INVITED COMMENTARY

Vitamin D treatment of hypoparathyroid patients

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Parathyroid hormone (PTH) is a major regulator of calcium and phosphate metabolism. The peptide, composed of 84 amino acids, is the main secreted and circulating form of bioactive PTH (1). Its secretion by the parathyroid cells is under the control of extracellular calcium concentrations, which are recognized by a membrane-associated polypeptide structure characterized by seven transmembrane domains (2). In response to increasing calcium concentrations, this structure transmits a signal inside the cells through a pertussis toxin-sensitive mechanism, which leads to a reduction of PTH secretion. The gene coding for this calcium sensor has been cloned and several mutations reported, which can account for a number of disturbances in the relationship between PTH secretion and calcium concentrations such as familial benign hypocalciuric hypercalcemia or some cases of familial hypoparathyroidism (3). PTH and its tumoral analog parathyroid hormone-related protein (PTHrP) (4) share and interact with a membrane-associated receptor, which is connected with cyclic AMP-dependent and inositol phosphate transduction mechanisms, mediating the action of PTH and PTHrP in regulating calcium and phosphate homeostasis and exerting the same spectrum of actions (5, 6). The gene coding for this receptor has been cloned, and mutations associated with an altered function have been reported (7). Another receptor, which selectively recognizes PTH, PTH receptor 2, has been recently characterized (8). It is mainly expressed in brain and pancreas. Finally, structure(s) capable of interacting with mid-regions or carboxy-terminal domains of the PTH molecule could also exist (9).

Although PTH/PTHrP receptor has been demonstrated in a variety of organs, not necessarily implicated in the control of calcium and phosphate metabolism, the main targets for PTH in the regulation of this metabolism are bone and kidney (10, 11). In bone, PTH stimulates both formation and resorption, the latter leading to the mobilisation of calcium and phosphate from bone mineral. In kidney, PTH stimulates tubular reabsorption of calcium and magnesium, whereas it decreases the tubular transport of phosphate. Besides the modulation of renal ions transport capacity, PTH and/or PTHrP increase the renal synthesis of the active vitamin D metabolite 1,25-dihydroxyvitamin D₃, or calcitriol. This latter stimulates bone resorption, which accounts for an important part of the calcemic action in hypoparathyroid states (12) and increases the intestinal absorption of calcium, magnesium and phosphate (13). Under carefully and strictly controlled physiological conditions of diet or weight, PTH appears to be devoid of any significant effect on the gut (14, 15). Similarly, a physiologically meaningful influence of vitamin D metabolites on the tubular reabsorption of calcium or phosphate has not been convincingly demonstrated (16). The contribution, if any, of vitamin D metabolites to the control of calcium and phosphate renal tubular transports would be minute.

Hypoparathyroidism can result from the congenital lack of parathyroid tissue, the removal of parathyroid glands during neck surgery or a progressive autoimmune destruction of the glands (17). A decrease in PTH secretion, despite a low extracellular calcium concentration, can also be encountered in magnesium deficiency (18), or in some cases of familial hypoparathyroidism where a mutation in the calcium sensor receptor renders this latter hypersensitive to calcium concentration (3). Pseudohypoparathyroidism is characterized by a state of resistance to PTH (19). Some resistance to PTH action can also be observed in magnesium deficiency (18). Hypocalcemia accounts for most of the symptomatology associated with hypoparathyroidism or pseudohypoparathyroidism. Thus, the aim of therapy consists in restoring blood calcium concentrations to levels where nerves and muscles are no longer hyperexcitable (20). Under these conditions, the most rational and easy way is to replace at least one of the two missing hormones, namely the 1α-hydroxylated derivative. Such compounds constitute the first choice of treatment. The main effects of vitamin D in the control of blood calcium are to increase both intestinal calcium absorption and bone resorption. This type of replacement therapy has the advantage of a rapid achievement of full action (less than one week) allowing an easy control of calcemia, and a relatively short biological half-life (less than one week), and thus a rapid reversal in case of over dosage (13). Furthermore, this treatment permits a more constant level of calcemia than overload with dietary or pharmacological calcium (12). The former use of high pharmacological doses of plain vitamin D
has been associated with the risk of prolonged and deleterious hypercalcemia (21).

In the paper by Mortensen et al. in this issue (22), which reports on calcium, magnesium and phosphate balance, as well as 47Ca kinetics, the main fluxes of these ions were measured in 15 hypoparathyroid patients. Three quarters of them were treated with 1α-vitamin D derivatives leading to full correction of hypocalcemia. Incidentally, since 50% of total calcium is bound to proteins, mostly albumins, an adjustment of calcemia for proteins or albumins provides a better appraisal of true calcium concentrations than total calcium. In this study, high calcium intakes and the vitamin D derivative-induced increase in intestinal calcium absorption were associated with hypercalcemia. Indeed, the daily urinary calcium excretion of 7-2 mmol was above the limit of 6-25 mmol/day usually recognized as the upper limit of the normal range in women, who constituted three quarters of the cohort studied by Mortensen et al. (22). Since a complete 24-h urinary collection may be difficult in a routine clinical setting, an adjustment for creatinine excretion could also be applied and is of practical utility. Thus, in order to avoid hypercalcemia, and thereby the risk of nephrocalcinosis, the aim of the therapy for hypoparathyroidism is to achieve blood calcium levels, which are usually measured in the fasting state, at the lower limit of the normal range. An increase in intestinal calcium absorption, as indicated by the high daily urinary calcium excretion in these hypoparathyroid patients, further demonstrates that PTH is not needed for the direct control of intestinal calcium transport. On the other hand, the decreased renal tubular reabsorption of calcium is in agreement with the lack of PTH, and also indicates that 1α-vitamin D derivatives do not exert any direct and major effect on the renal tubular reabsorption of calcium.

Hypoparathyroid states are associated with an increase in bone mass (23), suggesting a positive calcium balance in PTH-deprived states. The measurement of calcium balance and kinetics is a very tedious and difficult technique which only a few groups are performing. For instance, in the paper by Mortensen et al. (22), the calcium balance in healthy controls was negative by about 140 mg/day, indicating a loss of 1% of total body calcium stores over a 10-day period if this negative balance was constant. For practical reasons, the measurement of external calcium balance can be replaced by the determination of total bone mineral content, a precise method which provides information on long term balance. Similarly, information previously gathered from 47Ca kinetics or the analysis of bone turnover on transiliac bone biopsy specimens, can be obtained by the measurement of biochemical markers of bone formation and resorption, either in plasma or in urine (24). However, whereas the excretion of deoxypyridinoline is directly proportional to the amount of bone destroyed, markers of bone formation are not, essentially, the reflection of quantitative fluxes but of cellular activity. In the paper by Mortensen et al. (22) there is no available information on the values of hypoparathyroid patients before vitamin D treatment: they are very likely to have been low. Under vitamin D therapy, the levels of osteocalcin and procollagen carboxyterminal peptide were, however, lower than euparathyroid controls.

In this paper (22), the results of phosphate metabolism are more difficult to interpret. As pointed out before, the negative 120 mg/day in phosphate balance would also represent a loss of more than 1% of the total body stores over a 10-day period. Despite numerous studies demonstrating an increase in tubular reabsorption of phosphate in the absence of PTH, maximal tubular reabsorption of phosphate, which is the best indicator of the renal tubular capacity to reabsorb phosphate (25), was not increased in these hypoparathyroid patients. Among the several reasons which could be invoked, the increase in extracellular calcium concentrations plays an important role. Indeed, an elevation of calcemia is associated with a decrease in the renal transport of phosphate through a PTH-independent mechanism (26). Other modulators of renal tubular phosphate reabsorption are high dietary intakes of phosphate, which decrease its renal transport, through diet-mediated mechanisms independent of PTH (25), some residual PTH secretion in a few patients, or a decrease in glomerular filtration rate since the progressive early deterioration of renal function is associated with a decrease in phosphate reabsorption through mechanisms independent of PTH (27).

Altogether, this study by Mortensen et al. (22) highlights the complexity of the regulation of calcium, phosphate and magnesium homeostasis. From a clinical point of view, the physiology and pathophysiology emphasize the need for hypoparathyroid patients to have a protein/albumin-adjusted plasma calcium maintained at the lower limit of the normal range. The determination of daily urinary calcium excretion could help to detect a possible calcium overload in these patients.

References

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