



NEWSLETTER # 9 (1), 2018

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 July to December 2017, **22 CKD-MBD related articles**, including several editorial comments and experimental studies, have been published; 19 in [Nephrology Dialysis and Transplantation](#) and 3 in the [Clinical Kidney Journal](#).

- 1) Regarding **vitamin D**, **R. Shroff et al** ([Nephrol Dial Transplant 32 \(7\):1098](#)) and ([Nephrol Dial Transplant 32 \(7\):1114](#)), leading a core working group (WG) of the European Society for Paediatric Nephrology (ESPN) CKD-MBD and Dialysis WGs, together with a representative of the EDTA CKD-MBD WG (Dr M. Cozzolino), developed clinical practice recommendations for the use of *native* vitamin D [ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃)] in children with CKD Stages 2–5 and on dialysis. The second parallel document addresses treatment recommendations for *active* vitamin D analogue therapy. On the other hand, 3 experimental studies addressed different aspects of vitamin D receptor activators (VDRAs): a) **Mirkovic et al**, on behalf of the NIGRAM consortium ([Nephrol Dial Transplant 32 \(7\):1293](#)), concluded that the renoprotective effects of *paricalcitol* are blood pressure independent but do depend on dietary sodium status, stating that the combination of RAAS blockade, dietary sodium restriction and paricalcitol could be a promising intervention to further retard renal function loss in chronic kidney disease (CKD). As proteinuria was already abolished by lisinopril during the low-sodium diet, the addition of paricalcitol had no further effect on proteinuria or downstream inflammatory or pre-fibrotic changes; b) **M. Leifheit-Nestler et al** ([Nephrol Dial Transplant 32 \(7\):1493](#)) suggest that in CKD, cardioprotective effects of *calcitriol* stem from its *inhibitory* actions on the cardiac FGF23/FGFR4 system, and based on their counterbalancing effects on cardiac myocytes, high FGF23 and low calcitriol synergistically contribute to cardiac hypertrophy; and finally, c) **S. Panizo et al** ([Nephrol Dial Transplant 32 \(7\):1831](#)) conclude that VDRAs, particularly paricalcitol, attenuated cardiac fibrosis acting on COL1A1, MMP-2 and CTGF expression, partly through regulation of miR-29b and miR-30c. They also state that these miRNAs and miR-133b could be useful serum biomarkers for cardiac fibrosis and potential new therapeutic targets.
- 2) **Calcimimetics** were evaluated in two studies. **W.Y van der Plas et al** ([Nephrol Dial Transplant 32 \(7\):1902](#)) performed a systematic literature search comparing quality of life (QoL) in parathyroidectomized- (PTX) vs **cinacalcet**-treated patients. PTX improved QoL in

patients treated for ERC-5D-related secondary hyperparathyroidism, whereas cinacalcet did not. Authors recognized that this difference in QoL impact had not ever been compared directly. **M. Fukagawa et al** ([Nephrol Dial Transplant 32 \(7\):1723](#)) reported a phase 3, multicentre, randomized study, comparing intravenous **etelcalcetide** vs placebo in 155 Japanese patients with intact PTH levels ≥ 300 pg/mL, demonstrating the efficacy and safety of etelcalcetide in these patients.

- 3) **Phosphate binders** were subject of several studies. **J. Floege et al** ([Nephrol Dial Transplant 32 \(7\):1918](#)) report in a subanalysis of a Phase 3 study that **sucroferric oxyhydroxide** is non-inferior to **sevelamer** for controlling serum phosphorus in patients undergoing peritoneal dialysis (PD), while providing a relatively low pill burden and a high rate of adherence. The most common adverse events with both treatments were gastrointestinal: diarrhea and discolored feces with sucroferric oxyhydroxide and nausea, vomiting and constipation with sevelamer. In another study, **Covic A et al** ([Nephrol Dial Transplant 32 \(7\):1330](#)) describe initial increases in some iron-related parameters in sevelamer and sucroferric oxyhydroxide treated patients but they were more pronounced with the latter, likely due to minimal iron absorption from **sucroferric oxyhydroxide**. Interestingly, **C.M. Rhee et al** ([Nephrol Dial Transplant 32 \(7\):1233](#)) described in a randomized trial that high-protein meals (50–55 g) combined with **lanthanum carbonate** vs low protein meals (< 1 g) during dialysis were safe and increased serum albumin while controlling phosphorus in hypoalbuminemic (serum albumin <4.0 g/dL) hemodialysis (HD) patients. Finally, **C. Yuste et al** ([Clin Kidney J 10 \(4\):539](#)) described **sevelamer**-crystals-induced gastrointestinal (GI) lesions in 16 previously reported CKD patients treated with sevelamer. They concluded that patients with diabetes seemed more prone to these lesions and that this therapy should be avoided if possible in patients with a history of major abdominal surgery or chronic constipation.
- 4) From the pathophysiological perspective, **K.K. Stevens et al** ([Nephrol Dial Transplant 32 \(7\):1617](#)) describes in an elegant experimental study which includes vessels from patients with CKD, deleterious effects of **phosphate** on vascular and endothelial function via disruption to the nitric oxide pathway. The authors concluded that these directly detrimental effects of phosphate, independent of other factors in the uraemic environment, could explain the increased cardiovascular risk associated with phosphate in CKD. Beyond potential direct toxicity of phosphate, **J. Rossaint et al** ([Nephrol Dial Transplant 32 \(7\):1448](#)) reviewed the available evidence on the role of **fibroblast growth factor-23** (FGF23) in inflammation, immune cell function and recruitment, as well as the regulation of FGF23 during inflammation and the clinical implications of this process for the immune system in individuals with CKD.
- 5) Regarding **biomarkers**, **G. Pichler et al** ([Nephrol Dial Transplant 32 \(7\):1566](#)) report a systematic review and meta-analysis of bone- and vascular-derived molecular biomarkers FGF23, osteoprotegerin (OPG), RANK ligand, osteopontin (OPN), Klotho protein and bone morphogenetic protein-7 (BMP-7) in HD and renal transplant patients. **FGF23** was a predictor of all-cause and cardiovascular mortality, whereas the predictive value of **OPG**

was restricted to cardiovascular mortality. Authors concluded that further studies are needed in order to gain insight into the prognostic value of these biomarkers in renal transplant recipients. In a different study, **L. Lips et al** ([Nephrol Dial Transplant 32 \(7\):1217](#)) reported that (i) a high serum **sclerostin** (sScl) was associated with a lower mortality risk in patients with end-stage kidney disease; (ii) treatment with hemodiafiltration caused sScl to fall; and (iii) the relative decline in patients treated with hemodiafiltration was dependent on the magnitude of the convection volume.

- 6) According to a recent survey conducted among European nephrologists, **P. Evenepoel et al** ([Nephrol Dial Transplant 32 \(7\):1608](#)) found that **bone biopsies** are performed rather exceptionally, both for clinical and research purposes. In March 2016, the European Renal Osteodystrophy (**EU-ROD**) initiative was created under the umbrella of the ERA-EDTA CKD-mineral and bone disorder (MBD) Working Group to revitalize bone biopsy as a clinically useful tool in the diagnostic workup of CKD-MBD and to foster research on the epidemiology, implications and reversibility of ROD.
- 7) **V Day et al** ([Nephrol Dial Transplant 32 \(7\):1211](#)) reported a multicentre observational study quantifying the incidence of radiologically proven **bone fractures** by anatomical site in prevalent renal-replacement therapy (RRT) patients in West Scotland. The incidences were 37.6, 99.2 and 57.6 per 1000 patient-years in the transplant, HD and PD groups, respectively ($P < 0.05$). In the multivariable model, age and HD (relative to transplant or PD) were independently associated with increased risk of fractures. The risk of symptomatic bone fracture was high in RRT patients and was ~2.5 times higher in HD than in renal transplant patients, with the increased risk being independent of baseline factors. Fracture risk increased with age and lower serum albumin and was lower if the primary renal diagnosis is glomerular disease.
- 8) **Vascular implications** in CKD patients were described in three reports. **M. Abajo et al** ([Nephrol Dial Transplant 32 \(7\):1882](#)) showed that different mineral metabolism parameters might predict accelerated common carotid intima-media thickness progression from early CKD stages. They were serum phosphorus in stages 3 and 5D; low 25-hydroxyvitamin D and parathyroid hormone levels >110 pg/mL in stages 4–5 and intact parathyroid hormone levels out of the recommended range in stage 5D. Traditional cardiovascular risk factors, such as diabetes and systolic blood pressure, were predictors of progression in CKD stages 4–5, whereas high-density lipoprotein and low-density lipoprotein cholesterol predicted progression in women in stage 3. **R. Agarwal** ([Nephrol Dial Transplant 32 \(7\):1850](#)) reported a longitudinal study in non-dialysis dependent chronic kidney disease on **arterial stiffness** and its relationship to clinic and ambulatory blood pressure. His data supported the view that among those with CKD not on dialysis, targeting clinic blood pressure taken on multiple occasions using a standardized methodology or daytime ambulatory systolic blood pressure may slow the progression of arterial damage. **S.F. Adenwalla et al** ([Clin Kidney J 10 \(4\):503](#)) discusses the advantages and limitations of non-invasive methods that have been used to assess **aortic stiffness**, the

key studies that have assessed aortic stiffness in patients with renal disease and why these tools should be standardized for use in clinical trial work.

Miscellaneous content: **J. Ling et al** ([Clin Kidney J 10 \(4\):845](#)) described hypercalcaemia preceding the diagnosis of Pneumocystis jirovecii pneumonia in four renal transplant recipients. The presence of high calcitriol and calcidiol levels suggested an extrarenal source; in this case, the alveolar macrophages. All four patients had resolution of their hypercalcaemia after treatment of Pneumocystis jirovecii. Finally, **H.R. Mabillard and C.R.V. Tomson** ([Nephrol Dial Transplant 32 \(7\):1984](#)) review investigation and management of **renal stone disease**.

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on behalf of the ERA-EDTA WG