CONTROVERSIES AND TRENDS IN PTH CONTROL (ADULTS)

PART 1

Dr. Jordi Bover M.D., Ph.D., F.E.R.A.

University Hospital Germans Trias i Pujol (Can Ruti)
Badalona (Barcelona)
Spain
DISCLOSURES

- ABBVIE
- AMGEN
- VIFOR-FRESENIUS-PHARMA (CSL)
- SANIFIT (CSL)
- SANOFI
- RUBIO
- BAYER
- ASTRA-ZENECA

Chapter 4.2.
Treatment of abnormal PTH levels in CKD-MBD

5 guidelines / 8 statements:

2 (2B): G5D treatment & PTX
4 (2C)
2 (NG): G3a-G5 not on dialysis

Practice is essentially based on
VERY PLAUSIBLE ASSOCIATIONS
(co-correlation, residual confounding, conf by indication, biases…)
but lacking RCT’s

Even ≠ meta-analysis provide contradictory results
**PTH = DIFFICULT TOPIC/RISK BALANCE**

- **↓ Bone turnover**
- **Fractures**
- **CV calcification**
- **CV disease**
- **QOL**
- **Mortality**

- **↑ Bone turnover**
- **↑ PTG – Uremic toxin**
- **Fractures**
- **CKD progression**
- **CV calcification (?)**
- **CV disease**
- **QOL**
- **Mortality**

↑↑ prevalence (primary form of ROD in CKD?)

**Basal conditions vs overtreatment**

(age, diabetes, MIA-PEW, no treatment...)

(≠ VD, CM, ↑ Ca-dialysate, OP??...)

≠ Guidelines (i.e. JSDT)

Aggressive tx soon after initiation (60-180 → 60-240 pg/ml)

“The lower-the better”

May any single manoeuvre really improve survival in CKD? (Only dialysis/HDF/RT)

CKD complex, PTH also, do not expect answers but questions & opinions to be further discussed
**PTH: ≠ IDEAL TARGETS FOR ≠ ORGANS? PRIMARY GOAL?**

**Low bone turnover:**
- < 104/183 pg/ml
- < 90 (biointact)

(Sprague, Salam, Jorgensen 150? ≠ populations, bALP..other biomarkers?)

**Mortality (KDIGO):**
- < 2X pg/ml

**EXTREME OF RISK**

**High bone turnover:**
- > 323/327 pg/ml
- > 143 (biointact)

(Sprague, Salam, Jorgensen 250? ≠ populations bALP..other biomarkers?)

**Mortality (KDIGO):**
- > 9X pg/ml

**Fractures (DOPPS):**
- > 900 pg/ml

**EXTREME OF RISK**

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**Review**

Silver jubilee: 25 years of the first demonstration of the direct effect of phosphate on the parathyroid cell

Jordi Bover, Pedro Trinidad, Aquiles Jara, Jordi Soler-Majoral, Alejandro Martin-Malo, Armando Torres, João Frazão, Pablo Ureña, Adriana Dussio, Carolt Arana, Fredzzia Grateral, Gregorio Romero-González, Maribel Troya, Diana Samaniego, Luis D’Marco, José Manuel Valdivielso, Elvira Fernández, Maria Dolores Arenas, Vicente Torregrosa, Juan F. Navarro-González, María Jesús Lloret, J.A. Ballarin, Ricardo J Bosch, José L. Garriz, ACL de Francisco, Orlando Gutierrez, Jordi Ara, Arnold Felsenfeld, Antonio Canalejo, Yolanda Almadén.
CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

• 4.2.1: In patients with CKD G3a-G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of iPTH progressively rising or persistently above the UNL for the assay be evaluated by modifiable factors, including hyperphosphatemia, hypocalcemia, high P intake, and VD deficiency (2C).

Should PTH actually be the primary target? PTG activity (ALP/bALP…)

Should the primary goal be P according to many PHENOTYPE studies?

Progressively rising iPTH levels (TRENDS!!) should be treated, persistently above?

How? Modifiable factors first

High (excessive) P intake, hyperphosphatemia, VD deficiency, hypocalcemia
CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

• **4.2.1:** In patients with CKD G3a-G5 **not on dialysis**, the optimal PTH level is not known. However, we suggest that patients with levels of iPTH **progressively rising or persistently above** the UNL for the assay be evaluated by **modifiable factors**, including hyperphosphatemia, hypocalcemia, high P intake, and VD deficiency (2C).

- **High (excessive) P intake, hyperphosphatemia, VD deficiency, hypocalcemia**

Is NATIVE VD really required/ effective or it is just a proxy of “overall health”?

VITAL, D-HEALTH, VITAL by eGFR; D2d, VITAL-DKD VITAL --all cause & cancer-Meta-analysis CKD. Last: Yeung et al. AJKD 2023; VITALE Am J Transplant 2023
Some small RCT’s CKD: vascular endotelial function, PWV,
Vervloet MG. et al Kidney Int 2023

Shall calcidiol levels be measured (association), ↑ PTH surrogate?

Are higher targets needed in CKD patients? (Strugnell SA. Am J Nephrol 201; 50 ng/ml?) **Upper limit?**

Native VD + Active VD? Sequential? **Upper limit?**
Upregulation CYP24A1, ARMOR

Did not reduce all-cause death, Uncertain FR, CVD, kidney outcomes unpowered for CKD, eGFR < 30 and potentially for eGFR < 60 and calcidiol ≤ 20 ng/ml
PTH TARGET? NOT AIMING TO NORMALIZATION (POPULATION-WISE)?

KDOQI 2003

Table 15. Target Range of Intact Plasma PTH by Stage of CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (mL/min/1.73 m²)</th>
<th>Target &quot;intact&quot; PTH (pg/mL [pmol/L])</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30-59</td>
<td>35-70 [3.85-7.7 pmol/L] (OPINION)</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>70-110 [7.7-21 pmol/L] (OPINION)</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
<td>150-300 [16.5-33.0 pmol/L] (EVIDENCE)</td>
</tr>
</tbody>
</table>

ADAPTIVE RESPONSE + HYPORESPONSIVENESS to PTH
(= other hormones and which is NOT just a consequence of PTH fragments!!)

Hyporesponsiveness or resistance to the action of parathyroid hormone in chronic kidney disease

Nefrologia 2021

No suppression!
CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

• 4.2.2: In **adult** patients with CKD G3a-G5 **not on dialysis**, we **suggest** that CTR and VD analogs not be routinely used (2C). It is reasonable to reserve the use of CTR and VD analogs for patients with CKD G4-G5 with **severe and progressive HPT** (Not Graded).

Nothing should be used routinely…
but waiting for “SEVERE”? (exceedingly cautious, PRIMO and OPERA?)
Ureña-Torres P et al NDT 2022, Isakova T et al KDOQI AJKD 2017

Targets not defined → decreased attention to MM in predialysis

Native VD vs extended release calcifediol vs calcitriol and VD analogs?

Calcimimetics in non-dialysis CKD?  Primary HPT may coexist
The risk of medically uncontrolled SHPT depends on PTH levels at HD initiation, international and racial differences.

K. Chan et al Kidney Med 2019

Also “LOW” PTH levels may be of concern

BTM/PTH; FGF23/PTH; Wnt-inhibitors/PTH

Tabibzadeh N. et al. Nephrol Dial Transplant 2021

Tominaga N et al BMC Nephrol 2021
The risk of medically uncontrolled SHPT depends on PTH levels at HD initiation, international and racial differences.

Apart of potential ethnic differences:

Is it the result of different and/or inappropriate early diagnosis and follow-up of CKD?

K. Chan et al Kidney Med 2019
Prospective cohort

Independent effects of secondary hyperparathyroidism and hyperphosphataemia on chronic kidney disease (CKD) progression and cardiovascular (CV) events: an analysis from the NEFRONOA cohort

Background
Secondary hyperparathyroidism (SHPT) is a complication of CKD

Methods
Multicenter (n=81): Spain
NEFRONA cohort
CKD (eGFR < 60 ml/min/1.73 m²) without pre-existing CV disease
Data collected at baseline:
Clinical, biochemical, CV risk factors
Subgroup had repeat eGFR at 2 years
Prospective follow-up: 4 years
Outcomes: CV events, CKD progression
Secondary hyperparathyroidism (SHPT) PTH > KDOQI guidelines or treated with cinacalcet or activated vitamin D

Results
Full cohort: N=2445 with CKD
CV events (4 years) N=203 (8.3%)
SHPT N=1427 (65.5%)
Subgroup with repeat eGFR:
N=1283
CKD progression (2 years) N=301 (23.5%)
SHPT N=692 (63.5%)

Conclusion
Secondary hyperparathyroidism (SHPT) and hyperphosphataemia are independently associated with CKD progression, with a trend towards an association of SHPT with CV events after accounting for competing risks of non-cardiovascular death or kidney transplantation.

84 vs 143 pg/ml
Bozic M., et al. NDT (2021)
KDOQI 2003

D’Arrigo et al NDT 2023

Magagnoli L. et al, Nephrol Dial Transplant 2023 (older, PTH & P)
Incident SHPT was associated with:

- ↑ risk of death: 1.3 fold (1.1-1.8)
- ↑ risk of MACE: 2.2 fold (1.42-3.28)
- ↑ risk of CKD progression: 5.0 fold (3.5-7.2)
- ↑ risk of fractures: 1.3 fold (1.5-2.2)
CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

• 4.2.3: In patients with CKD G5D, we suggest maintaining PTH levels in the range of approximately 2 to 9 times the UNL for the assay (2C). We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

• 4.2.4: In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, CTR, or VD analogs (alphabetical order), or a combination (BEST?) of calcimimetics with CTR or VD analogs (2C).

Calcimimetics vs CTR/VD analogs: other MM abnormalities, adherence, availability and reimbursement policies? Economical Issues?

Calcimimetics first? Cinacalcet vs etelcalcetide (IV) / evocalcet / upacicalcet (IV) ...

Different targets? Is RELATIVE HYPOparathyroidism less of a problem with CM?

PTX?
Comparisons with Intermediate Outcomes in RCT’s

- Comparative Effects of Etelcalcetide and Maxacalcitol on Serum Calcification Propensity in sHPT
  - 425 dialysis patients
  - T50 increases (decreases calcification propensity) for both but the increase was greater with etelcalcetide
  - There was no difference in handgrip strength or cognition between the two drugs.


No significant difference was found in T50

Dörr K et al. Circulation Res 2021
ALFACALCIDOL IN DIALYSIS PATIENTS WITHOUT (NOT OVERT) SHPT

J-DAVID RCT Shoji T. et al. JAMA 2018
Japan, 976 prevalent HD, without sHPT = PTH ≤ 180 pg/ml (JSDT), 0.5 alfalcidol/day
PTH 85 (45-130) / 86 (47-127)
80% Ca-P binder, 68% dialysis bath 1.5 mmol/L
Crossover!!

J-DAVID post-hoc on CV outcomes according to ALP
Oka T et al Sci Rep 2022

959 available ALP [(234 (183-296) U/L]
Alfalcidol did not affect CV outcomes irrespective of “bone turnover” status
TARGET: LOWEST RISK OF MORTALITY IN DIALYSIS PATIENTS (EUROPE)

Floge J et al. Nephrol Dial Transplant 2011
Fractures = limits
Iimori et al. Nephrol Dial Transplant 2012

Fernández-Martín JL et al. Nephrol Dial Transplant 2015

Lamina C et al. Association of changes... (AROii) Nephrol Dial Transplant 2019
60% < 239; 5% > 710
↑ PTH OK, ↓ PTH trend (unpowered), cumulative risk

Population-wise
RECAP (OPINION)

• **Evidence levels** in all nephrology fields (beyond CKD-MBD too) are low/very low. 1\textsuperscript{st} = Early diagnosis and ↓ progression (CKD KDIGO containing 1A-1B evidences)

• Despite its **limitations**, PTH (trends) remain as an important marker of CKD-MBD.

• Modifiable factors: **High (excessive) P intake** (first), hyperphosphatemia, **VD deficiency** (↑ PTH, FR, special populations), **hypocalcemia** (last)
RECAP (OPINION)

- Better balance required between waiting for “severe” sHPT vs avoid iPTH normalization. “Progressively increasing” & compromise 2-3X times UNL at dialysis initiation? Order?: daily native → ERC? → Active VD? G5D 5-6X?

- **Targets** are **demanded** by clinicians/providers but **INDIVIDUALIZATION** is necessary. **OPPORTUNITY TO INDIVIDUALIZE CARE** by previously unaccounted factors such as AGE, GENDER, DIABETES, ETHNICITY, GEOGRAPHICAL AREA.

- **Regarding PTH...** would the JSDT and Prof. Fukagawa convince us why “lower may be better”, in fact “one size does not fits all”
CONTROVERSIES AND TRENDS IN PTH CONTROL

Masafumi Fukagawa, MD, PhD
Tokai University
Isehara, Japan
DISCLOSURES

- Kyowa Kirin: honoraria, consultancy, research grant
- Ono: honoraria, consultancy
- Kissei: honoraria
- Sanwa Kagaku: honoraria, consultancy
- Torii: honoraria
- Bayer Japan: honoraria
One size fits all?
lower cardiovascular risk. Parathyroidectomy is associated with better survival and analyses of JSDT registry data that the history of surgical practice, we have recently shown by propensity-matched development of cachexia, sarcopenia.

Moderate-to-severe SHPT PTH control by the use of cinacalcet was associated with a lower mortality rate in Japanese dialysis patients with this drug may in part be explained by decreased FGF23 levels by in patients with nodular hyperplasia cinacalcet treatment could suppress PTH secretion, even though that of serum phosphorus and calcium the association of PTH levels with mortality is weaker than that of serum phosphorus and calcium. Furthermore, new roles for high PTH levels in the classic concept of PTH as a uremic toxin.

What are the reasons for such a discrepancy?

Fukagawa et al: Kidney Dis, 2017
SHPT management among DOPPS countries

A Mean PTH (pg/mL)

Time since hemodialysis initiation (years)

US black/AA
US nonblack/AA
Europe
Japan

B % of patients

PHT (pg/mL)

- > 800
- 650-600
- 300-450
- 150-300
- 100-150
- 70-100
- 70

Chan K: Kidney Med, 2019
Pattern of Laboratory Parameters and Management of Secondary Hyperparathyroidism in Countries of Europe, Asia, the Middle East, and North America

Mario Cozzolino · Eugeniy Shilov · Zuo Li · Masafumi Fukagawa · Saeed M. G. Al-Ghamdi · Ronald Pisoni · Brian Bieber · Bhadrish Vallabh · Deepa H. Chand

ABSTRACT

Introduction

The DOPPS (Dialysis Outcomes and Practice Patterns Study) is an international collaborative study of secondary hyperparathyroidism (SHPT) in patients undergoing hemodialysis. The purpose of this analysis was to explore laboratory parameters and management strategies for SHPT in different countries.

Methods

The analysis included 20,612 patients in 543 facilities from 26 countries. Laboratory parameters were assessed, and management strategies were evaluated using data collected in the DOPPS study from 2012 to 2015.

Results

Serum intact parathyroid hormone (iPTH) concentration was highest in the UK (14%) and Canada (71%); calcium levels were highest in the USA (78%) and Canada (71%); and phosphorus levels were highest in China (79%) and Canada (60%).

Discussion

The study found that there was a broad distribution of laboratory assessments and management strategies across different countries. This highlights the need for a standardized approach to the management of SHPT to improve bone health in this population.
PTH distribution in Japan at the end of 2021
– JSDT Renal Data Registry –

The results in the current study were derived from the split data from the WADDA system of the JSDT by the authors. However, the interpretation and reporting of these data are the responsibilities of the authors and in no way should be seen as official policies or interpretations of the JSDT.

Derived from the split data from the WADDA system of the JSDT
Reasons for the different targets of PTH control

• Race

• Available drugs

• Medical Care System

• Purposes of PTH Control

• Individualization?
Survival Curve of Dialysis Patients (DOPPS)

Racial Difference
BMI
Food
Adherence
Dialysis Protocol
Time
Methods
Dialysate
Low inflammation
Water purity
Vascular access
More intensive Care
Patient-doctor contact
Routine laboratory tests
# Excess Risk of Cardiovascular Events in Patients in the United States vs. Japan with Chronic Kidney Disease is Mediated Mainly by Left Ventricular Structure and Function

**Cohorts, Participants**

<table>
<thead>
<tr>
<th>CKD-JAC (N=1097)</th>
<th>CRIC (N=3125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>28.7 (12.6)</td>
</tr>
<tr>
<td>UACR (mg/gCr)</td>
<td>520 (135-1338)</td>
</tr>
</tbody>
</table>

**Methods**

1) Compare clinical outcomes
   - CVD
   - ESKD
   - Death

2) Describe typical cardiac structure and function

3) Investigate mediation effects for the difference in the outcomes between cohorts

**Typical hearts for Japanese and US patients**

<table>
<thead>
<tr>
<th>CKD-JAC</th>
<th>TTE findings</th>
<th>CRIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 (7)</td>
<td>LAD (mm)</td>
<td>39 (6)</td>
</tr>
<tr>
<td>65.4 (9.4)</td>
<td>EF (%)</td>
<td>54.2 (8.6)</td>
</tr>
<tr>
<td>46.6 (14.9)</td>
<td>LVMI (g/m²²)</td>
<td>55.7 (19.3)</td>
</tr>
<tr>
<td>36%</td>
<td>LVH</td>
<td>59%</td>
</tr>
<tr>
<td>5%</td>
<td>ASH</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Outcomes**

ASH = septal: posterior wall thickness ratio ≥1.3

**Mediation effects**

% mediated CRIC vs. CKD-JAC

**CONCLUSION**

American patients with CKD are more likely to develop CVD events and death before ESKD as compared to Japanese counterparts. Differences in baseline TTE findings mediate the excess risks of CVD events in US patients over Japanese patients.

*Imaizumi et al, 2023*
Chronic Kidney Disease-Mineral and Bone Disorder in Asia

Masafumi Fukagawa\textsuperscript{a}, Hirotaka Komaba\textsuperscript{a, b}

\textsuperscript{a}Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, and \textsuperscript{b}The Institute of Medical Sciences, Tokai University, Isehara, Japan

### Table 3. Drugs available for chronic kidney disease-mineral and bone disorder in Asian countries and regions

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs (generic name)</th>
<th>Japan</th>
<th>Korea</th>
<th>China</th>
<th>Taiwan</th>
<th>Hong Kong</th>
<th>Singapore</th>
<th>Malaysia</th>
<th>Thailand</th>
</tr>
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<tbody>
<tr>
<td>VDRA</td>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Rocaltrol\textsuperscript{b} (calcitriol)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Alfaro\textsuperscript{b} (alfacalcidol)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Hornel\textsuperscript{b}/Fulstan\textsuperscript{b} (falecalcitriol)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td></td>
<td>Calcitriol generics</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Calcijex\textsuperscript{c} (calcitriol)</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Zemplar\textsuperscript{c} (paricalcitol)</td>
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<tr>
<td></td>
<td>Oxal\textsuperscript{c} (maxacalcitol)</td>
<td>✓</td>
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<td>✓</td>
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<td></td>
<td>Calcitriol generics</td>
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<tr>
<td>P-binder</td>
<td>Renagel\textsuperscript{d}/Phosblock\textsuperscript{d} (sevelamer HCl)</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Renvela\textsuperscript{d} (sevelamer CO\textsubscript{3})</td>
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<td>✓</td>
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<tr>
<td></td>
<td>Kiklin\textsuperscript{e} (bixalomer)</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Riona\textsuperscript{f}/Nephobil\textsuperscript{f} (ferric citrate)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>P-Tol\textsuperscript{g}/Velphoro\textsuperscript{g} (sucroferic oxhydroxide)</td>
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<td>✓</td>
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<tr>
<td></td>
<td>Calcium-based phosphate-binder generics</td>
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<tr>
<td>Calcimimetics</td>
<td>Regpara\textsuperscript{h} (cinacalcet)</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Parsabiv\textsuperscript{i} (etelcalcetide)</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

IV, intravenous. Shaded lines, no reimbursement. \textsuperscript{a} Approved but not yet launched, as of December 2016.

© 2017 S. Karger AG, Basel
DOI: 10.1159/000470909
Kidney Dis
Published online: April 13, 2017

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### Key Message:

As briefly summarized thus far, there remain substantial improvements in management in the near future. Policies for publishing and sharing of data regarding Asian CKD are ongoing. Economic development in Asia. Ongoing economic development in the near future. Policies for publishing and sharing of data regarding Asian CKD are ongoing.
Calcimimetic use in Japan at the end of 2019
– JSDT Renal Data Registry –

The results in the current study were derived from the split data from the WADDA system of the JSDT by the authors. However, the interpretation and reporting of these data are the responsibilities of the authors and in no way should be seen as official policies or interpretations of the JSDT.

Derived from the split data from the WADDA system of the JSDT
Purposes of PTH Control in CKD

• Easier control of serum phosphorus and calcium level

• Bone turnover
  • Bone fracture
  • Vascular calcification

• Prevent the progression of parathyroid hyperplasia

• Energy wasting

• Survival
• CV risk
Achievement of Ca and P Target

61 ~ 180 (HR < 1.2)

Odds ratio

Ref.

Taniguchi M et al. Ther Apher Dial 17, 2013

Formatio

Calcium

Resorptio

Extracellular phosphate

Bone

crude case-adjusted full-adjusted

~60 ~120 ~180 ~240 ~300 ~360 ~420 ~480 ~540 ~600 ~700 ~800 ~860
Progression of Parathyroid Hyperplasia

- Normal Parathyroid
- Diffuse Hyperplasia
  - Early Nodularity in diffuse Hyperplasia
  - Volume > 0.5cm³
    - PTH > 500pg/ml

Decrease
- VDR
- CaR
- FGFR-klotho

- Nodular Hyperplasia
  - Single Nodular Gland
PTH levels and Body Weight Loss in Dialysis Patients

% weight change (95% CI for difference to reference group)

Model 1 adjusted for country, study phase, and electronic health record data source (US phases 4–6 only), accounting for facility clustering.
Model 2 adjusted for covariates in Model 1 plus age, sex, time on dialysis, 13 comorbid conditions, single-pool Kt/V, and dry weight.
Model 3 adjusted for covariates in Model 2 plus albumin, hemoglobin, creatinine, calcium, and phosphorus.
Model 4 adjusted for covariates in Model 3 plus calcium-based binder, sevelamer, lanthanum, other phosphate binders, active vitamin D derivatives, and calcimimetics.

Komaba H et al. J Cachexia Sarcopenia Muscle, 2021
PTH and Fracture Risk

Tentori F et al. Kidney Int 85, 2014
Wakasugi M et al. Ther Apher Dial 2019
Secondary HPT and mortality

- Taniguchi M et al. Ther Apher Dial 17, 2013
PTH and Survival (JRDR data)

All-cause mortality

Goto S et al. Nephrol Dial Transplant, in press
Kaplan-Meier cumulative incidence of death between Cinacalcet and PTx

- No. at risk:
  - Cinacalcet: 2,682, 2,520, 2,283, 2,204, 2,044, 1,880, 1,755
  - PTx: 894, 843, 811, 773, 738, 687, 643

- HR 0.78, (95% CI, 0.67–0.91); P = 0.002

Komaba H et al. J Clin Endocrinol Metab, 2022
## Prognosed and PTH Tertile after PTx

<table>
<thead>
<tr>
<th>Postoperative PTH</th>
<th>PTx Median (IQR) posttreatment intact PTH (pg/mL)</th>
<th>n</th>
<th>Cinacalcet Median (IQR) posttreatment intact PTH (pg/mL)</th>
<th>n</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1 (&lt;35 pg/mL)</td>
<td>12 (7–20)</td>
<td>304</td>
<td>231 (148–401)</td>
<td>912</td>
<td>0.56</td>
<td>0.42–0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tertile 2 (35-163 pg/mL)</td>
<td>83 (53–121)</td>
<td>304</td>
<td>232 (140–383)</td>
<td>912</td>
<td>0.73</td>
<td>0.55–0.95</td>
<td>0.022</td>
</tr>
<tr>
<td>Tertile 3 (≥164 pg/mL)</td>
<td>321 (226–522)</td>
<td>304</td>
<td>213 (135–343)</td>
<td>912</td>
<td>1.02</td>
<td>0.79–1.30</td>
<td>0.90</td>
</tr>
</tbody>
</table>

The lower, the better?

### Exceptions?: Hypercalcemia, Immediate KT candidates

Komaba H et al. J Clin Endocrinol Metab, 2022
Ethnic differences in bone and mineral metabolism in healthy people and patients with CKD

Vanda Jorgetti¹, Luciene M. dos Reis¹ and Susan M. Ott²

Kidney Int, 2014

Table 1 | Main differences in bone and mineral metabolism parameters in black individuals compared with white individuals

<table>
<thead>
<tr>
<th></th>
<th>Normal or early CKD</th>
<th>Late stage CKD, including dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease/mortality</td>
<td>More rapid progression</td>
<td>Better survival</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>Intestinal calcium</td>
<td>More efficient</td>
<td></td>
</tr>
<tr>
<td>absorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine calcium</td>
<td>Lower excretion</td>
<td></td>
</tr>
<tr>
<td>Serum 25(OH)D</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Serum 1,25(OH)₂D</td>
<td>Higher</td>
<td></td>
</tr>
<tr>
<td>Serum PTH</td>
<td>Higher</td>
<td>Higher</td>
</tr>
<tr>
<td>Serum FGF23</td>
<td>Similar or lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Fracture rates</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>Higher</td>
<td>Higher</td>
</tr>
<tr>
<td>Bone formation rates</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Bone volume</td>
<td>Higher or similar</td>
<td>Higher</td>
</tr>
<tr>
<td>Bone response to PTH</td>
<td>Less resorption</td>
<td>Less resorption</td>
</tr>
<tr>
<td>Fracture association with vitamin D level</td>
<td>Fewer fractures with low vitamin D</td>
<td></td>
</tr>
<tr>
<td>Vascular calcifications</td>
<td>Fewer in diabetic patients</td>
<td>Fewer or similar</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular disease</td>
<td>Higher (or similar with equal access to care)</td>
<td>Fewer</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.
Bone metabolism in European and Japanese patients with end stage kidney disease: a comparative study

Tokai Cohort (Mongolian) Leuven Cohort (Caucasian)

Hypothesis: Response to PTH is better in Japanese patients
Lower Bone Turnover and Skeletal PTH Responsiveness in Japanese Compared to European Patients on Hemodialysis

Pieter Evenepoel,1,2,* Hanne Skou Jørgensen,1,3,* Hirotaka Komaba,4,* Sandro Mazzaferro,5,6, Marc Vervloet,7,8,† Etienne Cavalier,9,† and Masafumi Fukagawa4,*

Abstract
This study investigates whether skeletal PTH responsiveness is better preserved in Japanese vs European patients receiving HD.

Results: Japanese patients had lower levels of iPTH (207 vs 268 pg/mL; P < .001). Linear regression analyses revealed lower levels of bone turnover markers for any given level of PTH in Japanese vs Belgian patients when stratifying or matching according to PTH levels.

Conclusion: Male sex, obesity, and hyperphosphatemia were the main determinants of the bone turnover marker/PTH ratios.

*P.E., H.S.J., and H.K. and M.V., E.C., and M.F. contributed equally to this work.

Objective: Parathyroid hormone (PTH) treatment targets for patients receiving hemodialysis (HD) are lower in Japan than in Europe. Whether this translates to lower bone turnover is unknown and could depend on skeletal PTH responsiveness.

Context: Bone turnover and skeletal PTH responsiveness are important in bone health and vascular health in CKD.

Key Words: Bone turnover marker/PTH ratios; bone turnover; parathyroid hormone.

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https://doi.org/10.1210/clinem/dgac522

Clinical Research Article

Asian vs Caucasian

Lower response to PTH in Japanese

A Special Group
with a much lower basal PTH level?

???
• Should the PTH target ranges be individually optimized based on the control purposes and patients’ backgrounds?

  Age
  Sex
  Race
  Diabetes
  High risk patients
Questions and Comments