Perspectives on the relationship of urolithiatic markers and primary hyperparathyroidism

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Abstract
Abnormal parathyroid hormone (PTH) secretion by parathyroid glands leads to hypoparathyroidism or hyperparathyroidism. Most of the hyperparathyroidism cases are asymptomatic and occult urolithiasis is present in about one-fifth of these patients. The marker associated with hyperparathyroidism and urolithiasis may aid in early diagnosis and prophylactic management of these conditions. The aim of the present review is to list the most widely measured markers in urolithiasis. The literature related to urolithiasis and hyperparathyroidism was collected from PubMed and Google Scholar. Serum, urine and genetic markers that were found associated with both urolithiasis hyperparathyroidism were discussed. Further studies on these markers may provide scope for early risk identification and management of the hyperparathyroidism.

Keywords: Parathyroid hormone, hyperparathyroidism, urolithiasis, hypercalcemia, serum creatinine.

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Introduction
There are usually four parathyroid glands, two superior and two inferior parathyroid glands located behind the thyroid gland. The main function of this gland is synthesis and secretion of parathyroid hormone (PTH) which regulates serum calcium homeostasis (1). At the level of bone, it enhances calcium release from bone to serum by activating the osteoclast functions and impeding osteoblast functions (2). At the level of kidney, calcium reabsorption is facilitated by PTH through up-regulation of TRPV5 receptors at thick ascending loop of Henle, distal convoluted tubule and collecting duct (3).

The main disorders of parathyroid glands are hypoparathyroidism and hyperparathyroidism caused due to abnormal PTH secretion. Hypoparathyroidism is etiologically classified as primary and secondary or acquired (4). Hyperparathyroidism is caused due to increased secretion of PTH. Hyperparathyroidism may be classified as primary, secondary or tertiary. Primary hyperparathyroidism is seen in parathyroid hyperplasia, adenoma or carcinoma. The prevalence of hyperparathyroidism was varying from 1-7/1000 adults (5). Urolithiasis and nephrolithiasis are the major complications of primary hyperparathyroidism (6). Urolithiasis is a common disorder of hyperparathyroidism and also may signify incidence of benign adenoma (7). The recurrence of urolithiasis was suggestive of hyperparathyroidism(8). This review elaborates the biochemical and genetic markers associated with hyperparathyroidism induced urolithiasis. The serum, urinary, genetic and other markers associated were described.

Urolithiatic markers and primary hyperparathyroidism
Urolithiatic markers imply the risk of lithiasis in urinary tract. Different urolithiatic markers demonstrated by various studies may be classified as serum markers, urine markers, genetic markers and others. The serum markers are creatinine, uric acid, calcium, magnesium, blood urea nitrogen (BUN), albumin and blood pH. The urine markers include creatinine, calcium, phosphate, uric acid and vitamin D. Genetic markers are CaSR, PH1, NaPi2a, NHERF1, FGF23, DMP1, ENPP1, PHEX and GNAS-1. Other miscellaneous markers are cAMP and ulcerative colitis.

Serum markers
Hypercalcemia is the commonly seen in hyperparathyroidism. The increased PTH augments intestinal reabsorption of calcium through calcitriol...
mechanism, also intensifies osteoclastic bone resorption and reabsorption of calcium in renal tubules (9). Serum calcium levels were suggested to be the first line biochemical marker for diagnosis of primary hyperparathyroidism (10). PTH regulate the magnesium reabsorption at renal distal convoluted tubule and maintain magnesium homeostasis (11). Intravenous infusion of magnesium sulphate suppressed the PTH secretion and decreased the serum calcium levels in primary hyperparathyroid patients (12). Magnesium is also inhibits urolithiasis by forming renal oxalates complexes and hypercitraturia (13).

Serum creatinine was suggested as urolithiatic marker and was found positively correlated with calcium levels in serum. A descriptive retrospective study included 214 patients and evaluated the 24 hour urinary calcium in primary hyperparathyroidism patients revealed that 24-hour urine calcium correlates with serum creatinine (14). Initial studies demonstrated the role of PTH in uric acid metabolism and variations in uric acid clearance (15). In addition, a strong association between serum uric acid levels and PTH was also noted. Subsequently, association of hyperuricemia with hyperparathyroidism was also documented in various studies (16, 17). However, the mechanism of this association was not clearly demonstrated till now, but renal tubular involvement was suggested with altered uric acid secretion (18). A recent study demonstrated that the PTH down-regulates ABCG2 (Urate Exporter) expression on the plasma membrane to suppress intestinal and renal urate excretion leading to hyperuricemia in hyperparathyroidism (19).

The elevated BUN levels were observed in hyperparathyroidism patients (20). Elevated BUN levels (31-43 mg/dL) was found in 89 year old woman with primary hyperparathyroidism (21). A prospective study in 85 patients with persistent PTH elevation following curative parathyroidectomy showed increased BUN levels (22). However, further studies are required to confirm the relationship between BUN levels and hyperparathyroidism. As calcium binds to serum albumin, elevated serum albumin levels may significantly be associated with urolithiasis or increase susceptibility causing urolithiasis (23). Another study has suggested that serum albumin inhibitors may provide protection against urolithiasis (24). Further, PTH regulates serum pH through renal bicarbonate reabsorption. Hence, the increased PTH activity reduces renal bicarbonate reabsorption causing acidosis (25). In addition, pyruvate salts along with bicarbonate salts were found to be protective against urolithiasis (26).

**Urinary markers**

Urinary creatinine levels above 40mg/100mL was found to be associated with hypercalciuria, this makes Ca/Cr clearance ratio (>0.02) to be significant marker for primary hyperparathyroidism (27). Hypercalciuria with serum PTH abnormality is a definite marker for confirmation of urolithiasis (28). Also high urine pH reveals the chances of urolithiasis (29). Although hypercalcemia is not considered an important marker of urolithiasis now, still it has a role for screening the incidence of urolithiasis with urinary calcium/creatinine ratio. Urinary uric acid may be considered as an important marker for the diagnosis of calcium oxalate stone. Positive association was found between the 24 hour urine calcium/creatinine ratio and the uric acid/creatinine ratio (30). Elevated phosphorus excretion associated with hyperphosphatemia is intervened by PTH, which is one of the regulator or determinant of phosphorous clearance (9).

**Genetic markers**

Fibroblast growth factor-23 (FGF23) is produced in osteocytes and acts at kidney regulating urinary excretion of phosphorus and calcitriol production. Other genetic factors associated with hyperparathyroidism are calcium-sensing receptor (CaSR) gene, primary hyperoxaluria type 1 (PH1), Na+–Pi cotransport proteins (NaPi2a), Na+/H+ exchanger regulatory factor 1 (NHERF1) protein, dentin matrix acidic phosphoprotein 1 (DMP1), ectonucleotide pyrophosphatase/phosphodiesterase 1 gene (ENPP1), phosphate regulating endopeptidase homolog X-linked gene (PHEX), guanine nucleotide binding protein, alpha stimulating activity polypeptidel gene (GNAS-1), hyperparathyroidism 2 gene (HRPT2), Klotho gene and transient receptor potential vanilloid 5 (TPRV5) (31).

**Other factors**

The elevated cAMP levels found in hyperparathyroidism associated with urolithiasis suggests that that the PTH increase cAMP levels (32). Ulcerative colitis and pancreatitis were also found associated with hyperparathyroidism in few case reports, yet their mechanism and incidence has to be confirmed in the future studies (33, 34).

**Conclusion**

This review presented the relationship between urolithiatic markers and primary hyperparathyroidism. Further studies on these markers may provide scope for early risk identification for hyperparathyroidism and also aid in prophylactic management of the urolithiatic disorder.

**Authors’ contribution**

Both authors contributed equally to the manuscript.

**Ethical considerations**
References


