NEWSLETTER # 3, 2015

CKD-MBD related publications in NDT and CKJ

As previously mentioned and as a contribution of ERA-EDTA communication team, we hereby report and summarize the most recent papers published on the journals of our society dealing with CKD-MBD.

From July to December 2014, **25 CKD-MBD related articles** have been published, 23 in Nephrology Dialysis and Transplantation and 2 in the Clinical Kidney Journal.

1) The ERA-EDTA **CKD-MBD Working Group** published a "NDT perspective" discussing whether **CKD-MBD** should be considered a **syndrome or not** (Nephrol Dial Transplant 29 (10):1815). While it is agreed that this concept has influenced our current clinical hypotheses and guidelines, definitive proof of a benefit of interventions is still lacking. However, it is undisputed that CKD patients have an outstanding increased risk of morbidity and mortality. In this regard, prevalence of **subclinical atheromatosis** and associated risk factors in CKD was published by **A. Betriu** et al (Nephrol Dial Transplant 29 (7):1415) from the Spanish NEFRONA study data. It is not only shown the magnitude of subclinical atheromatous disease in a large CKD population but also that patient characteristics associated with plaques differ in different CKD stages. Among other factors (including classical risk factors), high phosphate (P) and hsCRP levels were associated with subclinical atherosclerosis in stages 4-5, and low levels of calcidiol were associated with the presence of plaque in dialysis patients. Other papers in this period of time deal with the cardio-renal syndrome but they do not specifically cover aspects of CKD-MBD.

2) In current clinical guidelines it is considered reasonable to use information on **vascular/valvular calcification** to guide the management of CKD-MBD. Beyond potential screening for the presence of vascular calcifications (VC), a narrative review and an accompanying analysis was performed on the Amiens CKD database by **S. Liabeuf** et al (Nephrol Dial Transplant 29 (7):1275) and focused on **selected VC biomarkers** (including P, FGF-23 and others). None outperformed age and the classical risk factors as a predictor of VC either in the aorta or in the coronaries. However, many other publications dealt with FGF-23, the role of vitamin K, and the important physiopathological bone-vascular link, as follows.

3) Increased circulating levels of **FGF-23** (hormonal component) or its expression and/or signaling ("local" component) have been implicated in the putative pathogenic link between CKD and cardiovascular morbidity. This issue was commented by **P. Messa** (FGF-23 and vascular calcifications: another piece of the puzzle. Nephrol Dial Transplant 29 (8): 1447) after **N.A. van Venrooij** et al (Nephrol Dial Transplant 29 (8):1525) reported the **upregulation of the klotho/FGF-23/FGFR system in the coronary arteries** of explanted

hearts in 56% of patients who received a heart transplantation. Colocalization with CD68 + cells (macrophages) was also observed. Nevertheless, the primary or secondary role of FGF-23 among other related factors such as renal function or inflammation, remains unclear. Importantly, a different "in focus" commentary by **M. Ketteler and P.H. Biggar** (FGF23: more a matter of the heart than of the vessels? Nephrol Dial Transplant 29 (11): 1987) followed the **J.J. Hsu** et al report (Nephrol Dial Transplant 29 (11): 2099). The latter confirmed previous results on the absence of association between FGF-23 concentrations and arterial stiffness (from patients of the MESA study), and the former emphasized that **FGF-23 appears to be more a myocardial than a vascular toxin**. An experimental model demonstrated that **FGFR blockade improved** cardiac structure and function in 5/6 nephrectomy rats with *previously established* left ventricular hypertrophy (LVH) (**G.S. Di Marco** et al Nephrol Dial Transplant 29 (11): 2028). Severe prolonged hyperphosphatemia (irrespective of FGF-23) may be sufficient to produce bone differentiation proteins in vascular cells, and induce severe VC as described from a recently discovered mutation in the study of **A. Shah** et al (Nephrol Dial Transplant 29 (12):2235), commented by **O. W. Moe** (Familial tumoral calcinosis: a valuable vehicle for discovery; Nephrol Dial Transplant 29 (12):2155)

4) There are known differences among differently measured FGF-23 levels and their clinical significance (Nephrol Dial Transplant 29 (8): 1447). In a study by **J. Chudek** et al (Nephrol Dial Transplant 29 (9): 1757) it is worth emphasizing that it was shown that at least in elderly persons the **increase in cFGF23 preceded both the increase in iPTH and iFGF23 as eGFR declined**. As mentioned before, a form of severe VC and tumoral calcinosis in a family with severe prolonged hyperphosphatemia was described by **A. Shah** et al (Nephrol Dial Transplant 29 (12):2235). They identified a loss-of-function FGF-23 mutation whose affected patients had high circulating plasma C-terminal FGF23 levels, but undetectable intact FGF23 or N-terminal FGF23, leading to loss of FGF23 function.

5) **Vitamin K** is also a factor in VC as commented by **M Ketteler** et al (Nephrol Dial Transplant 29 (7):1267). For instance, matrix Gla protein (MGP), one of the key calcification inhibitors is vitamin K-dependent, and inactive desphosphorylated-uncarboxylated MGP levels are high in CKD patients. The trial by **R. Caluwé** et al (Nephrol Dial Transplant 29 (7):1385) lends support to a straightforward and novel therapeutic approach to prevent VCs with **vitamin K_2** (menaquinone) supplementation in hemodialysis (HD) patients in a randomized dose-finding study. In a different issue, **T. Krueger** et al (Nephrol Dial Transplant 29 (9):1633) describes the VitaVask proof-of-principle pilot trial for treatment or prophylaxis of VC in HD patients with **vitamin K_1** supplementation (it is metabolized into K_2 as long as a sufficiently high dose is given). On the other hand, **F. Mac-Way** et al (Nephrol Dial Transplant 29 (11):2113) show for the first time a temporal association between warfarin, functional vitamin K deficiency and progression of aortic stiffness in HD patients, underlining the need to reevaluate the net cardiovascular benefit of long-term warfarin therapy in this population.

6) **Phosphate control** is usually maintained through dietary restrictions and P binders. **S. Wang** et al (Nephrol Dial Transplant 29 (11):2092) assessed the association of **P binder pill burden and adherence** P goal attainment. Not surprisingly, their results suggest that patients prescribed fewer P binder pills are less likely to have treatment gaps, and may be

more likely to achieve P targets. On the other hand, **J.K. Leypoldt** et al (Nephrol Dial Transplant 29 (7):1423) explored **dialytic P removal** and retrospectively demonstrated that a simplified form of P kinetic modeling can predict changes in predialysis serum P concentration after altering the HD prescription (from thrice weekly to short daily and long nocturnal HD therapies). The effect of treatment time was more influential.

7) Monitoring of serum **alkaline phosphatase** (ALP) is recommended in the management of CKD-MBD. **Y. Maruyama** et al (Nephrol Dial Transplant 29 (8):1532) reported in a large cohort study (185,277 patients), that higher serum ALP levels were independently associated not only with mortality but also with the incidence of hip fracture in Japanese HD patients. Thus, modulating ALP via interventions could potentially improve not only bone health but also survival. A comment by **W.L. Lau** and **K. Kalantar-Zadeh** (Nephrol Dial Transplant 29 (8):1450) claimed for increasing attention to ALP in the management of CKD-MBD.

8) A supplement on **Inherited Kidney Diseases** was published in Nephrol Dial Transplant (29 (Suppl 4)). Genetic diseases of renal P handling (Nephrol Dial Transplant 29 (S4):iv45), genetics of calcium homeostasis in humans (Nephrol Dial Transplant 29 (S4):iv55), and inherited disorders of renal hypomagnesemia (Nephrol Dial Transplant 29 (S4):iv63), among others, are presented in this issue. Novel calcium-sensing-related gene mutations in hypercalcemic hypocalciuric patients are described by **P. Stratta** et al in (Nephrol Dial Transplant 29 (10):1902)

9) Two articles devoted to CKD-MBD were published in the Clinical Kidney Journal. **F.J. Cano** et al (Clin Kidney J 7 (5): 457) described a **longitudinal FGF-23 and Klotho characterization in children** treated with **chronic peritoneal dialysis**. They showed that FGF23 levels were markedly increased, that Klotho levels were reduced in this population, and that FGF23 levels appeared to be regulated primarily by serum calcium. This relationship was lost in patients with P > 6 mg/dL. Finally, a case of renal **parenchymal calcification** secondary to systemic **AA amyloidosis** was also published (Clin Kidney J 7 (5): 490).