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Calcium supplements in chronic renal failure

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Alteration in calcium-phosphorus metabolism in chronic renal failure (CRF) is one of the fields within Nephrology that has undergone more changes in terms of theoretical concepts, clinical repercussions and treatment objectives. The subsequent opinions have always coincided with the appearance of new therapeutic measures on the market. These are very often completely different to the previous opinions and, at times, emphatically defended by the authors themselves.

While phosphorus retention and the importance of its control are concepts that have remained unchanged since their appearance more than 40 years ago, the opinions on the calcium balance in CRF have been less consistent and even controversial. Initial publications highlighted that patients suffering from these diseases had a negative calcium balance due to reduced intestinal absorption, which is dependent on vitamin D, and that poor calcium absorption was one of the causes of secondary hyperparathyroidism[1,2]. The classic book on this subject, published by D.S. David in 1977, indicates that to prevent and treat secondary hyperparathyroidism the negative calcium balance must be corrected via one of the following three procedures: calcium supplements in the diet to bring about passive absorption (which is gradient-dependent); administration of vitamin D to correct poor calcium absorption; or the transfer of calcium during dialysis using a concentration of calcium in the dialysis solution ≥ 6mg/dl (3mEq/l).[2] The author recommended that treatment should be started by administering calcium alkaline salts, which provide the said element and prevent phosphorus retention due to its binding effect on the latter. The oral dose of calcium required to correct the balance increased as the renal failure developed, and depended on whether the other two measures were adopted or not: (use of vitamin D analogues and concentration of calcium in the dialysis solution.)

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The theory of the existence of a negative calcium balance and the need for its correction to prevent the development of secondary hyperparathyroidism began to lose relevance as attention was being given to the appearance and development of vascular calcification. Current reviews of the pathogenesis of mineral metabolism alterations do not include poor calcium absorption as one of the factors involved in the appearance of secondary hyperparathyroidism.[3,4] Some authors even believe that not only is the calcium balance in CRF not negative, but rather the balance tends to be positive, since decreased urinary excretion of calcium compensates for intestinal absorption.[5] According to this approach the intake of calcium must be controlled, since its retention may contribute to the appearance of vascular calcification.

The study group for the K/DOQI Guide on bone metabolism and disease in CRF supports the theory of a positive calcium balance and the control of oral intake to prevent its retention. Recommendations 5.5 and 6.4, which are opinion-based recommendations, advise on reducing the oral intake of calcium up to a maximum of 2000mg/day (500mg/day as dietary content and 1500mg/day as calcium-based phosphorus binders).[6] The guide of the Spanish Society of Nephrology (*Guía de la Sociedad Española de Nefrología*), which has recently been published, adopts the same opinion.[7,8] In all these clinical guides the oral administration of calcium salts is restricted to its phosphorus binding effect, and, under no circumstances, would they be considered as a calcium supplement.

It is to be noted that limitations on oral calcium intake is not universally accepted and is a quite controversial subject. Friedman and other nephrologists believe that tests relating oral calcium supplements to vascular calcification are very weak and they defend the use of calcium-based binders in doses greater than the limit established in the guides.[9,10] This opinion is supported by a recent experimental study in which it was stated that not only did calcium carbonate not increase vascular calcifications but rather reduced these in apolipoprotein E deficient mice with CRF.[11]

Regardless of the controversy relating to the calcium balance in CRF and its possible influence on the appearance of vascular calcifications, the practical problem lies in ascertaining whether it is possible to control secondary hyperparathyroidism without administering a calcium supplement, as David suggested more than 30 years ago. There would be very few dialysis patients not receiving oral calcium supplements or vitamin D analogues or not using a concentration of calcium in the dialysis solution ≥ 3mEq/l. The three measures provide calcium to the organism and increase its concentration in the blood. However, it appears the scientific community is only concerned about the oral supplement, since it is the only calcium intake subject to control. Is it only the calcium absorbed passively in the intestine theoretically able to cause vascular calcifications? Is this not caused by calcium absorption resulting from vitamin D analogues or the calcium supply transferred directly to the blood after each dialysis session when a concentration of calcium of 3mEq/l is used in the dialysis solution, as recommended by the Spanish Society of Nephrology (*SEN*) Guide? There is no simple and reliable procedure to indicate the intake of calcium supplied by each of the above-mentioned procedures, nor which part of this calcium supply is deposited in the osseous and extra osseous tissues. The concentration of calcium in the blood does not indicate the calcium balance. However, it is the only parameter available to adjust the different treatments. Furthermore, daily practice indicates that the oral intake reduction of calcium salts to the doses recommended by the clinical guides in patients who are or are not treated with calcimimetics, must be counterbalanced with the administration of vitamin D analogues or a concentration of calcium in the dialysis solution ≥ 3mEq/l, to prevent hypocalcaemia and control PTH synthesis and secretion. Are these measures more reassuring than the increased oral dose of calcium salts? Is it better to keep a high PTH concentration rather than increasing the calcium supplement? It must be noted that some experimental studies suggest that vitamin D itself can induce vascular calcifications,[12,13] and that the development of vascular calcifications has been associated to the calcium transferred in each haemodialysis session when a solution with a concentration of 3mEq/l is used[14] and that hyperparathyroidism is another factor implicated in the calcium storage in the vessel wall.[15]

In 1989, Slatopolsky et al.[16] published that the administration of high doses of a calcium alkaline salt associated with a concentration of calcium of 2.5mEq/l in the dialysis solution, without vitamin D analogues, facilitates the control of serum concentrations of phosphorus and PTH with low risk of causing hypercalcaemia. This is the basic treatment regime followed in our Haemodialysis Unit for alterations in the metabolism of calcium-phosphorus since 1993, with an average oral intake of calcium of 3.5g/day.[17] If this regime is not successful in adequately controlling serum concentrations of phosphorus and PTH, other phosphorus binders or calcimimetics are added respectively. Vitamin D analogues are retained for the third level of treatment after calcimimetics, in case of hypocalcaemia not controllable with oral calcium supplements are used, or persistent hyperparathyroidism with concentrations of phosphorus and calcium in normal ranges.

In our opinion, clinical practice shows that the control of secondary hyperparathyroidism in chronic renal failure requires calcium intake via one of the three procedures indicated by David in 1977. If it is proved that calcium intake is one of the causes of vascular calcifications, the importance of this factor compared to uncontrolled hyperparathyroidism regarding calcium storage should be determined, as well as the less harmful administration method: oral supplements, increased intestinal absorption induced by vitamin D analogues or the transfer of calcium directly to the blood in dialysis sessions. In the mean time, we prefer to keep using the regime put forward by Slatopolsky 20 years ago.

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