

## **Recent papers of interest for the ESPN CKD-MBD working group May 2015**

### **1- FGF23 as a predictor not only of mortality but also of infectious complications in hemodialysis patients, JASN 2015**

J Am Soc Nephrol. 2015 May 13. pii: ASN.2014101009. [Epub ahead of print]

Low Vitamin D and High Fibroblast Growth Factor 23 Serum Levels Associate with Infectious and Cardiac Deaths in the HEMO Study.

Chonchol M, Greene T, Zhang Y, Hoofnagle AN, Cheung AK.

Longitudinal studies testing the relationship between repeated measures of vitamin D or fibroblast growth factor 23 (FGF23) and infectious and cardiac hospitalizations and death in hemodialysis patients have not been reported. We examined the association between yearly 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), and FGF23 serum levels and various clinical outcomes using time-dependent Cox regression models with repeated yearly measures and fixed-covariate Cox models with only baseline values after controlling for important clinical covariates in the HEMO study. During a median follow-up of 3 years, 582 of the 1340 participants died, and 499 and 514 participants had a hospitalization or death attributed to infectious and cardiac causes, respectively. Patients in the highest 25(OH)D quartile had the lowest risk of infectious events (hazard ratio [HR] 0.66 versus the lowest quartile; 95% confidence interval [95% CI], 0.49-0.89), cardiac events (HR, 0.71; 95% CI, 0.53-0.96), and all-cause mortality (HR, 0.46; 95% CI, 0.34-0.62) in time-dependent analyses. No significant associations of 1,25(OH)2D with clinical outcomes were observed in time-dependent or fixed-covariate Cox models. In contrast, the highest FGF23 quartile was associated with a higher risk of infectious events (HR, 1.57 versus the lowest quartile; 95% CI, 1.13-2.18), cardiac events (HR, 1.49; 95% CI, 1.06-2.08), and all-cause mortality (HR, 1.50; 95% CI, 1.07-2.12) in fixed-covariate Cox models. The addition of inflammation markers into the statistical models did not attenuate these associations. Thus, disordered mineral metabolism may affect outcomes in chronic hemodialysis patients.

### **2- Calcilytics may be helpful in hypocalcemia due to activating CaSR mutations, JBMR 2015**

J Bone Miner Res. 2015 May 12. doi: 10.1002/jbmr.2551. [Epub ahead of print]

Calcilytic Ameliorates Abnormalities of Mutant Calcium-Sensing Receptor (CaSR) Knock-in Mice Mimicking Autosomal Dominant Hypocalcemia (ADH).

Dong B, Endo I, Ohnishi Y, Kondo T, Hasegawa T, Amizuka N, Kiyonari H, Shioi G, Abe M, Fukumoto S, Matsumoto T.

Activating mutations of calcium-sensing receptor (CaSR) cause autosomal dominant hypocalcemia (ADH). ADH patients develop hypocalcemia, hyperphosphatemia and hypercalciuria, similar to the clinical features of hypoparathyroidism. The current treatment of ADH is similar to the other forms of hypoparathyroidism, using active vitamin D3 or parathyroid hormone (PTH). However, these treatments aggravate hypercalciuria and renal calcification. Thus, new therapeutic strategies for ADH are needed. Calcilytics are allosteric antagonists of CaSR, and may be effective for the treatment of ADH caused by activating

mutations of CaSR. In order to examine the effect of calcilytic JTT-305/MK-5442 on CaSR harboring activating mutations in the extracellular and transmembrane domains in vitro, we first transfected mutated CaSR gene into HEK cells. JTT-305/MK-5442 suppressed the hypersensitivity to extracellular Ca<sup>2+</sup> of HEK cells transfected with CaSR gene with activating mutations in the extracellular and transmembrane domains. We then selected two activating mutations locating in the extracellular (C129S) and transmembrane (A843E) domains, and generated two strains of CaSR knock-in mice to build ADH mouse model. Both mutant mice mimicked almost all the clinical features of human ADH. JTT-305/MK-5442 treatment in vivo increased urinary cAMP excretion, improved serum and urinary calcium and phosphate levels by stimulating endogenous PTH secretion, and prevented renal calcification. In contrast, PTH(1-34) treatment normalized serum calcium and phosphate but could not reduce hypercalciuria or renal calcification. CaSR knock-in mice exhibited low bone turnover due to the deficiency of PTH, and JTT-305/MK-5442 as well as PTH(1-34) increased bone turnover and bone mineral density in these mice. These results demonstrate that calcilytics can reverse almost all the phenotypes of ADH including hypercalciuria and renal calcification, and suggest that calcilytics can become a novel therapeutic agent for ADH.

### **3- Not only high levels of FGF23 but also low levels of Klotho play a role in the onset of left ventricular hypertrophy**

J Am Soc Nephrol. 2015 May;26(5):1150-60. doi: 10.1681/ASN.2014040325. Epub 2014 Dec 4.

Soluble Klotho Protects against Uremic Cardiomyopathy Independently of Fibroblast Growth Factor 23 and Phosphate.

Xie J, Yoon J, An SW, Kuro-O M, Huang CL.

Cardiac hypertrophy occurs in up to 95% of patients with CKD and increases their risk for cardiovascular death. In the kidney, full-length membranous Klotho forms the coreceptor for fibroblast growth factor 23 (FGF23) to regulate phosphate metabolism. The prevailing view is that the decreased level of Klotho in CKD causes cardiomyopathy through increases in serum FGF23 and/or phosphate levels. However, we reported recently that soluble Klotho protects against cardiac hypertrophy by inhibiting abnormal calcium signaling in the heart. Here, we tested whether this protective effect requires changes in FGF23 and/or phosphate levels. Heterozygous Klotho-deficient CKD mice exhibited aggravated cardiac hypertrophy compared with wild-type CKD mice. Cardiac magnetic resonance imaging studies revealed that Klotho-deficient CKD hearts had worse functional impairment than wild-type CKD hearts. Normalization of serum phosphate and FGF23 levels by dietary phosphate restriction did not abrogate the aggravated cardiac hypertrophy observed in Klotho-deficient CKD mice. Circulating levels of the cleaved soluble ectodomain of Klotho were lower in wild-type CKD mice than in control mice and even lower in Klotho-deficient CKD mice. Intravenous delivery of a transgene encoding soluble Klotho ameliorated cardiac hypertrophy in Klotho-deficient CKD mice. These results suggest that the decreased level of circulating soluble Klotho in CKD is an important cause of uremic cardiomyopathy independent of FGF23 and phosphate, opening new avenues for treatment of this disease.

#### **4- A timely review on vitamin D in pediatrics**

Eur J Pediatr. 2015 May;174(5):565-76. doi: 10.1007/s00431-015-2524-6. Epub 2015 Apr 2.

Vitamin D in childhood and adolescence: an expert position statement.

Saggese G, Vierucci F, Boot AM, Czech-Kowalska J, Weber G, Camargo CA Jr, Mallet E, Fanos M, Shaw NJ, Holick MF.

Vitamin D is a key hormone in the regulation of calcium and phosphorus metabolism and plays a pivotal role in bone health, particularly during pediatric age when nutritional rickets and impaired bone mass acquisition may occur. Great interest has been placed in recent years on vitamin D's extraskeletal actions. However, while recent data suggest a possible role of vitamin D in the pathogenesis of several pathological conditions, including infectious and autoimmune diseases, the actual impact of vitamin D status on the global health of children and adolescents, other than bone, remains a subject of debate. In the meantime, pediatricians still need to evaluate the determinants of vitamin D status and consider vitamin D supplementation in children and adolescents at risk of deficiency. This review is the result of an expert meeting that was held during the congress "Update on vitamin D and bone disease in childhood" convened in Pisa, Italy, in May 2013.

The collaboration of the international group of experts produced this "state of the art" review on vitamin D in childhood and adolescence. After dealing with vitamin D status and its determinants, the review outlines the current debate on vitamin D's health benefits, concluding with a practical approach to vitamin D supplementation during childhood and adolescence.

#### **WHAT IS KNOWN:**

- Vitamin D deficiency is a worldwide health problem.
- Vitamin D deficiency affects not only musculoskeletal health but also a potentially wide range of acute and chronic diseases.

What is New:

- We reviewed the literature focusing on randomized controlled trials of vitamin D supplementation during childhood and adolescence.
- This review will help pediatricians to appreciate the clinical relevance of an adequate vitamin D status and it will provide a practical approach to vitamin D supplementation.