Metabolic Bone Disease in Chronic Kidney Disease (MBD-CKD)

**Introduction**
- Renal osteodystrophy is an important aspect of renal failure
- An alteration of bone morphology
- A multi-factorial disorder of skeletal dysfunction

**The Kidney’s Role?**
- Regulation of calcium, phosphorous, and magnesium metabolism
- Involvement in the catabolism of PTH
- Excretion of aluminum (*CaCO₃*)
- Synthesis of calcitriol (1,25-dihydroxyvitamin D₃) using 1-alpha hydroxylase

**What Happens?**
- GFR decreased
- High Phosphorous
- Low Calcium
- Increased PTH release
  - **KIDNEY**
    - Increased alpha hydroxylase activity
    - Increased calcitriol production
    - Increased Reabsorption of Ca²⁺ in the distal tubule
  - **BONE**
    - Increased bone and soft tissue mobilization of Ca²⁺
  - **INTESTINE**
    - Increased intestinal Ca²⁺ absorption

**Chronic Kidney Disease-PTH**
- Alteration of PTH secretion (2° hyperparathyroidism)
- Higher threshold of PTH secretion in response to serum Ca²⁺ levels
- Skeletal resistance to calcemic actions of PTH and alterations to Ca²⁺ sensing receptors
- Normal rapid mobilization of Ca²⁺ and Phos from the skeleton is diminished

**Chronic Kidney Disease-Ca²⁺**
- Low levels of calcitriol impairs Ca²⁺ absorption (hypocalcemia/hypocalcuria)
- Ca-sensitive receptors found in kidney, parathyroid gland, brain, GI tract
- Changes in Ca-R expression will effect response (set-points)
Chronic Kidney Disease-VitD

- Proximal tubule is 1st site of synthesis
- Alpha-hydroxylase activity is affected by PTH, calcium, phos, IGF-1, other cytokine factors
- Impaired renal synthesis of calcitriol follows
- Can inhibit PTH gene transcription factors

Chronic Kidney Disease-PO4-

- High levels of phosphorous alone will increase parathyroid gland activity/hypertrophy
- Below 30% level of function, frank phosphorous retention occurs

Chronic Kidney Disease

- Bone histologic abnormalities can be seen even at 50% renal function
- Before renal function approaches 30% PTH levels begin to rise and decreased tubular resorption of phosphorous occurs to maintain a balance
- Reduction of phosphorous in the diet can maintain normal balance at Stages 2-3 (GFR 30-90 ml/min)
- Stages 4-5 require dietary restrictions as well as phosphate binders +/- vit-D supplementation

ClinicalManifestations

- Hypocalcemia, hyperphosphatemia, 2nd hyperparathyroidism, altered vitD metabolism
- Subperiostial absorption, osteosclerosis
- Linear growth failure, epiphyseal abnormalities, weight bearing joint abnormalities, avascular necrosis, bone pain, fractures
- Proximal myopathy, ocular disease, soft tissue necrosis
- Extraskeletal calcifications

K-DOQI Guidelines

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Serum Phosphorous (mg/dl)</th>
<th>Serum Calcium (mg/dl)</th>
<th>Alkaline Phosphatase (mg/dl)</th>
<th>Target iPTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>4.5-6.5</td>
<td>9.4-10.8</td>
<td>100-350</td>
<td>200-300</td>
</tr>
<tr>
<td>6-12</td>
<td>3.8-5.8</td>
<td>9.4-10.3</td>
<td>60-150</td>
<td>200-300</td>
</tr>
<tr>
<td>13-20</td>
<td>2.3-4.5</td>
<td>8.8-10.2</td>
<td>40-180</td>
<td>200-300</td>
</tr>
</tbody>
</table>

Sample 5-Year Data

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Recommended CaXP (product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children-12</td>
<td>&lt;65</td>
</tr>
<tr>
<td>12 and over</td>
<td>&lt;55</td>
</tr>
</tbody>
</table>
Discussion

- Based on 2005 guidelines, very little difference between 2005 and 2009 results
- Monthly labs, regular adjustments of diet, phos binders, ca supplementation, vit-D supplementation what is the problem?
- The universal issue of compliance! (and a little thing called nature that is sometimes impossible to replicate)

KDOQI Compliance

- Measures of compliance for the team include
  - Kt/V
  - Missed sessions
  - Interdialytic fluid gains
  - Serum PO₄ level
- Kidney Disease and Quality of Life questionnaire (KDQOL-SF36)

References


MICROALBUMINURIA IN PEDIATRIC HYPERTENSION: INFLUENCE OF OBESITY

Sudha Garimella MD
Grand rounds WCHOB 2009 MAY

DEFINITIONS

MICROALBUMINURIA

- Microalbuminuria is defined as abnormal urinary excretion of albumin between 30 and 300 mg/d
- 24-hour urine collection - 20 to 200 µg/min OR > 10 µg/min Nocturnal sample.
- Albumin to Creatinine ratio (mg/g) - 30 to 299 mg/g in a single spot urine sample.

WHY IS THIS IMPORTANT?

- MA is consistently associated with CKD, CVD, endothelial dysfunction and early mortality in Type 2 diabetes in adults and children.
- 25.4% (95% CI 22.3-28.3) had microalbuminuria and 9.4% (8.3-11.4) had macroalbuminuria or ESRD. Risk factors for microalbuminuria were diabetes duration (odds ratio 1.033, P < 0.0001), A1C (1.13, P < 0.0001), LDL cholesterol (1.003, P < 0.0074), blood pressure (1.008, P < 0.0074) and male sex was associated with the development of macroalbuminuria.

ADULT STUDIES - MA IN HYPERTENSION

- Microalbuminuria is a known risk factor for CKD and CVD in adults with hypertension.

- Prevalence and Clinical Correlates of Microalbuminuria in Essential Hypertension - The MAGIC Study Roberto Pontremoli et al Hypertension. 1997;30:1135-1143
- 787 untreated patients with essential hypertension. The prevalence of microalbuminuria was 6.7% increased urinary albumin excretion is associated with a worse cardiovascular risk profile and is a concomitant indicator of early target organ damage

MA and obesity

- Obesity has been independently identified as a risk factor for progression to ESRD in adults.
- Complex interplay between obesity and RAAS, Endothelial dysfunction and fibrosis leading to ESRD.
- MA is being investigated as a surrogate biomarker for ESRD
PEDIATRIC STUDIES

  - NO recommendations about MA
  - No progressive or retrospective large scale studies looking at the same risk factors as the adult studies prior to 2005.

PILOT STUDY AT WCHOB

- 2005 poster presentation at ASPN conference – MA in Pediatric Hypertension.
  - Prevalence of MA amongst hypertensive children attending renal clinic.
  - Exclusion criteria: pre-existing renal disease, secondary hypertension, diabetes, blood pressure-altering medications, illness, fever or recent excessive exercise
  - N=44, Mean age 14.6 years, MA 34% BMI mean 30.36

PILOT STUDY AT WCHOB

- 2008 Poster presentation at ASPN conference – Obesity as a risk factor for MA in hypertensive children.
  - N=95, MA in Hypertension alone=52.6%, MA in obese =30%, normal=11.8% and both H+O= 20%.
  - Obesity modifies cardiovascular risk factors including MA in children with HTN.

PROPOSED STUDY

- Prevalence of Microalbuminuria in Pediatric patients with Hypertension submitted to the mid west pediatric nephrology consortium
- Patients may be stratified according to BMI. The following parameters could be studied:
  - MACR
  - SBP/DBP ASSOCIATION
  - AGE/SEX/RACE DISTRIBUTION
  - OTHER FACTORS OF INTEREST : GFR, CRP, LVH, LIPID PROFILE AND INSULIN RESISTANCE, METABOLIC SYNDROME, NASH...
PROPOSED STUDY

- Patients are stratified into 4 categories
  - Normal BMI, Normal BP
  - Normal BMI, Hypertensive
  - Abnormal high BMI, Normal BP
  - Abnormal high BMI, Hypertensive
- First morning void
- Data collection - Age, Sex, BMI, SBP, DBP, UA, date and time of collection, age at diagnosis of HTN if+, chart review for available data on other parameters - LVH, GFR etc.

Website for data collection from each center will allow for center specific analysis.
- Estimated number of children in each category for meaningful analysis = 500. Normal should ideally be 2-3 times n.
- Study period: 1 year or target number reached.

BIBLIOGRAPHY - PEDIATRIC STUDIES

- Penina Tarshish, Pamela M. Diamantis, Carmen B. Isasi, Adriana E. Groisman. Pediatrics/Pediatric Nephrology, Jacobi Medical Center/AECOM, Bronx, NY; Epidemiology, Albert Einstein College of Medicine, Bronx, NY.
- Prevalence of Proteinuria and its Relationship to Body Mass in Adolescents. [2006] [3351.243]
  - Laurie Hornberger, Steve Simon, Sarah Hambly, Lorraine Brewer, [H S. Alan, Dept. of Pediatrics, Children’s Mercy Hospital, Univ. of Missouri-Kansas City, Kansas City, MO; Office of Medical Research, Children’s Mercy Hospital, Kansas City, MO.
- Is Microalbuminuria (MA) in Childhood Obesity Related to Glucose Toxicity? [2004] [831]
  - Tania S. Burgert, Catherine Yeckel, William Tamborlane, Sonia Caprio. Section of Pediatric Endocrinology, Department of Pediatrics, Yale University, New Haven, CT.