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COMMENTARY ON SILENT RENAL STONES IN PRIMARY HYPERPARATHYROIDISM: PREVALENCE AND CLINICAL FEATURES

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Asymptomatic primary hyperparathyroidism (PHPT), the most common clinical presentation of the disease, has been widely discussed and reviewed in the past several decades (1, 2). Asymptomatic PHPT is diagnosed typically when hypercalcemia is discovered in the context of multichannel biochemical screening. In asymptomatic PHPT, mild hypercalcemia, within 1 mg/dL above the normal limit, is not accompanied by overt skeletal disease or kidney involvement. Patients are described as “asymptomatic” because they do not have any of the classic clinical manifestations of hypercalcemia or an elevated parathyroid hormone (PTH) concentration. This definition leaves room for discussion because neurocognitive and constitutional features are present in some patients. If these elements, which are exceedingly difficult to quantify, are truly related to PHPT, then patients would not be asymptomatic. However, at the time of the most recent Workshop on the Management of Asymptomatic PHPT, it was concluded that these putative manifestations cannot be clearly related to the disease itself (1). Another point enters into this discussion, namely whether clear targets of the disease (e.g., the skeletal and renal systems), can be shown in individuals with asymptomatic PHPT. With regard to the skeleton, it is now well-established that many asymptomatic patients have reduced bone mineral density, particularly at the distal 1/3 radius, a site that reflects primarily the cortical compartment of bone (1). More recently, high-resolution imaging technology has made it possible to establish reductions in the trabecular compartment of bone in many subjects with PHPT (3). Until recently, the possibility that renal calcifications might also be seen in asymptomatic PHPT if sought had not been studied. The paper by Cassibba et al addresses this issue (4).

Kidney stones in PHPT have been known since the 1930s (5). The incidence of kidney stones in PHPT has declined from 30 to 57% in older studies to about 8 to 20% in the most recent series (6, 7). However, these reports are based upon symptomatic nephrolithiasis as

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DISCLOSURE

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gleaned from the patients' history or from hospital discharge codes. In the cross-sectional study by Starup-Linde et al, the prevalence rates of nephrolithiasis or nephrocalcinosis as determined by spiral computed tomography (CT) in PHPT patients were 15.2% and 10.1%, respectively (8). We do not have clear insight into the true incidence of nephrolithiasis or nephrocalcinosis among individuals who do not give such a history or have no previous documentation of this complication. The only available study applying imaging technology (ultrasound) to evaluate kidney stones in patients with asymptomatic PHPT reported a prevalence of 7% (9). Cassibba et al report in this issue of *Endocrine Practice* an incidence of nephrolithiasis by ultrasound of 11.35% among 141 patients with asymptomatic PHPT, which is significantly higher than an age- and sex-matched control group (2.13%) (4). Other studies have noted that in the normal population, without PHPT, the incidence of kidney stones found with abdominal ultrasound or CT is about 5% (10). The report by Cassibba et al has limitations such as its retrospective design and lack of validation of ultrasound reports, but it does offer insight into the likelihood that among asymptomatic patients with PHPT, an appreciable incidence of subclinical stone disease would be discovered, if sought. Because assessment for kidney stones is not routinely conducted in subjects who do not have any history, symptoms, or signs of renal involvement, it is likely that when such tests are performed, subjects who did not meet surgical guidelines for PHPT would be reclassified.

Detection of silent kidney stones in subjects with PHPT does not necessarily implicate the disease as a causative factor because some of these individuals may have kidney stones independent of PHPT. However, in a patient with PHPT, it is hard not to conclude that there is a causative relationship. Investigation of the natural history of PHPT, although limited, provides some support to an etiologic relationship between kidney stones and PHPT. In general, data from retrospective studies show a trend toward a reduction in kidney stones after parathyroidectomy, even in the presence of a persistent higher risk for stones compared to the control population (11). Interestingly, data from Rubin et al reported a recurrence of kidney stones in 6 of 8 patients with PHPT who did not undergo surgery, as compared to no recurrence among 9 patients who had surgery over a 15-year follow-up period (12). These observations have led to a revision of the guidelines for renal evaluation of patients with PHPT to include abdominal imaging (2). The routine evaluation of kidney involvement in PHPT could indeed help to more accurately classify individuals who are candidates for parathyroidectomy on the basis of renal involvement.

Cassibba et al also observed that among subjects with kidney stones, PHPT was more active and subjects were more likely to meet criteria for surgery, independent of the presence of kidney stones (4). This point recalls older notions of different subtypes of the disease (5). The distinction between hyperparathyroid patients with and without stone disease has been indeed widely investigated, with the data showing no clear associations among nephrolithiasis, bone involvement, and reduced renal function (4, 5, 13). A cross-sectional study including 114 PHPT patients even recently reported that nephrolithiasis was associated with better renal function (13).

A variety of mechanisms have been proposed to account for stone formation in PHPT. These studies have focused not only on serum and urinary findings but also on gene

polymorphisms and sex- and age-related differences. Cassibba et al did not find a difference in total urinary calcium excretion between those who did and did not form kidney stones (4). On the other hand, Walker et al showed a significant positive correlation between 24-hour urinary calcium excretion and nephrolithiasis (13). The most recent guidelines on PHPT management recommend a 24-hour urinary calcium determination in all patients with PHPT (2). If marked hypercalciuria (>400 mg/day) is present, the new guidelines recommend a more complete urinary biochemical profile to determine whether other urinary risk factors for stones, besides hypercalciuria, might be present. If they are present, surgery is now recommended (2).

Relationships between kidney stones and other indices such as serum calcium, phosphorus, and PTH have not been consistent among several reports (4, 5, 13). Cassibba et al did report higher serum calcium concentrations among patients with kidney stones as compared to nonstone formers (4). A better understanding of etiologic factors contributing to stone formation in PHPT should also take into account a potential role for 1,25-dihydroxyvitamin D, but again, the results have not been consistently reported (5, 13). Among sociodemographic factors commonly related to kidney stone formation in the normocalcemic population, the association between age and nephrolithiasis risk has been widely evaluated in patients diagnosed with PHPT. Studies are mostly concordant in describing a higher frequency of kidney stones among younger patients (4, 5, 11). This point raises the possibility of a different presentation of PHPT according to the age at the time of diagnosis. It also raises the possibility of genetic dispositions among young patients who present with nephrolithiasis (14, 15). Genetic studies have suggested an association between calcium-sensing receptor (CaSR) gene polymorphisms, urinary calcium excretion, and kidney stone formation both in normocalcemic and PHPT patients (14, 15). Studies of the CaSR could therefore offer further insight into who is more or less likely to form kidney stones.

The report by Cassibba et al underscores the need to be more proactive in evaluating nephrolithiasis and nephrocalcinosis among patients with asymptomatic PHPT. It is likely that more routine utilization of renal imaging will lead to an increase in the incidence of kidney stones, and along with it, the reclassification of such patients as surgical candidates. A more detailed evaluation for silent kidney stones is now included in the revised guidelines on the management of asymptomatic PHPT (1, 2). Further studies and documenting the effects of successful parathyroid surgery on subsequent incidence could help to elucidate the mechanisms of renal stone genesis in PHPT.

Abbreviations

PHPT	primary hyperparathyroidism
PTH	parathyroid hormone

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