

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

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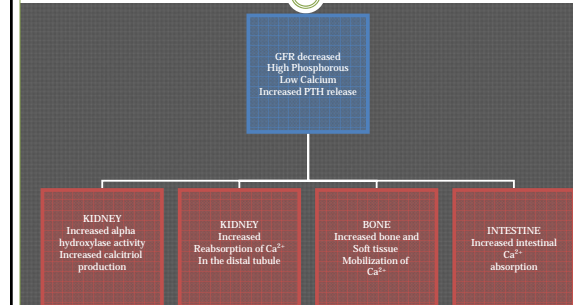
## Introduction

- 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 (\*CaCO<sub>3</sub>)
- Synthesis of calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) using 1-alpha hydroxylase

## What Happens?



## Chronic Kidney Disease-PTH

- Alteration of PTH secretion (2° hyperparathyroidism)
- Higher threshold of PTH secretion in response to serum Ca<sup>2+</sup> levels
- Skeletal resistance to calcemic actions of PTH and alterations to Ca<sup>2+</sup> sensing receptors
- Normal rapid mobilization of Ca<sup>2+</sup> and Phos from the skeleton is diminished

## Chronic Kidney Disease-Ca<sup>2+</sup>

- Low levels of calcitriol impairs Ca<sup>2+</sup> absorption (hypocalcemia/hypocalcemia)
- 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 1<sup>o</sup> 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-PO<sup>4-</sup>

- 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

## Clinical Manifestations

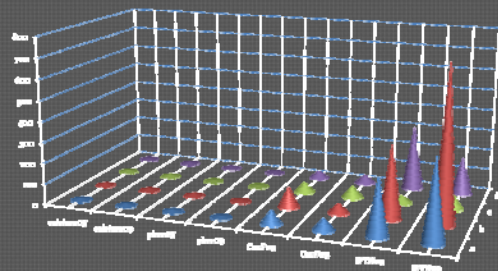
- Hypocalcemia, hyperphosphatemia, 2<sup>o</sup> hyperparathyroidism, altered vitD metabolism
- Subperiosteal absorption, osteosclerosis
- Linear growth failure, epiphyseal abnormalities, weight bearing joint abnormalities, avascular necrosis, bone pain, fractures
- Proximal myopathy, ocular disease,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

## K-DOQI Guidelines

Age (years)	Serum Phosphorous (mg/dl)	Serum Calcium (mg/dl)	Alkaline Phosphatase (mg/dl)	Target iPTH (pg/ml)
1-5	4.5-6.5	9.4-10.8	100-350	200-300
6-12	3.6-5.8	9.4-10.3	60-450	200-300
13-20	2.3-4.5	8.8-10.2	40-180	200-300

Age (years)	Recommended CaxP (product)
Children-12	<65
12 and over	<55

## Sample 5-Year Data



## 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 PO<sup>4-</sup> level
- Kidney Disease and Quality of Life questionnaire (KDQOL-SF36)

## References

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## 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?

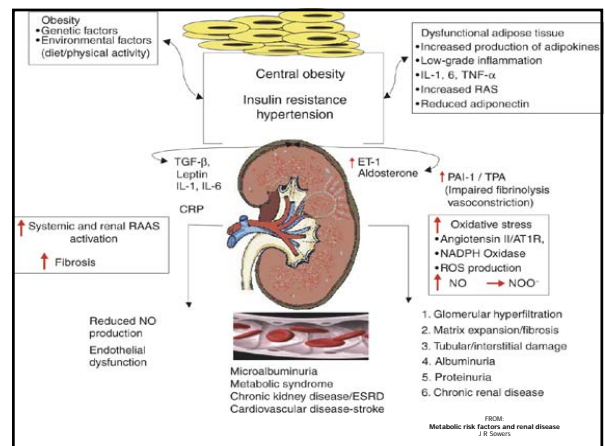
- MA is consistently associated with CKD, CVD, endothelial dysfunction and early mortality in Type 2 diabetes in adults and children.
- Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Ralle K et al Diabetes Care. 2007 Oct;30(10):2523-8. Epub 2007 Jul 13., Germany
- 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)
  - 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.
- Pulse pressure and isolated systolic hypertension: association with microalbuminuria. The GUBBIO Study Collaborative Research Group. Cirillo M et al Italy Kidney Int. 2000 Sep;58(3):1211-8.

## 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

- Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents 2004
  - 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.

## Being Overweight Modifies the Association Between Cardiovascular Risk Factors and Microalbuminuria in Adolescents

- Nguyen et al PEDIATRICS Volume 121, Number 1, January 2008
  - Cross-sectional data from the National Health and Nutrition Examination Survey(1999–2004) for 2515 adolescents 12 to 19 years of age
  - Microalbuminuria was present in 8.9% of adolescents.
  - Obesity was present in 10.3%
  - Hypertension was present in 2.9%

## Being Overweight Modifies the Association Between Cardiovascular Risk Factors and Microalbuminuria in Adolescents

- The prevalence of microalbuminuria was higher among nonoverweight adolescents than among overweight adolescents.
- The median albumin/creatinine ratio decreased with increasing BMI z scores
- Among non overweight adolescents, microalbuminuria was not associated with any cardiovascular disease risk factor except for overt diabetes mellitus.
- Among overweight adolescents, however, microalbuminuria was associated with impaired fasting glucose, insulin resistance, hypertension, and smoking, as well as diabetes mellitus.

## 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.



## PROPOSED STUDY

- 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.



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