Nicht-oxidiertes (nox-)PTH:

ein neuer Marker für CKD-MBD

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Dialysis associated with high cardio-vascular mortality

Vascular calcification predicts mortality

Comparison between curves was highly significant ($x^2 = 42.66, P < 0.0001$)
Markers & CKD stages

- KDIGO 2 (GFR MDRD < 80 ml/min/1.73 m²): FGF-23 up, klotho down (1,25-OH-vitamin D down)
- KDIGO 3a (GFR < 60): 1,25-OH-vitamin D down
- KDIGO 3b (GFR < 45): calcium down, PTH up (secondary HPTH)
- KDIGO 4 (GFR < 30): phosphate up

→ osteitis fibrosa and vascular calcification
↑ PTH, aldosterone, FGF23 + ↓ klotho = cardiovascular fibrosis and hypertrophy, vascular calcification

First to 3\textsuperscript{rd} generation PTH assays

Elecsys\textsuperscript{®} PTH, parathyroid hormone: A rapid, sensitive and specific immunoassay using fully automatic electro-chemiluminescence for bone metabolism assessment:


Figure 1: Schematic representation of the PTH-molecule and the epitopes recognized by the two monoclonal antibodies.
There is a problem with contemporary assays ...
iPTH and all-cause mortality on dialysis

ARO Initiative:
• ~8,000 patients on hemodialysis
• median follow-up 21 months

Kidney disease outcome quality initiative K-DOQI 2003
PTH concentration should be: 150–300 ng/l
iPTH and all-cause mortality on dialysis

Kidney disease improving global outcomes KDIGO 2009

PTH concentration should be in a range which is 2-9 times to the upper limit of the normal PTH range:

150–600 ng/l
New parameter:  
\( n\text{-oxPTH} = \text{non-oxidized PTH} \)

**noxPTH = active PTH**

Infusion of PTH(1-34) and oxidized PTH(1-34) into rats

► Only noxPTH biologically active!

Horiuchi, J Bone Min Res 1988; O’Riordan, J Endocrinol 1974; .....
noxPTH: test design

Parathyroid Hormone (PTH)

is subject to oxidation

oxidized PTH is biologically inactive

Plasma Probe

Patient sample:

Step 1: Affinity chromatography

Step 2: Immunoassay for bioactive PTH

Patient sample: PTH native (bioactive) + PTH oxidized (bioinactive)
iPTH versus noxPTH in dialysis patients

Hocher, Armbruster et al., PLoS ONE 2012
iPTH & noxPTH in CKD patients and healthy individuals

4C study: 620 children, KDIGO 2-4

342 adult hemodialysis patients

89 healthy controls:
iPTH: 33 ± 14, noxPTH: 7.7 ± 1.5 pg/ml, iPTH/noxPTH: 4.2 ± 1.4

Hocher, ...., Armbruster, Kidney Blood Press Res 2013
**iPTH versus noxPTH in dialysis patients**

- 340 hemodialysis patients followed over 5 years
- baseline iPTH 105 ± 160 pg/ml
- baseline noxPTH 11.8 ± 20.9 pg/ml

<table>
<thead>
<tr>
<th>Table 2. Correlation Matrix Showing Spearman’s Correlation Coefficients for the Correlating of iPTH to Either n-oxPTH or oxPTH</th>
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<tbody>
<tr>
<td>n-oxPTH</td>
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<tr>
<td>iPTH all patients (n = 340)</td>
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<td>iPTH, only patients with</td>
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<td>iPTH &gt; 70 ng/L (n = 138)</td>
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High correlation iPTH-oxPTH, but substantially lower iPTH-noxPTH correlation that becomes even weaker at higher iPTH!
iPTH versus noxPTH in dialysis patients

iPTH categories (KDOQI): 342 patients
Floege, NDT 2011: ~8.000 patients

→ a smaller, but typical hemodialysis cohort

Tepel, Armbruster et al., J Clin Endocrinol Metab 2013
iPTH versus noxPTH in dialysis patients: different meaning

Tertiles of noxPTH and iPTH

- noxPTH and iPTH have different meaning
- „iPTH“ – a blend of biological function (=noxPTH) and oxidative burden (=oxPTH)

Tepel, Armbruster et al., J Clin Endocrinol Metab 2013
High iPTH: the EVOLVE study

- 3883 patients with secondary hyperparathyroidism
- median iPTH: 693 pg/ml
- cinacalcet vs placebo on top of standard medication
- primary endpoint: death + cardiovascular events
- follow-up 5 years

![Graph showing primary composite end point with hazard ratio and log-rank test results.](image-url)
High iPTH: the EVOLVE study

- noxPTH, but not iPTH predictive for primary endpoint

What would have happened if they had enrolled on noxPTH basis??

Hocher et al., ASN 2015. Samples from: Chertow, NEJM 2012
The impact of noxPTH versus iPTH on mortality differs substantially: “biological function” vs. “oxidative stress (+ biological function)”. 

The individually varying iPTH/noxPTH ratio may give rise to different scenarios of PTH over-suppression which may cause adynamic bone disease, cardiovascular calcification, and excess mortality (Floege et al.: ARO Initiative, NDT 2011).
The complete risk curve for noxPTH is still to be drawn (EVOLVE samples) – we need more patients with high iPTH levels and also with tertiary HPTH. We also need more patients to define the normal range.

Show better/distinct association with bone metabolism of noxPTH compared to iPTH in CKD.

Show how the (until now neglected) oxidation status of PTH calibrators impacts on assay performance.
Thank you for your attention!
Plasma of healthy volunteers (n = 8, mean iPTH 22.9 ± 8.4) and CKD patients (n = 8, mean iPTH 394.1 ± 200.7) was incubated on the anti-oxPTH column for different time intervals; thereafter, a conventional iPTH sandwich assay was run. **Data (mean)** are given in mOD in percent of value at 0 min column time. Note: the standard time on column for the noxPTH assay is 60 min.
Pre-analytical investigations

Time until centrifugation

Percentage of n-oxPTH concentration in fresh plasma

Freeze-thaw cycles

Ursem et al., submitted, 2017
**PTH redox status linked to inter-assay differences**

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Ursem et al., submitted, 2017