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EDITORIAL

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Dear Readers,

As you will read in this issue, recent studies have confirmed that a deficiency of native vitamin D (cholecalciferol, or D3) plays an important role in the pathogenesis of altered mineral metabolism and perhaps also of some extra-skeletal complications in patients with chronic kidney disease (CKD). On the other hand, for some time now it has been known that the kidney is one of the most important organs in the regulation of vitamin D metabolism and of its endocrine activities.

The best known of these disorders in the course of CKD is the increase of parathormone: even if this increase is also caused by phosphatemia, a typical symptom of CKD, it has always been believed that active vitamin D metabolites (calcitriol and similar analogues) are required to manage this condition. The assumption here is that the activation of vitamin D is an exclusive function of the kidneys, especially of healthy ones. In truth, it has recently been observed that even if renal synthesis of calcitriol is decreased by the progressive reduction of the function of the kidneys, its complete failure occurs only when glomerular filtration is less than 15 mL/min. In addition, 1- α -hydroxylase activity is present in various tissues and organs other than the kidneys, where it carries out important autocrine and paracrine functions, which are related to potentially significant extra mineral effects. In addition, you will read that it has been recently observed that:

- the prevalence of 25OHD deficiency is notable and generally widespread in patients affected by CKD, and cannot be traced to the loss of renal function;
- supplementation with cholecalciferol is able to correct, at least in part, secondary hyperparathyroidism, which often characterizes anamneses of osteomalacia and high-turnover renal osteodystrophy bone disease, which is at the base of increased fracture risk;
- vitamin D deficiency seems to be involved in other CKD complications (proteinuria, cardiovascular risk, anemia and progression of renal dysfunction); in particular it

has been observed in placebo studies that cholecalciferol supplementation reduces proteinuria and improves vascular functions (defined as the variation of the endothelium-dependent flow in the brachial artery and of the carotid-femoral pulse-wave velocity);

- significant side effects have not been reported in the course of cholecalciferol supplementation in patients with CKD, which confirms the good safety profile of native vitamin D for this condition as well.

Indeed, new guidelines [1-3] for the treatment of secondary hyperparathyroidism in patients with non-dialysis stage 3-5 CKD recommend a reduction of the intake of phosphate and a rationing of 25OHD, supplementing them with vitamin D in the case of deficiency, using the same recommended strategies as for the general population. They further warn against the routine use of calcitriol and other active forms of vitamin D in these patients, given the high risk of hypercalcemia; it should only be used in patients with stage 4-5 CKD with severe and progressive hyperparathyroidism.

With regard to the use of various vitamin D metabolites, in this issue you will also find summaries of the pharmacokinetic and pharmacodynamic motivations – and also with regard to evidence-based outcomes – behind the safe and rational use of cholecalciferol, calcifediol or calcitriol in different clinical conditions. In particular, readers will be reminded that even in conditions of severely compromised activity of the renal 1- α -hydroxylase enzyme, levels of 25OHD must be kept in the normal range to guarantee an adequate substrate for extra-renal 1- α -hydroxylase. On the other hand, as far as calcifediol is concerned, the authors write that its most rational use should be in cases of patients with chronic kidney disease and severely reduced liver functions.

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Meanwhile, there is still doubt on a clinical level as to whether an equivalent dose of calcifediol or cholecalciferol has better intestinal absorption. This doubt is warranted because of the different pharmacokinetics of the two substances, a difference which could be compensated by more generous doses of cholecalciferol bio-equivalents. In any case, the doses of calcifediol which are still recommended for postmenopausal osteoporosis in the package insert – 10-25 drops and even more per day– certainly seem excessive; for some time, it has been known [4] (and recently confirmed [5]) that a dose of 20-25 drops of calcifediol a week allows optimal 25OHD serum levels to be reached.
What do you think?

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