New Insights in Vitamin D Metabolism in CKD

Dear Colleagues,
The symposium will focus on new insights in vitamin D metabolism in health and chronic kidney disease. Knowledge in this field is expanding rapidly justifying regular updates. A better knowledge of the fundamentals of the renal and extrarenal vitamin D endocrine system will undoubtedly help to define the optimal vitamin D replacement therapy in CKD. This symposium will be an interactive meeting with state of the art presentations, clinical debate and a voting system for case reports. The symposium aims to offer an optimal balance between updates in basic science and clinical practice. This is done in cooperation with national and international key opinion leaders. We hope that this symposium will meet your expectations in terms of educational value and we wish you a pleasant stay in Brussels.

Prof. P. Evenepoel

Renal and extrarenal vitamin D metabolism in CKD
Prof. P. Evenepoel

Over the past several decades, the biological sphere of influence of vitamin D3 has broadened substantially from the target organs required for calcium homeostasis (intestine, bone, kidney, and parathyroids). The pluripotent steroid hormone 1.25 dihydroxyvitamin D3 [1,25(OH)2D3] generates physiological responses in ≥ 36 cell types that possess the vitamin D receptor by both regulating gene transcription (the classic genomic responses) and by rapidly activating a variety of signal transduction pathways at or near the plasma membrane (rapid or nongenotropic responses). Much, however, remains to be investigated how these responses translate in clinical outcomes. In addition to the kidney’s endocrine production of circulating 1,25(OH)2D3, autocrine/paracrine production of this steroid hormone is observed in ≥ 10 extrarenal organs. The factors governing renal and especially extrarenal vitamin D metabolism are complex and only partly understood. Several lines of evidence indicate that chronic kidney disease (CKD) affects not only renal vitamin D metabolism but also has an important impact on extrarenal vitamin D metabolism. A better knowledge of the fundamentals of the vitamin D endocrine system may help to define the optimal vitamin D replacement therapy in CKD. Of note, there is a clear paradigm shift in vitamin D replacement therapy in recent years. For a long time, pharmacological replacement with active vitamin D has been the cornerstone of secondary hyperparathyroidism therapy in advanced CKD. However, safety concerns originating from experimental and clinical data linking active vitamin D therapy with accelerated vascular calcification, question the validity of this strategy and put pharmacological replacement with active vitamin D under pressure. Conversely, the awareness that low levels of 25(OH)D3 are common in patients with CKD together with the increased body of evidence suggesting that extrarenal vitamin D metabolism may confer beneficial effects beyond bone health, boosts nutritional vitamin D replacement in CKD patients across all stages of disease. It should be emphasized that this paradigm shift has not been triggered by hard evidence and that adequately designed and powered intervention studies remain urgently required.
**Vitamin D, klotho and vascular pathobiology**

Dr. M. Vervloet

Klotho, an anti-aging protein discovered 16 years ago, was first recognised as a transmembrane protein, in adult-life expressed predominantly in distal renal tubular segment. Similarities between klotho-deficient mice and the uremic syndrome suggested that the specific deficiency of klotho in CKD may account for part of the pathology encountered in advanced kidney disease. In its membrane bound form it can form a heterodimer with Fibroblast Growth Factor Receptor type 1, strongly enhancing the affinity of the latter for its ligand FGF-23. As such, klotho is involved in phosphorus metabolism. The recognition that both FGF-23 and klotho are upregulated by active vitamin D revealed a homeostatic mechanism for phosphorus balance, implying enhanced renal phosphorus excretion to counterbalance increased gastrointestinal uptake by calcitriol. Recently, the discovery of numerous FGF-23 independent effects of klotho at distant sites from the kidney, substantiated the hypothesis that klotho-deficiency in CKD contributes to cardiovascular complication in particular. Deficiency of this protein makes endothelial cells from large arteries more prone to apoptosis, as such exposing the underlying medial layer of these arteries. Vascular smooth muscle cells that form the predominant cellular constituent of this layer, are protected by klotho from enhanced phosphorus entry into them and prevents to some extent the phenotypic of these cells into bone-forming osteoblast-like cells. Moreover, loss of protection against oxidant stress in the absence of klotho could contribute to devastating changes in the micro-environment of vessel wall tissues. These important findings form a theoretical basis for the hypothesis that targeting klotho levels might be a future treatment goals. Recent experimental studies support this assumption by showing that increasing levels of soluble, circulating klotho by different compounds that activate the vitamin D receptor indeed offers vasculoprotection. Currently, several important questions remain unanswered. Are assays available to measure klotho levels reliable? If so, can the decline in klotho levels, which is only modest in stage V CKD, really be important? Are there differential effect of different klotho fragments? The nearly abolished presence of klotho in renal tissue in advanced CKD, forms a conundrum, giving the relatively preserved circulating levels. The coming years will likely bring exciting new insights into the relationship between klotho and for instance vitamin D, which may lead to improved patient care.

**Native vitamin D: Rationale and cost-effectiveness of monitoring and supplementation in CKD**

Dr P. Ureña

Native vitamin D, cholecalciferol and ergocalciferol, are pre-hormones that play an essential role in mineral and bone homeostasis, mainly through its dominant active metabolite 1,25(OH)2D3. It stimulates intestinal absorption, and kidney reabsorption of calcium and phosphate. In the parathyroid gland, vitamin D suppresses parathyroid hormone (PTH) production. Consequently, low circulating vitamin D levels invariably result in elevated serum PTH concentrations in healthy individual as well as in patients with chronic kidney disease (CKD). Low circulating vitamin D levels are also associated with a variety of non-skeletal alterations, including arterial hypertension, cardiovascular diseases, proteinuria, diabetes mellitus, multiple sclerosis, cancer, and immune system dysfunction. Generally, the circulating levels of 25(OH)D, calcidiol or calcifediol are used to estimate the vitamin D storage pool size in the body. It also allows to define the vitamin D status according to either
a single criterion or a combination of criteria or of changes in several of them: serum PTH concentration, circulating 1,25(OH)2D3 levels, intestinal calcium absorption, muscle strength, and bone mineral density. The definition of deficiency as < 10 ng/mL (25 nmol/L) has been widely recognized because of its association with muscle weakness, bone pain, fractures, and high PTH. The definitions of normality and insufficiency, however, remain controversial, with normal values proposed ranging between 10 to 32 ng/mL (25–80 nmol/L). Despite the lack of strong scientific evidence, the Kidney Disease: Improving Global Outcomes (KDIGO) recommended in 2009 that circulating 25(OH)D levels should be monitored in patients with CKD stages 3–5D and treatment strategies adopted for vitamin D deficiency and insufficiency similar to those for the general population. Several epidemiological studies have shown that more than 50% of CKD patients are vitamin D deficient (< 15 ng/ml), and that the lack of vitamin D is independently associated with measured glomerular filtration rate, race, season, obesity, diabetes mellitus, proteinuria and albuminemia. Many other factors also contribute to vitamin D deficiency in CKD, including reduced conversion of native vitamin D to calcidiol, increased vitamin D degradation, reduced sun exposure, insufficient dietary supply, lower efficacy of UV light to stimulate cutaneous vitamin D production, and urinary losses of carrier proteins. Low circulating vitamin D levels in CKD are ultimately found associated with the disease progression towards end-stage renal disease and with mortality. For these reasons, native vitamin D supplementation has regained a great interest, also because of the hypothesis that extra-renal 1 -hydroxylase activities could contribute to the beneficial, paracrine, pleiotropic actions of locally produced calcitriol. Supplementation with native vitamin D usually improves many of mineral and bone disorders, including decreasing circulating levels of PTH, bone-specific alkaline phosphatase, and histological signs of osteitis fibrosa. However, scientific evidences demonstrating the beneficial effect of native vitamin D supplementation on non-classical organs are still inconsistent and need to be confirmed by large randomized clinical trials. Native vitamin D supplementation is of easy usage with long-term dosing intervals, of low costs (compared to other anti-hyperparathyroidism therapies), and little need for follow-up monitoring. It is also of a relative wide safety margins since the rare cases of hypercalcemia and hyperphosphatemia seen after native vitamin D supplementation.

Active Vitamin D: Rationale and cost-effectiveness of monitoring and supplementation
Prof. J. Cunningham

Abstract to be received