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CKD-MBD related publications in the ERA-EDTA journals

The ERA-EDTA acknowledges the high clinical and scientific relevance of the syndrome CKDMBD, reflected by several key publications in the journals of our society. We hereby summarize the content of several recent important papers, providing a link to their abstracts.

From July to December 2015, 21 CKD-MBD related articles, including several editorial comments and experimental studies, have been published; 10 in Nephrology Dialysis and Transplantation and 11 in Clinical Kidney Journal.

1) The important COSMOS study (**Fernandez-Martín JL et al**, (Nephrol Dial Transplant 30:1542) provides evidence of the *association* of serum **phosphorus, calcium and PTH levels** and mortality, and suggests survival benefits of controlling CKD-MBD biochemical parameters in dialysis patients. Using Cox proportional hazard regression models and penalized splines analysis, it was found that both high and low serum phosphate (P), calcium (Ca) and PTH were associated with a higher risk of mortality. The serum values associated with the minimum relative risk of mortality were 4.4 mg/dL for P, 8.8 mg/dL for Ca and 398 pg/mL for PTH. The lowest mortality risk ranges obtained using as base the previous values were 3.6–5.2 mg/dL for P, 7.9–9.5 mg/dL for Ca and 168–674 pg/mL for PTH. Decreases in serum P and Ca and increases in serum PTH in patients with baseline values of P >5.2 mg/dL, Ca >9.5 mg/dL and PTH <168 pg/mL, respectively, were associated with improved survival. Other directional changes could not be analyzed. **Danese MD et al** (Nephrol Dial Transplant 30: 1336) also refined the definition of clinically important mineral and bone disorders in hemodialysis patients and concluded that only patients with at least two of three **CKD-MBD biomarkers out of target** (high or low Ca, P, PTH) represent a subgroup of patients at elevated predefined risk of adverse clinical events.

2) The effect of **parathyroidectomy** (PTX) on patient survival in CKD patients was analyzed by **Ivarsson KM et al** (Nephrol Dial Transplant 30: 2027). A nested index-referent study was performed within the Swedish Renal Registry (SRR) and it was shown that PTX was associated with improved survival in patients on maintenance dialysis but not in patients with renal allograft. An associated editorial by **Piergiorgio Messa** (Nephrol Dial Transplant 30: 1944) concluded that although it is important to collect new data supporting the safety and suggesting a clinical advantage for PTX patients, a more definite opinion cannot be without a multi-centre trial specifically directed to explore this issue.

3) Interestingly, **Mehta R et al** (Nephrol Dial Transplant 30:1534) tested the associations of serum P and plasma **FGF23 with retinopathy** in a cross-sectional analysis of 1800 participants in the CRIC Study who underwent fundus photography. Among individuals with moderate-to-severe CKD, higher serum P but not FGF23 was independently associated with more severe retinopathy and microvascular retinal venous dilatation. Retinopathy (OR, 3.03), previous amputation (OR, 15.50) and higher **serum P levels** (MD, 0.40 mg/dL) were associated with **foot ulceration** in a systematic review and meta-analysis in dialysis patients by **Kaminski MR et al** (Nephrol Dial Transplant 30:1747). **Di Lillo et al** (Clin Kidney J 8:732) describe that the extent of **aortic valve calcification** is associated with **FGF-23 and PTH** in naïve CKD patients with mild to moderate CKD. An interesting related editorial analyzing the link between mineral bone markers (especially FGF23) and cardiovascular disease in CKD is provided by **Cozzolino M and Pasquali** M (Clin Kidney J 8:729)

4) **Kurita et al** (Clin Kidney J 8:744) showed novel contributions of **dysregulated serum magnesium** (Mg) to mortality in hemodialysis patients with secondary hyperparathyroidism in a 3-year cohort study on. Different associations of Mg levels with serum potassium, albumin, C-reactive protein, PTH, prevalence of atrial fibrillation, cerebrovascular disease and all-cause death were described, although further studies are needed to examine whether or not correction of serum Mg improves survival.

5) Bone turnover inhibitors, **osteoprotegerin** (inhibitor of osteoclastogenesis) and **sclerostin** (inhibitor of osteoblastogenesis), but not DKK1, were independently associated with *coronary* artery **calcifications** with potential additive effects in non-dialysis CKD patients in the article by **Morena M et al** (Nephrol Dial Transplant 30:1345). In long-term hemodialysis patients, **Yang C-Y et al** (Nephrol Dial Transplant 30:1356) analyzed circulating inhibitors of the Wnt/β-catenin signalling pathway and found that sclerostin (but not Dkk-1) was *inversely* associated with *aortic* calcifications and future cardiovascular events. **Kirkpantur A et al** (Clin Kidney J 8:737) also found an independent direct association between serum sclerostin levels and **carotid-intima-media thickness** in prevalent hemodialysis patients.

6) In elegant **experimental** studies, **Ochi A et al** (Nephrol Dial Transplant 30:1683) have shown that the uremic toxin **indoxyl sulfate** (but not p-cresyl sulfate) suppresses hepatic **fetuin-A** expression (a liver-derived circulating protein with potent calcification-inhibitory activity) in HepG2 cells via the aryl hydrocarbon receptor. However, some attention should be paid to the absence of effect in mouse and human primary cultured hepatocytes. In another study, heterogeneous susceptibility for **uremic media calcification** and concomitant **inflammation** within the arterial tree was described by **Kirsch AH et al** (Nephrol Dial Transplant 30:1995) in mice and patients with CKD stage 4–5. Taking their results together, the authors found that there was a similar heterogeneous pattern of calcification in both mice and humans, where the abdominal aorta was more prone to media calcification when compared with the thoracic aorta.

Moreover, in uremia, smooth muscle cells of the abdominal aorta showed a phenotypic switch to an inflammatory and osteoblastic phenotype.

7) **Brandenburg V et al** (Clin Kidney J 8:567) published a "Blueprint for a European calciphylaxis registry initiative: the **European Calciphylaxis Network (EuCalNet)**". In 2006, Dr Brandenburg established an internet-based registry in Germany (http://www.calciphylaxie.de) to allow online notification of patients with established or suspected CUA. The next phase will be to allow international patient registration via http://www.calciphylaxis.net as part of the multinational EuCalNet (European Calciphylaxis Network) initiative, which is supported by the ERA-EDTA scientific working group 'CKD-MBD'.

8) **Jean G et al** (Clin Kidney J 8:378) published on the usefulness and feasibility of measuring **ionized calcium** in hemodialysis patients, using a freezing technique and that hypocalcemia is highly prevalent in hemodialysis patients and poorly predicted by Albumin-Ca level, among other findings. **Jean G et al** in another report (Clin Kidney J 8:388) described the **kinetics of serum 25-hydroxyvitamin D** in hemodialysis patients treated with monthly oral 100.000 IU of cholecalciferol. Serum Ca and albumin levels both increased during the study period. Serum phosphate level did not change significantly, and serum parathyroid hormone (PTH) level decreased. Serum 25- hydroxyvitamin D levels reached a plateau level after 12 weeks of therapy.

9) Beyond CKD-MBD, a review on **vitamin D** analogues to target **residual proteinuria** and potential impact on cardiorenal outcomes has been published by **Humalda JK et al** (Nephrol Dial Transplant 30: 1988). Both clinical and experimental intervention studies have demonstrated that vitamin D can reduce residual proteinuria through both RAAS-dependent and RAAS-independent pathways, but future research should prospectively explore this issue in an interventional trial exploring clinically relevant cardiorenal end points.

10) Among other reports, the possibility of **lanthanum absorption** in the stomach and its presence in a regional lymph node was described (Clin Kidney J 8:572).

11) The successful treatment of hypercalcemia associated with a **CYP24A1 mutation** with low-dose **fluconazole** was described by **Sayers J et al** (Clin Kidney J 8:453). These mutations are known to cause a range of clinical phenotypes and presentations including idiopathic infantile hypercalcaemia and adult-onset **nephrocalcinosis** and nephrolithiasis, and In the context of raised or borderline high serum calcium levels, suppressed PTH and persistently elevated 1,25 dihydroxy-vitamin D levels, this rare condition should be considered. An associated editorial by **Dusso A et al** (Clin Kidney J 8:456) updates the current knowledge on the topic. In a different scenario, the successful use of **hydrochlorothiazide** in managing hypercalciuria in a child with **Lowe Syndrome** (at risk of nephrocalcinosis and nephrolithiasis from hypercalciuria) was described by **Butani L** (Clin Kidney J 8:459). The

clinical and molecular characteristics of **familial hypomagnesemia with hypercalciuria** and nephrocalcinosis were described by **Claverie-Martin F.** (Clin Kidney J 8:656).

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on behalf of the ERA-EDTA WG