CKD-MBD – An Official ERA-EDTA Working Group
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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 CKD-MBD syndrome, 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 January to June 2020**, **23 CKD-MBD related articles**, including several editorial comments and experimental studies, have been published; 20 in Nephrology Dialysis and Transplantation and 3 in the Clinical Kidney Journal.

**1)** Several reports dealt with **vascular calcification (VC).** **P. Djuric et al** (Nephrol Dial Transplant 35 (1):162) assessed in a randomized clinical trial the effect of sodium thiosulfate (STS) on cardiovascular (CV) calcifications in 60 hemodialysis (HD) patients. STS failed to retard abdominal aortic calcification progress (primary goal), but it positively affected VC progress in iliac arteries and heart valves as well as several other CV functional parameters. **B. Ponte et al** (Nephrol Dial Transplant 35 (3): 495) showed that dialysis initiation significantly improved calcification propensity (as measured by the $T_{50}$ method) and fetuin-A levels. Factors associated with $T_{50}$ changes over time were fetuin-A, phosphate (P) and magnesium (Mg). **N. El Hangouche et al** (Nephrol Dial Transplant 35 (3): 526) showed that among renal transplant recipients, the burden of pretransplant mitral annular calcification was an independent predictor of post-transplant risk of cardiac death or myocardial infarction.

**R. Caluwé et al** (Nephrol Dial Transplant 35 (1):23) reviewed how to evaluate vitamin K (VK) status and the rationale for VK supplementation in dialysis patients while several trials on the effects of VK on surrogate markers of VC are currently ongoing. **L. Dai et al** (Nephrol Dial Transplant 35 (Supplement 2):ii31) discussed the link between senescence and early vascular ageing (mediated by medial VC) in the context of CKD, with a focus on the role of nuclear factor erythroid 2–related factor 2 (NRF2) and VK in DNA damage signalling, senescence and inflammaging.

In experimental studies, **N. Kaesler** et al (Nephrol Dial Transplant 35 (1):65) reported that nicotinamide *increases* while $MgCO_3$ *reduces* ectopic calcification severity associated with CKD and P overload. **T.B. Drüeke** and **Z.A. Massy** (Nephrol Dial Transplant 35 (1):18) concluded in an associated editorial that "nicotinamide as a single player has lost the battle" but "it remains to be shown whether there is any place for low-dose nicotinamide treatment as add-on therapy to established P binders". Finally, **A.D. ter Braake et al** (Nephrol Dial Transplant 35 (5):765) demonstrated *in vitro* that $Mg^{2+}$ dose-dependently delayed the maturation of primary calciprotein (CPP) particles to CPP2 and thereby prevented P-induced VC.

**2)** In regard to the relationship between **P** and **vitamin D** (VD), differential effects of P binders on VD metabolism in CKD were analysed by **C. Ginsberg et al** (Nephrol Dial Transplant 35 (4):616). They performed a secondary analysis of the Phosphate Normalization Trial in which patients with moderate to advanced CKD were randomized to receive either placebo, sevelamer, lanthanum or calcium acetate for 9 months. In these patients, the administration of different P binders resulted in different changes in VD metabolism parameters [including $24,25(OH)_2$ VD levels and several VD ratios]. **M.C. Hu et al** (Nephrol Dial Transplant 35 (3):411) showed in rats with normal kidney function that cardiac phosphotoxicity was exacerbated by either high dietary VD (exacerbating high P-induced hypertrophy) or low dietary VD (accelerating high P-induced fibrosis) in rats with normal kidney function.

**3**) Regarding **Klotho and ageing**, **J.A. Neyra et al** (Clin Kidney J 13(2):235) explored methods to improve the reliability of Klotho assays (i.e. immunoprecipitation–immunoblot assay vs commercial ELISA), and **M.D. Sánchez-Niño et al** (Clin Kidney J 13(2):125) wrote an associated editorial about

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this elusive kidney-derived anti-ageing factor. Klotho also appeared to be a novel therapeutic target in peritoneal fibrosis via Wnt signaling inhibition as reported by **H. Kadoya et al** (Nephrol Dial Transplant 35 (5):773).

**4)** Regarding associations of **mineral metabolism parameters** with **CKD progression** or **mortality**, **H. Kim et al** (Nephrol Dial Transplant 35 (3):438) described the effect of interactions between proteinuria, activity of fibroblast growth factor 23 (FGF23) (measured by the fractional excretion of phosphate (FEP)/FGF23 ratio) and serum P on renal progression in the KNOW-CKD study. They showed that proteinuria is associated with decreased biologic activity of FGF-23 (resistance to FGF23) and increased serum P. Furthermore, diminished activity of FGF23 was an independent risk factor for renal progression in proteinuric CKD patients. **S. de Seigneux et al** (Nephrol Dial Transplant 35 (3):382) wrote an associated editorial analyzing the link between proteinuria and alterations of mineral metabolism, including the reduction of renal Klotho expression by albuminuria. **C. Lamina et al** (Nephrol Dial Transplant 35 (3):478) analyzed the association of temporal changes in bone mineral parameters (calcium, P, PTH) with mortality in HD patients included in the ARO cohort. They found that the ranges associated with the lowest mortality were largely consistent with the current KDIGO guidelines, but for calcium (2.36 mmol/L, well below the upper limit of normal) and the lower margin of optimal PTH (239 ng/L), as pointed out by **M. Vervloet** (Nephrol Dial Transplant 35 (3):385) in the associated editorial. Even more importantly, moving parameters over time into the optimal range was associated with risk reduction. It was also stressed that many patients are at risk because of a low PTH, and the study showed that increasing PTH was associated with improvement of mortality risk.

**5) Calcimimetics** were evaluated in two studies. **M Wolf et al** (Clin Kidney J 13(1):75) described that etelcalcetide potently lowered FGF23 in HD patients with secondary hyperparathyroidism, and that the effect remained detectable among patients who received concomitant treatments aimed at mitigating decreases in serum calcium. On the other hand, a position statement on cinacalcet use in paediatric dialysis was published by **J. Bacchetta et al** (Nephrol Dial Transplant 35 (1):47) on behalf of the European Society for Paediatric Nephrology and the EDTA CKD-MBD Working Group.

**6) Iron** indices, hepcidin, and bone mineral metabolism parameters are closely interrelated in non-dialysis CKD patients as shown by **H.K. Min et al** (Nephrol Dial Transplant 35 (1):147). **J. Floege et al** (Nephrol Dial Transplant 35 (6):946) analysed iron kinetics following treatment with sucroferric oxyhydroxide (SFOH) or ferric citrate (FC) in healthy rats and models of anaemia, iron overload or inflammation. They showed that iron uptake was higher from FC versus SFOH in most models, suggesting different physicochemical properties and mechanisms of iron absorption of SFOH and FC.

**7)** The natural history of mineral metabolism, bone turnover and bone mineral density in *de novo* **kidney transplant recipients** treated with a steroid minimization immunosuppressive protocol were analyzed by **P. Evenepoel et al** (Nephrol Dial Transplant 35 (4):697) in a 5-year prospective observational study. They described that bone mineral density changes were not only limited but also highly variable, and they were related to remodelling activity rather than corticosteroid exposure. **A.J. van Ballegooijen et al** (Nephrol Dial Transplant 35 (4):706) described that combined vitamins D and K deficiency were highly prevalent among 461 kidney transplant recipients and were associated with increased mortality and graft failure risk. Interestingly, low VK status was also strongly associated with an increased risk of premature mortality and graft failure for patients treated with VD versus no-VD treatment.

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7) Finally, contents of the fully virtual 57th ERA-EDTA Congress 2020 can be found in the 2020 Nephrol Dial Transplant Supplement # 3.


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on behalf of the EDTA CKD-MBD Working Group

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