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Should vitamin D deficiency be corrected before parathyroidectomy?

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ABSTRACT

Background: Vitamin D deficiency is common in patients with hyperparathyroidism, but the importance of replacement before surgery is controversial. We aimed to evaluate the impact of vitamin D deficiency on the extent of resection and risk of postoperative hypocalcemia for patients undergoing parathyroidectomy for primary hyperparathyroidism.

Methods: We identified patients with primary hyperparathyroidism undergoing parathyroid surgery between 2000 and 2015 using a prospectively maintained database. Patients with normal (≥30 ng/mL) vitamin D were compared to those with levels less than 30 ng/mL.

Results: There were 1015 (54%) patients with normal vitamin D and 872 (46%) patients with vitamin D deficiency undergoing parathyroidectomy for primary hyperparathyroidism. Vitamin D deficiency was associated with higher preoperative parathyroid hormone (median 90 *versus* 77 pg/mL, $P < 0.001$) and calcium (median 10.5 *versus* 10.4 mg/dL, $P < 0.001$) compared with normal vitamin D. To achieve similar cure rates, patients with vitamin D deficiency were less likely to require removal of more than one gland (20% *versus* 30%, $P < 0.001$) than patients with normal vitamin D. Patients with vitamin D deficiency had similar rates of persistent (1.5% *versus* 2.0%, $P = 0.43$) and recurrent (1.7% *versus* 2.6%, $P = 0.21$) hyperparathyroidism. Postoperatively, both groups had equivalent rates of transient (2.3% *versus* 2.3%, $P = 0.97$) and permanent (0.2% *versus* 0.4%, $P = 0.52$) hypocalcemia.

Conclusions: Restoring vitamin D in deficient patients should not delay the appropriate surgical treatment of primary hyperparathyroidism. Deficient patients are more likely to be cured with the excision of a single adenoma and no more likely to suffer persistence, recurrence, or hypocalcemia than patients with normal vitamin D.

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Introduction

Vitamin D deficiency is common in patients presenting with hyperparathyroidism,[1-4] but the causal relationship between the two is unclear. Many believe that vitamin D deficiency is a symptom of primary hyperparathyroidism driven by the accelerated conversion of 25-hydroxyvitamin D to its active metabolite, 1,25-dihydroxyvitamin D.[5,6] Others postulate that a preexisting deficiency leads to a physiological and eventual pathologic overproduction of parathyroid hormone (PTH) to compensate for poor calcium absorption.[1,7] Consequently, the importance of restoring vitamin D levels to the normal range before parathyroidectomy is controversial.

Practice patterns vary with some groups replacing vitamin D before surgery,[8,9] after surgery,[7] or not at all.[3] Some clinicians are reluctant to replete vitamin D before parathyroidectomy out of concern for exacerbating hypercalcemia,[4] but uncorrected vitamin D deficiency may place patients at a higher risk of postoperative hypocalcemia due to the inability to absorb calcium. Replacing vitamin D before parathyroidectomy might also play a role in confirming the diagnosis of primary hyperparathyroidism when PTH levels do not suppress adequately after correction of the deficiency. In addition, guidelines from the International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism recommend repleting vitamin D levels in asymptomatic patients and are now calling for the establishment of safe replacement protocols.[10,11]

Therefore, we aimed to evaluate the impact of vitamin D deficiency on the extent of resection required to successfully treat primary hyperparathyroidism. We hypothesized that if vitamin D deficiency was the inciting event causing physiologic hyperplasia, then, we would see a greater proportion of multigland disease in patients with vitamin D deficiency. Our secondary objective was to determine the risk of postoperative hypocalcemia based on preoperative vitamin D levels.

Methods

Patients

We identified patients with primary hyperparathyroidism undergoing parathyroid surgery between 2000 and 2015 using a prospectively maintained database. Exclusion criteria were age less than 18 y, personal history of multiple endocrine neoplasia, prior parathyroid surgery, and missing preoperative vitamin D level. We defined serum 25-hydroxyvitamin D level 30 ng/mL or greater as being normal in accordance with recommendations from the Endocrine Society,[12] whereas vitamin D deficiency was defined as levels less than 30 ng/mL. We did not use a lower value to define vitamin D deficiency to have a comparison group that was unarguably normal. Because disagreement exists regarding what truly constitutes vitamin D insufficiency and deficiency, we performed a subgroup analysis in severely deficient patients. Severe deficiency was considered 10 ng/mL or less. Patients being evaluated for hyperparathyroidism routinely had a vitamin D level checked. If primary hyperparathyroidism was confirmed and the patient was deficient in vitamin D level, we did not replace vitamin D until after surgery. Patients with normal vitamin D levels preoperatively were compared with patients with deficient levels. Approval from the institutional review board of the University of Wisconsin was obtained. Because the database-collected data that were already being collected for medical diagnosis and treatment, patients were presented with no more than minimal risk, and informed consent was deemed unnecessary.

Parathyroidectomy

Parathyroidectomy was performed as previously described.[13-15] When patients had good preoperative localization, surgeons preferred a minimally invasive or focused approach. Conversion to a bilateral exploration occurred at the operating surgeon's discretion based on intraoperative findings and PTH levels. Intraoperative PTH levels routinely included a baseline drawn immediately after induction and levels drawn 5, 10, and 15 min after excision of the pathologic gland or glands. We calculated the percent drop in intraoperative PTH levels from baseline to the 15-min level except in cases where the 15-min level was unavailable, in which case, we substituted the last level drawn. The absence of persistent disease at 6 mo defined cure.

Hypocalcemia

Postoperatively, patients were discharged on 1000 mg of calcium carbonate twice daily and instructions to take an additional 2000 mg for episodes of perioral or digital numbness and tingling. This regimen was discontinued at their postoperative appointment. We considered a PTH of less than 10 pg/mL at postoperative follow-up or a calcium level less than 8 mg/dL within 6 mo of surgery to be transient hypocalcemia. If the PTH was less than 10 pg/mL at their 6-mo follow-up or if the patient required more than 2000 mg of calcium supplements or calcitriol administration greater than 6 mo from surgery to prevent symptoms of hypocalcemia, then, we considered the hypocalcemia to be permanent.

Statistical analyses

Descriptive statistics included frequency and percent for nominal variables and median and interquartile range for continuous variables. Chi-square tests compared nominal variables, whereas the Mann–Whitney *U* test compared continuous variables. Subanalyses evaluated patients with severe vitamin D deficiency. A multivariate analysis included demographic and laboratory variables that differed significantly between the normal and vitamin D–deficient groups to determine whether preoperative vitamin D level independently predicted multigland disease. All statistical analyses were performed with SPSS 23 (IBM, Chicago, IL).

Results

Patient characteristics

In patients undergoing an initial parathyroidectomy for primary hyperparathyroidism, vitamin D deficiency was