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COMMENTARY

Does calcium intake influence the development of primary hyperparathyroidism?

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Commentary on: Paik JM, Curhan GC, Taylor EN. Calcium intake and risk of primary hyperparathyroidism in women: prospective cohort study. *BMJ* 2012;**345**:e6390

Adequate daily calcium intake is an important factor for bone health and a constant aspect of all therapeutic regimens for osteoporosis.[1] Over the past several years, however, calcium supplements have been discussed as a potential adverse contributor to negative cardiovascular outcomes.[2–4] The matter is controversial because other studies, conducted with equivalent rigor, have argued, on the other hand, that calcium supplementation is not detrimental and, in some situations, beneficial to cardiovascular health.[5,6]

Calcium intake is also an important issue in another skeletal disorder, primary hyperparathyroidism. As primary hyperparathyroidism is classically associated with hypercalcemia, most physicians advise their patients to limit dietary calcium intake. The thinking is that calcium intake, at some level, could lead to further elevation of serum calcium, hypercalciuria and renal stone formation. Countering this view, several studies addressing this issue have provided evidence that supports a more liberal intake of calcium in primary hyperparathyroidism. Insogna *et al.*[7] found that exogenous calcium variably suppresses parathyroid gland activity in primary hyperparathyroidism. A calcium intake of $\sim$1000 mg per day, in comparison with 400 mg per day, was associated with significant reduction of fasting serum levels of parathyroid hormone and 1,25-dihydroxyvitamin D. Locker *et al.*[8] found that parathyroid hormone levels tended to be lower in the group of patients consuming a diet with the higher amount of calcium ($>$800 mg per day, mean 1023 $\pm$ 73). Jorde *et al.*[9] provided moderate calcium supplementation (500 mg per day) to patients with asymptomatic primary hyperparathyroidism whose dietary calcium intake was low. There was an associated subsequent significant decrease in serum parathyroid hormone after 4 weeks, and a significant increase in BMD at the femoral neck at 1 year.

These studies influenced the recommendations of the 2008 International Workshop on the Management of Primary Hyperparathyroidism.[10,11] It recommends that calcium intake in primary hyperparathyroidism should not be different from recommendations for the general population. The recent recommendation from the Institute of Medicine[12] for postmenopausal women is a daily intake of 1200 mg per day. This recommendation also seems reasonable for subjects with primary hyperparathyroidism and was essentially stated in the Workshop report,[10,11] and more recently by Marcocci and Cetani.[13]

While recommendations for calcium intake in primary hyperparathyroidism are rather straightforward, and seem reasonable, how calcium intake may contribute to the development of primary hyperparathyroidism is a more vexing issue. This question has been addressed in a recent article by Paik *et al.*[14] in the *British Medical Journal*. These investigators conducted an epidemiological survey of calcium intake, as it relates to the incidence of primary hyperparathyroidism. The question addressed in this report is whether low-calcium intake might be associated with increasing recognition of primary hyperparathyroidism. The hypothesis appears to be based on the thinking that low dietary calcium intake might chronically stimulate parathyroid tissue and ultimately lead to the disorder that is recognized today. The fact that most cases of primary hyperparathyroidism are sporadic, without a clear genetic basis, leads one to consider that an environmental factor like calcium intake might be important. The study is based upon data from the Nurses' Health Study, a large, prospective study of 121 700 women residing in 11 US states. A total of 58 345 women form the population base for this cohort. These individuals were 39–66 years old and had no history of primary hyperparathyroidism. The wealth of demographic and epidemiological information from the Nurses' Health Study has allowed Paik *et al.*[14] to test the hypotheses related to dietary and supplemental calcium intake, and the appearance of primary hyperparathyroidism.

During 22 years of follow-up, they found that the incidence of primary hyperparathyroidism was significantly higher in women with a lower daily calcium intake; higher total calcium intake (dietary plus supplementation) was associated with a lower incidence of primary hyperparathyroidism. Importantly, they demonstrated that even a modest amount of calcium

supplementation (500 mg per day) was associated with a reduced incidence of primary hyperparathyroidism.

The kind of primary hyperparathyroidism that Paik *et al.*[14] identified is the most common variant, namely the single adenoma. Their diligence in tracking the historical information met with confirmation by medical records of adenomatous disease in a majority (75%) of cases. Their hypothesis, however, might have led them to investigate the occurrence of multiglandular parathyroid disease as the more likely pathology in the setting of reduced calcium intake. The frequency of multiglandular disease, however, was not a feature of the report. The idea that chronic stimulation of the parathyroid system by low-calcium intake would select out a parathyroid cell clone that eventually would dominate as a single adenoma, while possible, occurs very infrequently in situations of major secondary hyperparathyroidism (for example, malabsorption or renal disease).[15] In the clinical setting of this report, the association of low-calcium intake with single-gland disease seems to be at odds with their hypothesis.

Not surprisingly, considering a study of the magnitude of the Nurses' Health Study, details of some measurements, like vitamin D, are not provided. We do not know what threshold was used to exclude subjects who were determined, by medical records, to be vitamin D-deficient. We do not know what the actual levels of 25-hydroxyvitamin D were among the quintiles. We are provided only with estimates of vitamin D intake (dietary and supplemental). How these estimates might have related to 25-hydroxyvitamin D levels cannot be determined from the paper.

The authors took their index of calcium intake as the baseline data from the beginning of the 22-year surveillance period. Although the food frequency questionnaire was updated during the study, they give no indication about variability in this index and how this might have been taken into account in the analysis. The design of the study, moreover, did not permit them to determine average length of time on a low-calcium diet and the emergence of primary hyperparathyroidism.

The lowest quintile of calcium intake was 787 mg. Although lower than current recommendations by the Institute of Medicine,[12] this lowest quintile cannot be considered to be markedly low. From this lowest quintile, calcium intake progressively increases. But the relationship between calcium intake and primary hyperparathyroidism shows a progressive reduction in the incidence of primary hyperparathyroidism, with an increasing dietary calcium intake, not total calcium intake.

The authors state that phosphorus and calcium were highly and directly correlated ($r \geqslant 0.68$), and thus they did not include an estimate of phosphorus intake in their analysis. As phosphorus intake is potentially an independent variable, it is not clear how the relationship that they have demonstrated for calcium intake might also relate to phosphorus intake.

The group of women in the highest quintile of calcium intake also had the highest protein, magnesium and vitamin D intake. This highest quintile also had reduced alcohol intake, smoked less and was more physically active. These points did not lead the authors to take each of these variables for analysis separately, as they did for calcium intake. It is possible that the relationship shown for calcium intake and primary hyperparathyroidism might also have been shown for one or more of these other variables. With regard to vitamin D, the range of estimated intake is from low to average (254–465 IU per day). Even though their analysis did not identify vitamin D as an independent variable, the range appears to be too narrow to be sure of this point.

Thus, the interesting report of Paik *et al.*[14] raises more questions than it answers. This may be the mark of a good paper, but it also leads to great uncertainty about whether one can comfortably draw any firm conclusions from their interesting paper on the relationship between dietary calcium intake and the development of primary hyperparathyroidism.

Conflict of Interest

The authors declare no conflict of interest.

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