Bone Effects of SHPT therapy: differences between calcimimetics and vitamin D analogs
• Is bone biopsy always necessary? What is normal in bone histomorphometry: different reference ranges among study groups impacting mostly the definition of normal turnover and mineralization
• ROD physiopathology: recent advances
• .....
Osteoporosis in CKD

Current Knowledge:
- CKD increases the risk for fracture
- Fractures are osteoporotic (hip, humerus, ..)

Combination of Risk factors for fractures
- For primary osteoporosis: Age, low BMI, female gender, falls, prevalent fracture
- From secondary OP: Hypogonadism, diabetes, PP inhibitors, loop diuretics, Glucocorticoids...
- From CKD: KT history, PTX history, dialysis vintage, acidosis, Phosphate...

Recent data after 2000
- 7566 dialysis patients, 1504 KT patients, Danish background population (4 091 776)

(HR) for any fracture:
- Dialysis: 3.14 (95% CI):2.97–3.31 ] 1.85 after adjustment
- KT: 1.94 (95% CI: 1.72–2.18) 1.82 after adjustment

Trend for decreased incidence of fractures in KT patients?

References:
Ball AM, et al. JAMA 2002; 288: 3014–3018
Alem AM, Kidney Int 2000; 58: 396–399
Perrin et al Transplantation 2016
Is it different from the general population?

- Degree of bone secondary mineralisation of bone in patients with various type of ROD lesions (HD or KT) (synchroton radiation microtomography)

44 bone samples: 19 ♂ and 11 ♀, mean age: 55 ± 18 yrs.
30 CKD, 8 Low bone TO (LTO), 15 High Bone TO (HTO), 5 HTO-Mineralization Defect (HTO-MD, mixed disease)
2 Normal Bone TO (NTO).

n=14 Non uremic age matched osteoporotic patients

(Personal data)
Is it different from the general population?

- CKD
- LTO
- HTO
- Non uremic OP
- Trabecular architecture deterioration
  - Increase in cortical porosity
  - Diagnosis
  - Treatment

Sharma et al Am J of Nephrol 201847(6):376-384, personal data
Which drugs should we use, for whom and when?

- **Current Knowledge:**
  - DXA BMD predicts Fx risk in CKD regardless of CKD stage
  - T score <-2.5 discriminant
  - Target Population: Pts at high risk Female, age >50...etc
  - Sensitivity/ specificity issues

- **Better identification of patients at Risk**
  - TBS, 3D Shaper
  - MRI
  - FRAX score (or other scores for evaluating the risk for fracture in CKD?)
  - Add BTM

- **KDIGO (2020, Eval KT candidates)**

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VE.Gómez-Islas et al Bone Rep 2020, 13, 100298

Eun Song et al Transplantation Proceedings, 51, 2704e2709 (2019)
Evenepoel et al Kidney International (2019) 95, 1461–1470
Which drugs should we use, for whom and when?

- Current Practice:
  - Patients with prevalent fracture

- Current questions:
  - Regardless of CKD stage?
  - Primary prevention?
    - In HD patients identified at high risk?
    - In HD patients identified at high risk on KT waiting list?
    - KT patients at risk (1st year?)
Which drugs should we use?

Treatment of ROD

• Phosphate binders (Ca/non Ca)
• Iron based Phosphate binders
• Vitamin D & derivatives
• Dialysate calcium concentration
• Cinacalcet, Etelcalcetide
• PTX

Stage 5d

Current questions:

Effects of SHPT therapy: Differences between calcimimetics and vitamin D analogs on

• BMD
• BTM
• Fractures

Which drugs should we use?

### Treatment of Osteoporosis

- **GFR > 30ml/mn**
  - Bisphosphonates,
  - Teriparatide, abaloparatide
  - Denosumab
  - Raloxifene
  - Romososumab

- **GFR < 30ml/mn**
  - Denosumab

17 studies/10,214 patients With stage 2–5 CKD, or KT

![Forest plots of relative risk of vertebral or clinical fractures](Chen HH et al Frontiers in Pharmacology 2022, 822178)

Are BPs safe for renal function and effective in CKD 3-5?

- GFR < 45 ml/min (CKD3-5), > 40 year of age, follow-up 3-4 yrs
- CPRD cohort: 53,986 unexposed patients / 2613 under BPs
- SIDIAP: 40,800 unexposed / 1408 BPs patients under BPs
PS Matched


Annualized change in total hip BMD as a function of BP treatment and baseline CKD stage

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Non-users (N = 3908)</th>
<th>BP users, all (N = 1793)</th>
<th>BP users, MPR ≥ 80% (N = 1121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 1</td>
<td>90.8 (15,411)</td>
<td>1.25 (1.15, 1.36)</td>
<td>0.9 (0.8, 1.1) (N = 729)*</td>
</tr>
<tr>
<td>CKD 2</td>
<td>90.8 (15,411)</td>
<td>1.25 (1.15, 1.36)</td>
<td>1.0 (0.7, 1.1) (N = 683)*</td>
</tr>
<tr>
<td>CKD 3A</td>
<td>90.8 (15,411)</td>
<td>1.25 (1.15, 1.36)</td>
<td>1.0 (0.6, 1.4) (N = 86)*</td>
</tr>
<tr>
<td>CKD 3B</td>
<td>90.8 (15,411)</td>
<td>1.25 (1.15, 1.36)</td>
<td>0.4 (0.5, 1.2) (N = 18)</td>
</tr>
<tr>
<td>CKD 4</td>
<td>90.8 (15,411)</td>
<td>1.25 (1.15, 1.36)</td>
<td>1.5 (1.0, 4.0) (N = 7)</td>
</tr>
<tr>
<td>CKD 5</td>
<td>90.8 (15,411)</td>
<td>1.25 (1.15, 1.36)</td>
<td>[N &lt; 5]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for age, sex, prior MOF, recent GC use BMD change, adjusted*</th>
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</table>

* Adjusted for baseline differences in age, sex prior MOF, race
* p < 0.05 compared with non-user group

Abrahamsen B et al. Bone 137 (2020) 115371
Is denosumab effective and safe in CKD?

124 HD pts, 37% with diabetes, 71.

78 HD pts Dmab + Ca vit D for 2 weeks
Vs alendrmate

• No change in vessel status (ABI, PWv, CACs…) .after 1 year

• Risk of mild to severe hypocalcemia increase with CKD severity

Ansastasilakis AD, et al. JBMR 2017;32:1291–96;
Cummings SR, et al. JBMR 2018;33:190–8;
Should treatment be based on bone turnover assessment?

- Current practice:
  - When ROD is severe it should be improved before anti OP treatments are prescribed.
  - Anti resorptive drugs in HTO, anabolic drugs in low turnover

But:

- 6 months Dmab (+calcitriol and calcium) in HD patients with serum PTH >1000pg/ml and Alk Phos 500UI/l: BMD increased by 23%. No evaluation of Vascular safety or long term evolution (Chen-Liang et al J Clin Endocrinol Metab, 2014, 99(7):2426–2432).

- BPs increase BMD to a greater extent when baseline BTM are higher,
- BPs increase BMD in patients with baseline BTM in the normal range.
- Anti vertebral fracture efficacy is not affected by BTM pre treatment levels (Bauer DC et al J Bone Miner Res 2006;21:292–299.)

- Teriparatide prevents vertebral fractures in PM osteoporosis (increased turnover)
  Bisphosphonates prevent fractures in glucocorticoid induced osteoporosis in which bone formation is low.
Is bone biopsy always necessary?

- Is bone biopsy popular?

- Should we simplify the procedure?
  - Change trephine?
  - Get rid of tetracycline labeling?
  - Ask radiologists to perform the biopsy?
  - Replace biopsy with BTM?

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Salam S et al Bone 142 (2021) 115689

Evenepoel et al Nephrol Dial Transplant (2017) 32: 1608–1613, on 68
Is bone biopsy always necessary before anti OP treatment?
What is normal in bone histomorphometry?:
different reference ranges among study groups impacts results
Bone histomorphometry Working group

AUSTRIA – Pr Astrid Fahrleitner-Pammer
BELGIUM – Pr. Patrick d’Haese
– Geert Behets, PhD
– Pr Pieter Evenepoel
DENMARK – Dr. Ditte Hansen
– Dr. Hanne Skou Jørgensen
FINLAND – Pr Heikki Kröger
– Pr Eero Honkanen
– Dr. Xiaoyu Tong
FRANCE – Pr. Justine Bacchetta
– Pr MH Lafage-Proust
– Pr. Martine Cohen-Solal
– Dr. Pablo Ureña-Torres
– Dr. Pascale Chavassieux
ITALY – Pr Sandro Mazzaferro
MACEDONIA – Pr Goce Spasovski
NETHERLANDS – Pr Nathalie Bravenboer
– Dr. Neveen Hamdy
– Dr. Renate de Jongh
– Pr. Erik Fink Eriksen
– Dr. Ana Carina Ferreira
NORWAY – Pr Jorge Cannata-Andia
– Dr. Mathias Haarhaus
– Pr Andrea Thrombetti
– Dr. Maude Gerbaix
– Dr. Marie-Josée Begin
– Dr. Alex D Lalayiannis
– Dr. Rukshana Shroff
– Dr. Syazrah Salam

Literature survey → identification of European HM users/experts → Mailing survey → Bone histomorphometry Working group → Delphi methodology (Estimate-Talk-Estimate) →

Biopsy Procedure
Sample processing
Quantification methods
Diagnosis criteria
Final report
Agreement: Diagnosis criteria: low and high bone turnover

- We agreed on the type of lesion
- High Bone TO: high bone formation + no mineralization defect + other features
- Low Bone TO: low bone formation + no mineralization defect + other features
Disagreement: Normal Population references

- **Reference Values Condition diagnosis results**

FROM REFERENCES PREVIOUSLY PUBLISHED IN THE LITERATURE, PLEASE STATE REFERENCE(S):

- Thomsen J.S., Osteoporosis Int, 2015
- Bach-Gansmo F.L., Bone, 2016
- For children: Glorieux et al, Bone 2000
- Luciene M at al: J Bone Miner Metab 2007; 25(6):400-6
- S.Vedi et al Metabolic Bone Disease and Rel Res 4, 4, 1982: 231-236

FROM REFERENCE GENERATED IN YOUR LABORATORY, OR BY YOUR TEAM

- -
- -
- -
- -
- -
- -

ETHNICITY SPECIFIC (IF POSSIBLE)

- 2

AGE SPECIFIC

- 4

GENDER SPECIFIC

- 4

- 5

- 8
HM diagnosis of renal osteodystrophy: a call for harmonization of reference ranges

• Jorgensen S H et al, EUROD group, Kidney International (2022) 102, 431–434
ROD and Osteoporosis in CKD

ROD physiopathology: recent advances
ROD physiopathology: current knowledge

- ROD is defined by lesions that affect bone turnover & primary mineralisation
- = what happens at the bone surface

- What if what is below the surface also matters?
ROD physiopathology: recent advances

- Why dysfunction(s) could be a target in CKD-MBD?
Osteocytes death in the context of CKD

- Osteocytes apoptosis is decreased in young CKD patients, associated with defect in Ocy maturation and increased by Vit D derivatives.

- Osteoblast apoptosis is increased by dietary Phosphate load in CKD rats with low turnover.

- Osteocyte apoptosis is decreased in the adenine CKD model.

Table 4. Osteoblastic and osteocytic apoptotic rates (%).

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Nx+PTx 0.6%</th>
<th>Nx+PTx 1.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoblast apoptotic, %</td>
<td>1.2 (0.9-1.8)</td>
<td>0.4 (0.3-0.8)</td>
<td>1.3 (0.9-1.5)</td>
</tr>
<tr>
<td>Osteocyte apoptotic, %</td>
<td>0.5 (0.3-1.0)</td>
<td>0.2 (0.15-0.25)</td>
<td>0.4 (0.3-0.5)</td>
</tr>
</tbody>
</table>

Nx+PTx 5/6 nephrectomy and total parathyroidectomy: a: p < 0.05 vs. sham; b: p < 0.05 vs. Nx+PTx 1.2%.

Peireira RC et al. KI, 94, 5, 2018, 1002-1012.
Osteocytes death in the context of renal osteodystrophy

- DMP1 overexpression in late osteoblasts/osteocytes improves bone health in the Col4a3−/− Mouse model of CKD
- CKD (High bone turnover) → increase in osteocyte apoptosis decreased by DMP1 overexpression in late Ob/Ocy

RNA seq on human bone biopsies in CKD according to Turnover

The tale of the 6 blind men and the elephant

KDIGO controversies conference

DO NOT EVER give calcium!

CA SR agonists regardless of calcemia

Avoid negative calcium Balance!

We do not need a bone Biopsy!!

We need a bone Biopsy!

Let’s treat CKD-related osteoporosis without RCTs

Osteoporosis

Bone Histology

Vascular calcifications

Group Calcium & Phosphate

We need a bone Biopsy
The issue of normal reference values

Salusky et al., Kidney Int 33:975-982 (1988)

<table>
<thead>
<tr>
<th></th>
<th>Osteitis Fibrosa</th>
<th>Mild lesions</th>
<th>ABD</th>
<th>OM</th>
<th>MUO</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoid area/V</td>
<td>&lt;12%</td>
<td>&lt;12%</td>
<td>&lt;12%</td>
<td>&gt;12%</td>
<td>&gt;12%</td>
<td>&lt;12%</td>
</tr>
<tr>
<td>BFR, µm2/mm2/day</td>
<td>&gt;97</td>
<td>&gt;613</td>
<td>&lt;97</td>
<td>&lt;97</td>
<td>&lt;97</td>
<td>97&lt;BFR&lt;613</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Malluche HH . JBMR , 26, 6: 1368-1376, 2011, Malluche HH Calcif Tissue Int. 1982; 34: 449–455

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone turnover</td>
<td>Activation frequency&lt; 0.49/year ± BFR/BS&lt; 1.80 mm³/cm² /yr,</td>
<td>Ac.f. &gt; 0.72/year ± BFR/BS &gt; 3.80 mm³/cm² /year</td>
<td>=0.49 &lt;Ac.f.&lt; 0.72/year ±1.80 &lt;BFR/BS &gt; 3.80 mm³/cm² /year</td>
</tr>
<tr>
<td>Defective mineralization</td>
<td>Osteoid thickness&gt; 20 µm + mineralization lag time &gt; 50 d</td>
<td></td>
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</tbody>
</table>