Low Vitamin D Can Mask Hyperparathyroidism

Ever since food began to be fortified with vitamin D, the manifestations of pHPT have become less severe.

BY JEFF EVANS
Senior Writer

ARLINGTON, VA. — A level of vitamin D that is low but near or within the normal range may mask the presentation of patients with primary hyperparathyroidism, Dr. Shonni J. Silverberg reported at a conference sponsored by the American Society for Bone and Mineral Research.

In the United States, the presentation and epidemiology of primary hyperparathyroidism (pHPT) and vitamin D deficiency have developed concomitantly since food began to be fortified with vitamin D about 75 years ago. During this period, the prevalence of vitamin D deficiency has declined dramatically while the clinical manifestations of pHPT have become less severe. Symptomatic pHPT, or osteitis fibrosa cystica, has decreased because of lower levels of parathyroid hormone (PTH) in the disease. The weight and size of parathyroid adenomas also has declined substantially during this period, said Dr. Silverberg, professor of clinical medicine at Columbia University in New York.

"The question [was] whether or not calcium and vitamin D nutrition affects clinical expression of tumor growth in primary hyperparathyroidism. There has long been a hypothesis of 'double trouble,' which states that the clinical manifestations of primary hyperparathyroidism may be more severe in the presence of vitamin D deficiency," she said.

Epidemiologic data show that classical pHPT still exists in areas of the world where vitamin D deficiency is endemic. When one analyzes the relationship between the two conditions in the United States and in developing countries where vitamin D deficiency is endemic, vitamin D (25-hydroxyvitamin D) levels are "somewhat inversely proportional" to the degree of PTH elevation, according to Dr. Silverberg. In this situation, people with very low vitamin D levels and pHPT may have PTH levels 15-20 times the upper limit of normal, but those with higher vitamin D levels—while still being in the lower range of normal—and pHPT may have PTH levels 1.5-2 times the upper limit of normal.

In patients with mild pHPT, sufficient—but still low-normal—levels of vitamin D oppose the hypercalcemic effect of excess PTH and thereby lower serum calcium levels and urinary calcium excretion back to their normal ranges.

Many of these people may be referred from doctors in the community who are reluctant to make a diagnosis of pHPT in patients with an elevated PTH level, normal serum calcium level, and a sufficient level of vitamin D, Dr. Silverberg said.

Low-normal levels of vitamin D oppose the hypercalcemic effect of excess PTH, leading serum and urinary calcium levels to be within normal ranges.

A study of women in New York and Beijing found that nearly all New Yorkers with pHPT were asymptomatic, whereas 94% of women with pHPT in Beijing were symptomatic and often had fractures and severe bone disease. There were very marked differences in serum levels of calcium, PTH, and vitamin D levels between women in the two cities (Int. J. Fertil. Womens Med. 2000;45:158-65).

In a study of 49 patients in Saudi Arabia (where vitamin D deficiency is endemic) who underwent a parathyroidectomy for pHPT, 19 patients had severe bone disease. These 19 patients had high levels of PTH and alkaline phosphatase, and increased thyroid gland size and weight, but their vitamin D levels were not significantly different from those without severe bone disease. The study investigators concluded that marked vitamin D deficiency may play a part in osteitis fibrosa cystica, but manifestation of bone disease with pHPT is multifactorial (J. Endocrinol. Invest. 2004;27:807-12).

A study in France showed that 38% of normal individuals were vitamin D insufficient (using a 20-ng/mL cutoff), compared with 91% of those with pHPT, regardless of its severity. The proportion of patients with pHPT who had vitamin D insufficiency also was similar regardless of whether their serum calcium level was lower or greater than 12 mg/dL (J. Endocrinol. Invest. 2006;29:511-5).

These results raise the question of whether there is a cutoff level of vitamin D at which pHPT becomes symptomatic, Dr. Silverberg said.

A study of patients with pHPT in Turkey found that individuals with vitamin D levels less than 15 ng/mL had significantly higher serum PTH, alkaline phosphatase, and parathyroid adenoma weight than did those with vitamin D levels of 15-25 ng/mL or more than 25 ng/mL (World J. Surg. 2006;30:321-6). Similar results were found in a study of U.S. patients.

The investigators of a separate case-control study that controlled for the effects of age, sex, body mass index, and season corroborated the finding that low vitamin D levels could worsen the clinical presentation of pHPT, but they did not find any association between low vitamin D levels and thyroid adenoma size. The percentage of patients with a vitamin D level less than 20 ng/mL varied significantly between the summer and winter months in the study's two control groups, but not among patients with pHPT (Clin. Endocrinol. [Oxf.] 2005;63:506-13).

Dr. Silverberg and her colleagues found that 53% of 124 U.S. patients with mild pHPT had an insufficient level of vitamin D (less than 20 ng/mL). The researchers also noticed a seasonal variation in the manifestation of pHPT in the summer in which vitamin D levels rose while PTH levels dropped. When the patients were split into tertiles based on vitamin D levels, the investigators found that serum PTH levels and alkaline phosphatase activity were significantly higher among patients in the lowest tertile of vitamin D (less than 16 ng/mL) than in patients in the middle (16-24 ng/mL) and highest tertiles (more than 24 ng/mL). Another analysis of the same data suggested that the relationship was valid throughout the range of levels for vitamin D and serum PTH. Histomorphometric studies of the patients' bones also were consistent with an enhanced effect of PTH in those with a low level of vitamin D (Am. J. Med. 1999;107:561-7). "It is very important, however, to remember that the results we are describing are [cross-sectional] … and that there is absolutely no way, based on anything that we or anybody else knows at this point, to infer a causal association in these data," she said.

But another study of women with pHPT did not find any association between vitamin D levels and the severity of pHPT. In that study, low vitamin D levels were associated with age and renal function, but there was no association between vitamin D level and bone mineral density after investigators controlled for age, PTH excess, and body mass index (Clin. Endocrinol. [Oxf.] 2004;60:81-6).

The surgical literature shows that after patients with pHPT undergo a parathyroidectomy, a substantial percentage of patients have persistently elevated PTH levels despite others signs of being cured of their hyperparathyroidism. The most consistent finding across these studies is low vitamin D levels either just before or immediately after surgery. In this case, pHPT has become secondary HPT, she noted.

One small study of vitamin D repletion in patients with suspected pHPT did not provide conclusive results. In a study of 229 patients with osteoporosis, 15 had low vitamin D levels and concomitant high PTH levels (J. Clin. Endocrinol. Metab. 2000;85:3541-3). After a single treatment of 500,000 U of vitamin D_2, five patients still had elevated PTH levels and were presumed to have pHPT. But two of those five patients had serum calcium levels less than 9 mg/dL, "which certainly raises the question in my mind about the diagnosis," Dr. Silverberg said.

In those five patients, the bone mineral density after 13 months had increased by 6% in the spine and 8% in the hip. Although the investigators concluded that the increase in BMD resulted from the effect of vitamin D on pHPT, the patients' calcium levels make the diagnosis of pHPT questionable, she said. ■

Little Support for Adding T_3 to T_4 Therapy for Hypothyroidism

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — The scientific evidence does not support adding T_3 therapy to T_4 therapy for patients with hypothyroidism, but some patients insist on it, according to Dr. Hossein Gharib.

Most patients do well on T_4 therapy alone, but some complain of fatigue, low energy, weight gain, or depressed mood despite adequate thyroid hormone replacement on T_4 therapy. They may read on the Internet that some patients with hypothyroidism or their treating psychiatrists report mood improvements after adding T_3 to therapy, he said at Perspectives in Women's Health sponsored by OB.GYN. NEWS.

In humans, 20% of T_3 is secreted by the thyroid gland. Standard treatment for hypothyroid disease replaces only T_4. "There is a feeling among physicians that when symptoms persist despite normal T_4 and TSH levels, we should switch to T_4 plus T_3 therapy," said Dr. Gharib, professor of medicine at the Mayo Medical School, Rochester, Minn.

Data from thyroid clinics and endocrinology practices, however, do not show any physiologic benefit from adding T_3 to therapy, he said. "There are several good studies in the last 5 years that have looked at this, and none of them support a physiologic response," he said.

Adding T_3 to therapy increases the cost of care and requires additional monitoring of hormone levels. If the patient insists on trying it, and thyroid hormone levels are in normal ranges, Dr. Gharib documents the conversation and adds T_3 to therapy. When adding T_3, he added, the dose of T_4 should be lowered by about 20%.

Conventional treatment for hypothyroidism calls for individualized dosing of T_4 therapy (based on body size and hormone levels) to reach a target TSH level of 0.3-3.0 mIU/L.

Ask patients who complain about symptoms of hypothyroidism after years of successful T_4 therapy about several possible changes in their habits that may be responsible, Dr. Gharib suggested.

The patient may have become less adherent to therapy, or a pharmacist may have convinced the patient to switch to less expensive generic T_4 therapy. Alternatively, the patient may be taking one of an increasing number of drugs that necessitate a boost in T_4 dosage. Calcium and ferrous sulfate are common inhibitors of T_4 absorption. "Take these two agents at different schedules than thyroxine," he advised.

Dr. Gharib indicated no association with the companies that make the treatments he discussed. OB.GYN. NEWS is published by the International Medical News Group, a division of Elsevier. ■