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Low 24-hour urine calcium levels in patients with sporadic primary hyperparathyroidism: is further evaluation warranted prior to parathyroidectomy?

Kathleen O'Connell, M.D.[a], Tina W. Yen, M.D.[a], Joseph Shaker, M.D.[b], Stuart D. Wilson, M.D.[a], Douglas B. Evans, M.D.[a], Tracy S. Wang, M.D., M.P.H.[a,*]

[a]Department of Surgery, Division of Surgical Oncology, [b]Department of Medicine, Division of Clinical Endocrinology, Metabolism, and Nutrition, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226, USA

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Abstract

BACKGROUND: Low 24-hour urine calcium (uCa) levels in patients with primary hyperparathyroidism (pHPT) raise concern for familial hypocalciuric hypercalcemia. This study evaluated patients with a low 24-hour uCa level for potential differences that may guide the extent of preoperative evaluation needed.

METHODS: A retrospective review was conducted of 1,139 sporadic pHPT patients who underwent parathyroidectomy between December 1999 and May 2011.

RESULTS: Of the 54 (5%) patients with greater than or equal to one low 24-hour uCa (<100 mg), 28 (52%) patients had only one low level, 9 (17%) had multiple low levels, and 17 (31%) had a repeat 24-hour uCa greater than 100. In the latter group, 4 of the 9 (53%) patients were on a thiazide and had normalization after cessation. Among the groups, differences existed only in serum creatinine ($P = .0011$) and glomerular filtration rate ($P = .0007$).

CONCLUSION: This study suggests that sporadic pHPT patients with low 24-hour uCa levels may not require further evaluation with genetic testing for familial hypocalciuric hypercalcemia, especially if previous eucalcemia is documented.

Primary hyperparathyroidism (pHPT) is the most common cause of hypercalcemia, with an estimated incidence of 22 cases per 100,000 person years in the United States.[1] pHPT is characterized by increased serum calcium levels secondary to inappropriately elevated levels of parathyroid hormone (PTH); definitive therapy with curative parathyroidectomy may prevent end-organ damage, such as nephrolithiasis and osteodystrophy. The majority of patients with pHPT have sporadic disease; less commonly, pHPT occurs as a component of a familial syndrome, such as multiple endocrine neoplasia (MEN) types 1 and 2.[2]

Familial hypocalciuric hypercalcemia (FHH) accounts for approximately 2% of all cases of patients with hypercalcemia.[3] FHH1 is an autosomal dominant disorder caused

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* Corresponding author. Tel.: +1-414-805-5755; fax: +1-414-805-5771.
E-mail address: tswang@mcw.edu

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by inactivating mutations in the calcium sensing receptor (CASR) gene, of which over 200 mutations have been identified to date.[3] FHH1 accounts for about two third of FHH cases. FHH2 is caused by mutations of G protein alpha 11[4] and FHH3 is caused by mutations of Adapter Protein 2 Sigma 1.[5] The biochemical profile of FHH is very similar to pHPT and is often difficult to differentiate. FHH is characterized by mild hypercalcemia, normal or elevated PTH levels, relatively low renal calcium excretion, and a family history of hypercalcemia.[6] FHH is a benign condition that does not require treatment, whereas surgical intervention to reduce the associated long-term complications is usually advised in pHPT. Consequently, it is important to accurately differentiate whether hypercalcemia is secondary to pHPT versus FHH prior to planned parathyroidectomy.

The most common measurement used to distinguish between patients with pHPT and FHH is the calcium-to-creatinine clearance ratio (CCCR), which is calculated as (24-hour urine calcium/plasma calcium)/(24-hour urine creatinine/plasma creatinine). The 2009 consensus panel on Guidelines in the Management of Asymptomatic pHPT set the CCCR threshold value at less than .01 for the diagnosis of FHH and greater than .02 for the diagnosis of pHPT.[7] Although these cut-off values are not perfect and there is overlap between the diseases, the workup of patients with newly diagnosed hypercalcemia should include a 24-hour urine collection for evaluation of calcium excretion.[8]

Not all patients with low 24-hour urine calcium (uCa) levels have FHH; other etiologies for low 24-hour uCa levels include increasing age, use of thiazide diuretics, and chronic kidney disease. In the evaluation of patients with suspected pHPT and a low 24-hour uCa, evaluation of these causative factors (ie, discontinuation of thiazide diuretic), if possible, is recommended, followed by a repeat measurement of 24-hour uCa and creatinine levels. In patients in whom there is no other known etiology and for those with persistently low 24-hour uCa levels, genetic testing for CASR mutations is recommended, which can be time consuming and costly, particularly because FHH is rare and most patients will indeed have pHPT. Therefore, the objective of this study was to identify potential differences in patients with an initial low 24-hour uCa level that may guide the extent of evaluation recommended prior to parathyroidectomy.

Methods

This study was an Institutional Review Board–approved retrospective review of patients with pHPT who underwent parathyroidectomy by a single group of endocrine surgeons from December 1999 to December 2011. A prospectively collected parathyroid database was reviewed for patients with biochemically confirmed, sporadic pHPT who had at least one low 24-hour uCa measurement, defined as greater than 100 mg/24 hours. Patients with familial, recurrent, persistent, secondary, or tertiary hyperparathyroidism, and those with no documentation of 24-hour uCa levels were excluded.

The resulting cohort of patients was subsequently divided into 3 groups: patients with only one documented 24-hour uCa, which was low; patients with multiple low 24-hour uCa levels, and patients with a repeat 24-hour uCa greater than 100. Data collected included patient demographics, signs/symptoms of hyperparathyroidism, use of thiazide diuretic, laboratory values closest to surgery (serum calcium and creatinine, ionized calcium, PTH, vitamin D, glomerular filtration rate [GFR], uCa), postoperative laboratory values (serum calcium and PTH), number of parathyroid glands removed, and final histopathology results. Any family history of hypercalcemia or previous parathyroid disease is routinely obtained; for patients with suspicion of familial parathyroid disease, attempts are made to obtain serum calcium levels ideally from parents or other first-degree relatives.

At our institution, initial evaluation of patients with hypercalcemia and suspected pHPT includes measurement of serum calcium, creatinine and glomerular filtration rate, intact PTH, and 25-hydroxy vitamin D levels, as well as a 24-hour uCa and creatinine collection. Prior to 2009, 24-hour uCa levels were obtained at the discretion of the referring provider or surgeon; since 2009, collection of 24-hour uCa and urine creatinine levels have been a routine part of the biochemical evaluation of patients with pHPT. All patients undergo preoperative localization studies including a high-quality cervical ultrasound and Sestamibi/technetium-99m scintigraphy (performed with single photon emission computed tomography after March 2009); an angiographic ("four-dimensional") computed tomography scan is performed if the results of the former 2 studies are discordant or negative. Intraoperative PTH monitoring is routinely performed and our institutional protocol has previously been described;[9] briefly, criterion for cure includes a greater than or equal to 50% decrease from the baseline or excisional PTH, whichever is higher, and returns to normal range, at 10 minutes postexcision of the abnormal parathyroid gland(s). Biochemical cure after parathyroidectomy is defined as serum calcium of less than 10.2 mg/dL at 6 months following parathyroidectomy. Patients with normocalcemia for at least 6 months after surgery who then had a serum calcium greater than or equal to 10.2 mg/dL were considered to have recurrent disease.

Simple descriptive statistics were performed; a P value of less than or equal to .05 was considered statistically significant.

Results

Of the 1,035 patients in the database who underwent parathyroidectomy for sporadic pHPT, 735 (70%) patients had 24-hour uCa testing performed. Of these, 54 (7%) patients had at least one preoperative low 24-hour uCa measurement and comprise the study cohort. No patient