Editorial Comment | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2011.02501.x

The calciotropic hormones PTH and vitamin D: from bone to blood vessels

Understanding of the vitamin D system and its biological effects has changed dramatically in recent years with the identification of 25-hydroxyvitamin D (25-D) and 1,25-dihydroxyvitamin D (1,25-D) as 'real' hormones that have several nonclassical effects beyond mineral metabolism and parathyroid hormone (PTH) control. Indeed, recent studies have been proposed and realized to investigate the actions of either native 25-D or active 1,25-D on the cardiovascular and renal systems [1]. These advances have the potential to change the view of vitamin D beyond its role in mineral metabolism alone: from bone to blood vessels.

I read with interest the article by Karhapaa *et al.* [2] in this issue of the Journal regarding the association between the levels of both 25-D and 1,25-D and renal function (estimated glomerular filtration rate; eGFR) and PTH. The findings of this study may cause surprise in the nephrology and endocrinology communities, because the expected biochemical result is low levels of both 25-D and 1,25-D in patients with chronic kidney disease (CKD). The most interesting and novel results from this study are, in my opinion, that 1) higher 25-D levels were associated not only with low serum PTH levels but also, surprisingly, with lower eGFR levels, independent of age, serum calcium and phosphate levels and body mass index, and 2) high plasma 1,25-D levels and an increased 1,25-D/25-D ratio were associated with improved renal function (higher eGFR) and increased serum PTH levels.

With the decline in renal function, there is a reduction in 1,25-D concentration, at eGFR levels of 40–50 mL min^{-1} (CKD Stage III), because of decreased production of 1,25 hydroxyvitamin D-1-α-hydroxylase by the kidney [1]. Karhapaa and co-workers [2] included in their study 909 men without known CKD and living in Eastern Finland. They showed that 23% of participants had plasma 25-D levels lower than 50 nmol L^{-1} and that eGFR was below 60 mL min^{-1} in 1.2% of these subjects. Of interest, they also demonstrated that serum PTH levels were associated with 1,25-D when 25-D levels were included in the multivariate analysis.

The results of this interesting study may be important from a clinical point of view. First, it should be kept on mind that PTH and vitamin D are two calciotropic hormones that regulate bone and mineral metabolism [3]. Increasing evidence suggests a role of mineral metabolism in cardiovascular disease risk. Indeed, elevated serum PTH levels, calcium and phosphate disorders and 25-D deficiency are directly associated with cardiovascular risk factors [4]. It is clear that both lower levels of 25-D and higher levels of PTH are associated with high blood pressure, diabetes, insulin resistance and dyslipidaemia [5]. Furthermore, in a recent analysis of the NHANES (National Health and Nutrition Examination Survey) study, lower levels of 25-D and higher levels of calcium and PTH appear to be associated with different cardiovascular risk factors and may therefore affect cardiovascular disease through different mechanisms [6].

Recently, Melamed *et al.* [7] reported the potential advantages of and problems associated with increasing vitamin D levels by supplementation, acknowledging that levels of 25-D above 50 ng mL^{-1} may be detrimental to health and may increase mortality. In any case, increases in plasma calcium and/or phosphate levels may represent indirect evidence of undesirable high levels of 25-D.

Results from recent clinical studies have suggested a strong association between vitamin D deficiency and cardiovascular disease in the general population [8]. The cardiovascular effects of reduced vitamin D include smooth muscle cell calcification, proliferation and fibrosis, which lead to arterial stiffness, atherosclerosis and left ventricular hypertrophy [3]. Serum 25-D levels are significantly depleted in most patients with chronic heart failure and may be independently associated with poor clinical outcomes [9] and increased risk of myocardial infarction [10].

Patients with kidney disease develop a type of mineral metabolism impairment in which high levels of PTH and vitamin D deficiency coexist and cause not only bone pathology, but also severe cardiovascular disease.

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Progressive deterioration of kidney function and decreased production of vitamin D exacerbated by elevated levels of fibroblast growth factor 23 reduce the ability of the kidney to regulate PTH secretion [11]. Hypocalcaemia represents a pathogenetic mechanism that induces prolonged stimulation of the parathyroid glands in patients with CKD, potentially resulting in reduced bone mineral density. As kidney failure progresses, patients begin to develop increased extraskeletal levels of calcium and phosphate. In contrast to the findings of Karhapaa *et al.* [2], the results of the prospective observational Study to Evaluate Early Kidney disease (SEEK) study demonstrated that decreases in the serum levels of both 1,25-D and 25-D preceded increases in intact PTH, calcium and phosphate [12]. In this sense, several analyses in patients with impaired kidney function have shown that disorders of mineral homoeostasis are correlated with increased rates of cardiovascular events and mortality. It is clear that because of these metabolic changes associated with CKD, the term 'chronic kidney disease–mineral and bone disorder' (CKD–MBD) was introduced to describe the systemic nature of the disorder [13]. Although the primary feature of CKD–MBD is a change in bone metabolism, perhaps the most serious complication associated with mineral imbalance in patients with CKD is cardiovascular disease.

Therefore, a poor vitamin D status in the general population, and in particular amongst the patients with CKD, is associated with an increased risk of heart disease, cardiovascular mortality and sudden cardiac death [14]. Results from small interventional studies suggest that native (25-D) and active (1,25-D) vitamin D treatments improve cardiovascular outcome. Currently, there is a need for large, randomized clinical trials to specifically evaluate the cardiovascular effects of vitamin D. The key outcomes in such studies should include different cardiovascular risk factors such as blood pressure and left ventricular hypertrophy.

Measurement of vitamin D and PTH warrants consideration from a laboratory perspective. It has been demonstrated that PTH measurements are far from accurate, due to the fact that several different assays are commonly used, which give very different results [15]. Also, it is important to consider that 1,25-D has a short half-life of several minutes, whereas 25-D has a longer half-life of a number of weeks. For this reason, as well as because of lower assay costs, 25-D is widely used to assess the vitamin D status, in preference to 1,25-D [16].

In conclusion, clinicians should be aware of the potential benefit of measuring vitamin D and PTH, independent of renal function. The 'optimal' vitamin D levels remain to be determined; however, the definition of 'vitamin D deficiency' when 25-D levels fall below 20 ng mL^{-1} (about 50 nmol L^{-1}) should be accepted. The two calciotropic hormones, vitamin D and PTH, not only contribute important information about patients' bone health, but also provide a new opportunity to prevent and treat cardiovascular disease in the general population and in patients with CKD.

Conflict of interest statement

No conflict of interest was declared.

M. Cozzolino
From the Department of Medicine, Surgery, and Dentistry, University of Milan, Renal Division, S. Paolo Hospital, Milan, Italy

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Correspondence: Mario Cozzolino, MD, PhD, DMCO, University of Milan, Renal Division, S. Paolo Hospital, Via A. di Rudinì, 8-20142-Milan, Italy.
(fax: 0039-02-89129989; e-mails: mario.cozzolino@unimi.it; mariocozzolino@hotmail.com).

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