Parathyroid Hormone Assays: Biochemical Conundrums and Confusing Clinical Applications

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Topics

- Physiologic regulation and significance of CAP 1-84 CIP (7-84) PTH fragments
- Incidence of adynamic bone disease, osteoporosis and mortality among chronic dialysis patients
- Relationship between low-turn over bone disease and arterial calcifications
- Utility of 3rd generation PTH assays in the daily management of ESRD patients
- Therapeutic options for minimizing low turnover Bone disease
PTH Fragments: What are they and are They Clinically Important?

The Parathyroid Glands

HPLC

7-84
1-84

Intact PTH Assay:
More Than Meets the Eye
Physiologic and Pathophysiologic Effects of PTH Carboxy Fragments in Dialysis Patients

- PTH 1-34 fragments are sufficient to activate "classic" PTH receptor
  Activation of PTHr increases intracellular c-AMP
  Increases serum Ca++

- Carboxy PTH fragments are synthesized and secreted by parathyroid gland and comprise 80% of circulating PTH
  Secretion is altered by changes in ionized Ca++

- Carboxy PTH fragments bind to separate C-PTH receptor
  7-84 binding to C-PTH receptor antagonizes 1-84 PTH
  39-84 and 53-84 PTH fragments synergize effects of 7-84
  Fails to generate c-AMP levels
  Inhibit bone resorption
  Osteocyte apoptosis
  Associated with adynamic bone disease

Brossard et.al. Sem. Dialysis 15(3) 196-201, 2002
PTH Secretion and Storage: Release of 7-84 Fragments in Response to Changes in Extracellular Ca++
Putative Evidence for Separate Carboxy Terminus PTH 7-84 Receptor
What is the effect of increasing extracellular Ca++ on the release of 1-84 and 7-84 fragments?
Serum Ionized Calcium Concentrations Differentially Regulate Synthesis of (7-84) and (1-84) PTH
Administration of PTH (7-84) Antagonizes the Physiologic Effects of Intact PTH (1-84)

• Study Question: What are the effects of the carboxy terminal peptide PTH (7-84) on the physiologic effects of intact PTH?

• Study Methods:
  Male Sprague Dawley rats underwent total thyroid and parathyroidectomy at 90 days

• Alzet minipump infusion X: Animal Sacrifice
  PTH (1-84)  Bone Morphometry
  PTH (7-84)  Osteoclast #
  PTH (1-84+(7-84))  Osteoblast #

Carboxy Terminal PTH (7-84) Antagonizes Phosphaturic Effects of Intact Hormone


Carboxy Terminal PTH (7-84) Antagonizes Hypercalcemic Effect of Intact Hormone

Human 7-84 PTH Inhibits Vitamin D3 Induced Mobilization of Calcium from Neonatal Mice

Divieti et.al. Endocrinology 143(1) 171-176, 2002
How do carboxy fragments of PTH alter bone formation?
PTH (7-84) Reduces Bone Resorption Through Reduction of Osteoclast Formation

Human 7-84 PTH Inhibits Vitamin D3 Induced Formation of Osteoclast Resorption Crypts

Divieti et al. Endocrinology 143(1) 171-176, 2002
Evolving Opinions of PTH (7-84): Inconsequential to Confirmed Inhibitor

<table>
<thead>
<tr>
<th>Before 1999</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
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<tbody>
<tr>
<td><strong>Position:</strong> DPC</td>
<td>JCE&amp;M</td>
<td>Kidney Int’l.</td>
<td>Kidney Int’l. &amp; JASN and Divietti, et.al.</td>
<td>to be published</td>
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<tr>
<td>(new MAB 30% lower values)</td>
<td>“A cross reactant that can be eliminated. Therefore, not important to measure” <strong>Position:</strong> Nichols, Roche</td>
<td>“An inhibitor to PTH”</td>
<td>“A marker and cause of adynamic low bone turnover”</td>
<td>“A new paradigm &amp; marker for over-suppression”</td>
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Therefore important to measure to diagnose bone status

**Position:** Scantibodies
“Are there clinical means for monitoring the levels of circulating PTH carboxy fragments?”
Superior Specificity of 3rd Generation PTH Assays: Primacy of Detection Antibodies
Clinical Detection of PTH (7-84) By Commercial Assays

![Bar Chart]

- Scantibodies 3rd Generation CAP™ IRMA
- DSL 2nd Generation intact PTH IRMA
- Diasorin 2nd Generation N-Tact PTH IRMA
- DPC 2nd Generation immulite PTH ICMA
- Scantibodies 2nd Generation tPTH IRMA
- Nichols 2nd Generation intact PTH IRMA

Gao, et al. ASBMR 2000 Abstract #455
“So if there are all these circulating active fragments, where should we target our PTH levels?”
Correlation Between Bone Morphometry and Intact (1-84) PTH: DOQI Guidelines

- **High Turnover**
  - >300
  - Intact PTH (1-84) >300

- **Normal Bone**
  - 150-300
  - Intact PTH (1-84) 150-300

- **Low Turnover**
  - <150
  - Intact PTH (1-84) <150
What are the clinical effects of the carboxy PTH fragments—do they matter?
Spectrum of Renal Bone Disease in End-Stage Renal Failure Patients not on Dialysis

Spectrum of Renal Disease in ESRD: Evolving Patterns

Are there racial differences in PTH levels? Does this impact our treatment of African Americans?
Differential Intact PTH Levels Between African Americans and Caucasian Dialysis Patients: Impact on Incidence of Adynamic Bone Disease

Fig. 2. Intact parathyroid hormone (PTH) in African-Americans (AA) and Caucasians (C) with low and high bone turnover (BT). *P < 0.01 compared to PTH levels in all other groups.

Sawaya et.al. Kidney Internal. 64:737-742, 2003
Utility of PTH 1-84/7-84 Ratio in Prevention of Adynamic Bone Disease Among African American Patients

Premise: Adynamic bone disease represents a great risk for African American ESRD patients as adynamic bone disease leads to the mortal conditions of arterial and soft tissue calcification. Many patients with iPTH >100 pgm/mL have adynamic bone disease and are being overdosed with I.V. vitamin D analogs.

Question: Can use of the 1-84 PTH/7-84 PTH ratio versus the Bio-Intact™ PTH to guide I.V. vitamin D analog/calcium supplement therapy, reduce adynamic bone disease among African American ESRD patients?

Experiment: Two groups of African American ESRD patients located at two dialysis clinics in the Henry Ford Healthcare System (Detroit, MI) will have their I.V. vitamin D analog/calcium supplement therapy guided by either the Bio-Intact™ PTH assay (group 1) or the 1-84 PTH/7-84 PTH ratio (group 2). Following three years of therapy, patients with iPTH >100 pgm/mL will be bone biopsied and assessed for the incidence of adynamic bone disease.

Fehmi et.al. Presented Dialysis Conference San Francisco 2006
Utility of PTH 1-84/7-84 Ratio in Prevention of Adynamic Bone Disease Among African American Patients

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Utility of PTH 1-84/7-84 Ratio in Prevention of Adynamic Bone Disease Among African American Patients

Fehmi et.al. Presented Dialysis Conference San Francisco 2006
Elimination of Adynamic Bone Disease with (iPTH>100 pg/ml) Following 3 Years of Vitamin D Management using 1-84/7-84 Ratio

African American ESRD patients at two dialysis clinics at Henry Ford Healthcare System were bone biopsied following three years of I.V. vitamin D analog/calcium supplement therapy that was guided by the Bio-Intact PTH™ assay (17 pts) or the 1-84 PTH/7-84 PTH ratio (20 pts)

Fehmi et.al. Presented Dialysis Conference San Francisco 2006
Decreasing PTH Levels Contribute to significant Vascular Calcifications?
Correlation Between Low Turnover Bone Disease and Arterial Calcifications

- **Study Objective:** To determine whether patients with low versus high turnover bone disease are predisposed to arterial calcifications

- **Study Design:** A single cohort observational study of 58 non-diabetic ESRD patients on hemodialysis
  Duration of dialysis: 1-25 years

- **Methods:** Arterial calcifications documented by US

- **Bone Biopsy- Tetracycline labeling**
  - High turnover
  - Low turnover

- **Ultrasound-carotids**
  - Abd aorta
  - Iliac/Femoral

- **Serum Chemistries:** PTH(1-84), Vitamin D3

Correlation Between Low Turnover Bone Disease and Arterial Calcifications


P<0.0001

“Normal” Intact PTH 150-300

Serum PTH (pg/ml)

Arterial Calcification Score

AC-0

AC-1

AC-2

AC-3

AC-4

P<0.0001

387

567

316

202

71
Hyperphosphatemia?
**Spectrum of Renal Bone Disease in End-Stage Renal Failure Patients not on Dialysis**

- **Study Objective:** Determine the prevalence of renal osteodystrophy among a non-selected population of dialysis patients.
- **Study Design:** Prospective, open-label, cross-sectional study of bone morphology in 84 patients with ESRD that have not been initiated on dialysis.
- **Methods:** Transiliac biopsy obtained prior to initiating dialysis.
- **Medications:** CaCO$_4$ four time/day

Effect of Calcium Phosphorous Product Index on Survival Among Dialysis Patients

Ca\(^{++}\) 9.8-PO\(_4\) <6.0 mg/dl
35% 3-year mortality

Ca\(^{++}\) 9.8-PO\(_4\) >7.0 mg/dl
70% 3-year mortality

Reduced Survival Among Dialysis Patients with Established Osteopenia or Osteoporosis

3 Year Mortality Rate:
- Normal Density: 22%
- Osteopenia: 65%
- Osteoporosis: 75%

Calciphylaxis?
Case#1

March 2004: 63 WM with ESRD secondary to Type II Diabetes M has been compliant with dialysis, but consistently demonstrates poor dietary control. Recent history of refractory pruritis.

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<thead>
<tr>
<th>Labs</th>
<th>TP</th>
<th>Alb</th>
<th>Ca</th>
<th>PO4</th>
<th>PTH-Intact</th>
<th>KT/V</th>
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<tr>
<td>137</td>
<td>98</td>
<td>93</td>
<td>4.6</td>
<td>22</td>
<td>12.9</td>
<td>118</td>
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Action: Run time increased from 3:15 to 3:45 hrs
Vitamin D3 lowered from 7.0-3.0 ug/Tx
Sevelamer (1600 mg Qac) instituted for PO4 control

July 2004: Patient returns with complaints of painful skin lesions that have been progressive over the last 4 weeks.
PTH-Intact: 215
Fractionated PTH CAP-95 / CIP-120 Ratio-0.8
Case #1
Case #1

Sub-Q-Dermis

Ca^{++} Staining

Striated Muscle

Ca^{++} Staining
Acral Calciphylaxis: Association with High Turnover Bone Disease
Proximal Calciphylaxis: Association with Low Turnover Bone Disease
Summary and Conclusions

- Renal osteodystrophy is a complicated syndrome involving hormonal regulation by PTH/Vitamin D3 and interactions with calcium/phosphate metabolism

- Progressive change from high to low turnover bone disease

- Clinical complications of low turnover bone disease include increased incidence of pathologic fracture and accelerated vascular calcification

- Third generation PTH tests have identified a biologically active form of PTH (7-84) that antagonizes hypercalcemic effects of intact PTH (1-84)

- Total PTH levels is insufficient to identify all patients with low turnover bone disease. Patient management is facilitated by of 1-84/7-84 ratios