CKD-MBD related publications in the ERA journals  
From July to December 2021

The ERA 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 July to December 2021, 36 CKD-MBD related articles, including editorial comments and experimental studies, have been published; 19 in Nephrology Dialysis and Transplantation and 17 in the Clinical Kidney Journal (some only available in advance form).

1) Several reports dealt with vascular calcification (VC). N. Seyahi et al (Clin Kidney J 15 (1): 101-108) examined coronary artery calcification (CAC) progression and long-term cardiovascular outcomes in kidney transplant (KT) recipients. They found that CAC at baseline and CAC progression robustly predicted the risk of death and cardiovascular events in these patients. E. Guillén-Olmos et al (Clin Kidney sfab205) analyzed their local series of calciphylaxis in KT recipients with a functioning graft, emphasizing that calciphylaxis can still occur after KT, in many cases during the first year and in patients with a good renal function. On the other hand, B. Van Berkel et al (Clin Kidney J 15 (2): 295-302) aimed to define the prevalence, progression and implications of breast artery calcification (BAC) in female patients with CKD across various stages of disease (CKD G2–5D-5T). They found that BAC was common among CKD patients (34.7%), progressed at a slower pace in KT patients as compared with CKD 5D, and associated with dismal cardiovascular outcomes. BAC score, kidney function, serum phosphate at baseline and vitamin K usage seemed to be important determinants of progression. However, vitamin K supplementation improved vitamin K status, but did not hinder or modify the progression of arterial calcification in dialysis patients in the RenaKvit trial by K. Levy-Schousboe et al (Clin Kidney J 14 (9): 2114-2123). In another study, the associations of plasma dp-ucMGP (matrix-Gla protein) with incident CKD and microalbuminuria were driven by the respective baseline effects of renal function and age according to D. Groothof et al (Nephrol Dial Transplant 36 (12): 2290-2299). All the potential beneficial effects of vitamin K supplementation were reviewed by M. Kettele et al (Nephrol Dial Transplant 36 (12): 2196-2198).

2) Clustering phosphate and iron-related markers and prognosis in dialysis patients was studied by H. Morooka et al (Clin Kidney J 15 (2): 328-337) using unsupervised machine learning methods. Authors found that the use of phosphate binders was associated with a lower risk of all-cause death in two clusters which were characterized by older age and higher prevalence of diabetes mellitus, among other factors. M. Vervloet et al (Clin Kidney J 14 (7): 1770-1779) published an European real-world prospective observational study on the safety and effectiveness of sucroferric oxyhydroxide for treatment of hyperphosphatemia in dialysis patients. Efficacy and safety of PT20, another iron-based phosphate binder, were published by M. Sampson et al (Nephrol Dial Transplant 36 (8): 1399-1407) in a Phase IIb study in hemodialysis patients. K. McCullough et al (Clin Kidney J 14 (8): 1886-1893) reported the DOPPS study-based association between European hemodialysis patient satisfaction with phosphate binders with serum phosphate levels, and M. Cozzolino et al (Clin Kidney J 14 (8): 1859-1860) published a related editorial comment advocating the need of an individualized choice as a desirable option to improve the poor adherence associated with these medications. Enhancing motivation and adherence to dietary recommendations in CKD patients was reviewed by R.A. Pereira et al (Nephrol Dial Transplant 36 (12): 2173-2181).

On the other hand, early recognition, prevention and a multidisciplinary approach to hypophosphatemia is essential in the cancer patient according to S. Adhikari et al (Clin Kidney J. 14 (11): 2304-2315). Finally, L.D. Dubourg et al (Nephrol Dial Transplant; afo331) described tubular phosphate handling reference values (TmP/GFR) from child to adulthood in the era of IDMS-standardized serum creatinine.
3) P. Ureña-Torres et al. (Nephrol Dial Transplant, gfab308) commented on a previous report (M. Bozic et al.) regarding the independent effects of hyperphosphatemia and secondary hyperparathyroidism (SHPT) on CKD progression and cardiovascular events. Higher serum phosphate was also independently associated with kidney disease progression in IgA nephropathy as reported by G. Yu et al. (Clin Kidney J 14 (9): 2108-2113), and the susceptibility for adverse health outcomes of patients developing SHPT in CKD was underlined by Y. Xu et al. (Clin Kidney J 14 (10): 2213-2220). These authors described that incident SHPT was associated with increased risk of death, higher risk of MACEs, CKD progression and fractures. In their commentary, P. Ureña-Torres et al. (Nephrol Dial Transplant, gfab308) also underlined the need to establish cut-off points for a safe high PTH level in non-dialysis patients and questioned whether reservation of active vitamin D analogues only for severe SHPT was exceedingly cautious. However, a systematic review and meta-analysis by M. Cozzolino et al. (Clin Kidney J 14 (11): 2437-2443) warned about the risk of hypercalcemia in non-dialysis CKD patients with SHPT treated with active vitamin D. J. Bover et al. (Clin Kidney J 14 (10): 2177-2186) published a meta-analysis on the impact of nutritional vitamin D (NVD) supplementation. Their results suggested that NVD could be used to increase 25(OH)D to a certain extent, while the potential of NVD to actively reduce PTH in non-dialysis-CKD patients with SHPT was limited. R. de Alarcón et al. (Nephrol Dial Transplant, gfab353) reported on the pharmacogenetic role of vitamin D-binding protein and vitamin D receptor polymorphisms in the treatment response of dialysis patients with SHPT. Two cases of severe hypercalcemia early after KT in two patients with severe SHPT previously treated with etelcalcetide was reported by G. Dachy et al. (Clin Kidney J 14 (8): 1977-1979). Finally, gradual implementation of therapeutic advances over the last decade (including non-calcium phosphate binders, cinacalcet and vitamin D3, among other changes) was associated with a parallel reduction in short-term risk of death and MACE among Swedish hemodialysis patients according to M. Evans et al. (Nephrol Dial Transplant 36 (7): 1298-1306).

4) Regarding bone disease, A.D. Lalayannis et al. (Nephrol Dial Transplant 36 (10): 1872-1881) reported that routinely used biomarkers but not DXA, were moderate predictors of cortical bone mineral density (BMD), measured by peripheral quantitative computed tomography, and therefore DXA should not be routinely performed in children and young adults with CKD 4–5D. R. Hiramatsu et al. (Nephrol Dial Transplant 36 (10): 1900-1907) reported a 2-year observational non-controlled study where high bone turnover was an independent risk factor for denosumab-induced hypocalcemia, and that denosumab significantly increased BMD at lumbar spine and femoral neck. Wnt signalling inhibitors such as sclerostin and DKK1 circulating levels were associated with low-turnover bones disease in patients with CKD G3-G4 according to R. Neto et al. (Clin Kidney J 14 (11): 2401-2408). Patterns of renal osteodystrophy 1 year after KT were described by H.S. Jørgensen et al. (Nephrol Dial Transplant 36(11): 2130-2139). The majority of KT recipients, including patients with osteoporosis (15-46%), had normal bone turnover.

5) The intersection of mineralocorticoid receptor activation (MRA) and the FGF23–Klotho cascade promotes renal and cardiovascular injury through multipronged, albeit complementary, mechanistic pathways, according to M. Epstein and M. Freundlich (Nephrol Dial Transplant 37 (2): 211-221). A. Kale et al. (Nephrol Dial Transplant, gfab340) focused on how the renin-angiotensin-aldosterone system and endoplasmic reticulum stress connect with Klotho regulation in kidney disease. They also highlighted novel approaches to implement Klotho as a therapeutic target.

6) Phosphate binders were included in the 2020 update on basic kidney research by C. Li and H-J Anders (Nephrol Dial Transplant 36 (7): 1145-1147). In miscellaneous experimental studies, A. Neradova et al. (Nephrol Dial Transplantation, gfab314) showed that neither phosphate binder therapy nor vitamin K2 supplementation alone prevented VC. However, the combination of high vitamin K2 with phosphate binder treatment significantly attenuated VC. A chronic high phosphate intake in mice did not cause major renal alterations, but affected negatively bone health, increasing bone resorption and decreasing bone mineral density as reported by M. Ugrica et al. (Nephrol Dial Transplant 36 (7): 1183-1191). Y. Nishiguchi et al. (Nephrol Dial Transplant 37 (3): 444-453) demonstrated that osteocrin, a bone-derived humoral factor, exerts a renoprotective role in

Finally, a phenotype-driven genetic panel for the genetic evaluation of a paediatric patient with nephrocalcinosis was performed by J. Patterson et al (Clin Kidney J, sfab279) and revealed a rare association of Bartter syndrome type II and amelogenesis imperfecta. A. Janiec et al (Nephrol Dial Transplant 36 (8): 1484-1492) described the long-term outcome of the survivors of infantile hypercalcaemia with CYP24A1 and SLC34A1 mutations (greater risk of progressive CKD and nephrocalcinosis).

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