MECHANISMS IN ENDOCRINOLOGY

Kidney involvement in patients with primary hyperparathyroidism: an update on clinical and molecular aspects

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Abstract

Primary hyperparathyroidism (PHPT) is the third most common endocrine disease. Kidney is a target of both chronic elevated PTH and calcium in PHPT. The classic PHPT complications of symptomatic kidney stones and nephrocalcinosis have become rare and the PHPT current presentation is asymptomatic with uncertain and long-lasting progression. Nonetheless, the routine use of imaging and of biochemical determinations have revealed the frequent occurrence of asymptomatic kidney stones, hypercalciuria and reduced kidney function in asymptomatic PHPT patients. Though the pathogenesis is far from being elucidated, PHPT is associated with reduced renal function, in terms of estimated glomerular filtration rate, and related increased morbidity and mortality. In the last decade, the effort of the Kidney Disease: Improving Global Outcomes (KDIGO) panel of experts highlighted that even mild reduction of kidney function is associated with increased risk of cardiovascular disease. These considerations provided the basis for the Fourth Workshop recommendations of a more extensive diagnostic workout about kidney features and of wider criteria for parathyroid surgery including asymptomatic kidney disease. Moreover, kidney involvement in PHPT is likely to be affected by variants of genes coding the key molecules regulating the calcium and ions renal handling; these features might have clinical relevance and should be considered both during diagnostic workout and follow-up. Finally, the effects of parathyroid surgery and of medical treatment on kidney involvement of PHPT are reviewed.

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Invited Author's profile

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder due to inappropriate parathormone (PTH) release from tumour parathyroid glands. PTH mainly acts through the activation of the G-protein coupled receptor PTHR1. Kidney cells are targets of the PTH biological activity, which regulates renal calcium and phosphate handling. Clinical kidney injuries, namely kidney stones and stone-related complications, such as urinary tract infections, hydronephrosis and kidney failure, were considered expected complications in the era of symptomatic PHPT, while they have become rare in the currently prevalent asymptomatic presentation of PHPT. Nonetheless, extensive screening of patients with asymptomatic PHPT revealed that a consistent proportion experiences hypercalciuria, asymptomatic renal microlithiasis detected by ultrasound examination and mild decreases in kidney function.

In the recent past, the effort of the Kidney Disease: Improving Global Outcomes (KDIGO), an international kidney disease guideline development entity, that has produced guidelines on kidney diseases since 2008, highlighted that mild kidney function impairment affects healthy (1). Because of the morbidity and mortality associated with reduced kidney function, early diagnosis is important and should be pursued in at-risk populations.

This burden of considerations pushed the Panel of the Forth Workshop on asymptomatic PHPT to extend the recommendations for parathyroid surgery to the occurrence of hypercalciuria and/or lithogenic biochemical urine, of asymptomatic kidney stones detected by imaging and of a slightly reduced estimated glomerular filtration rate (2). Besides the attention to mild injury of kidney function promoted by the KDIGO panel of experts, molecular insight about renal handling of calcium, phosphate and other electrolytes have been accumulated and some of them have been shown to modulate the clinical presentation of PHPT.

The aim of the present review was to provide a revision of the clinical and molecular aspects of kidney involvement in the current asymptomatic PHPT patients. The main source of data acquisition included PubMed search strategies. Papers published in the last 10 years, from 2005 until now, were screened until April 30th, 2016. Original studies and meta-analysis were included, while case reports were reported only when any other consistent evidence was available. Search strategies used the following as key words: 'primary hyperparathyroidism' and 'kidney stones', or 'kidney disease', or 'CKD', or 'nephrolithiasis'

for the clinical setting, while 'calcium sensing receptor' and 'calcium gene', or 'phosphate gene', or 'VDR' were used for the molecular aspects. The search retrieved 50 records related to the clinical setting and 13 records related to the molecular aspects. Both authors working independently and reviewed all abstracts and selected full-text manuscripts for eligibility. Discrepancies in data extraction were resolved by consensus. Non English language papers and studies only reported in conference abstracts were excluded. In addition, the bibliographies of relevant citations were evaluated for any additional appropriate citation.

Clinical aspects

Kidney stones in PHPT patients

Symptomatic kidney stones occurred in PHPT series from 1970s and 1980s in 40–60% of PHPT patients. In the last two decades, symptomatic kidney stones diagnosis dramatically dropped to 10–20% of PHPT patients. Indeed, imaging screening revealed that asymptomatic kidney stones occur more frequently. In asymptomatic PHPT patients, stones are common with a prevalence ranging from 25% to 55% in different series (3, 4, 5), with stones being bilateral in 16.4% of PHPT patients (5). Moreover, kidney stones occur with a similar prevalence in normocalcaemic (15%) and hypercalcaemic (19%) PHPT patients (6). Renal calcifications (kidney stones and nephrocalcinosis) were associated with higher calcium/creatinine excretion rate in a series of surgically proven PHPT patients (4), while any difference could be detected in another series (5).

The precise pathogenesis of urinary stone formation in the general population, and also in PHPT patients, is unknown: it is likely related to crystal formation, mainly in the early stages of nucleation, aggregation and agglomeration of crystals. The presence of multiple inorganic and organic constituents in urine, and interactions between promoters and inhibitors further modulate the stone formation. Crystals retention is a key factor. In PHPT patients with kidney stones, both interstitial apatite plaques, also known as Randall plaques, which are common in idiopathic calcium oxalate stone formation, and intratubular crystal deposits, common in calcium phosphate stone formation, have been found (7). Several factors may promote precipitation of crystals: increased renal calcium excretion and increased urine

phosphate, increased urine oxalate, increased urine sodium, decreased urine citrate concentrations and proteinuria. Hypercalciuria is the main risk factor for kidney stone development in PHPT patients (8). Evidence, not confirmed by other studies, also suggested that relative high urine oxalate excretion and low urine citrate levels contribute to kidney stone risk in PHPT patients (3), while the role of urine phosphate, magnesium, sodium and potassium has not been established (8). Therefore, recent guidelines (9, 10) suggested determining the risk of kidney stones in PHPT patients with 24-h urine calcium >400 mg by evaluating the urinary stone risk profile.

Effects of parathyroidectomy (PTX) on kidney stones recurrence

Recent studies confirmed that successful parathyroidectomy (PTX) reduces kidney stones recurrence in PHPT patients. Successful PTX with serum calcium normalization is associated with reduced recurrence of kidney stones, diagnosed on the basis of symptoms, in a cohort of 640 surgically treated PHPT patients followed up for about 5 years, of whom 10% had stone formation (11). Similarly, significant reduction in kidney stones recurrence (1.5–3.5%) was reported in a series of 332 PHPT patients with a prevalence of 20% of stone formation (12).

Calcium renal handling in PHPT patients

Renal calcium handling in PHPT patients is extremely variable, from hypercalciuria, to normocalciuria and also hypocalciuria (Fig. 1). Oversaturations of urine

with calcium phosphate and with calcium oxalate are known risk factors for nephrolithiasis, while risk factors for nephrocalcinosis are not clearly defined (Fig. 1). Hypercalciuria, defined as urine calcium excretion >4 mg/kg body weight/24 h in the presence of conserved kidney function, occurred in about two-thirds to three-quarters of PHPT patients in recent series (3, 13). Obesity has been indicated as a risk factor for hypercalciuria and kidney stones in PHPT patients (14). Normocalcaemic PHPT patients have significantly lower mean 24-h renal calcium excretion than that in age- and sex-matched hypercalcaemic PHPT patients (6), though the prevalence of kidney stones was similar in the two groups. Finally, hypocalciuria, defined as urinary calcium <100 mg/24 h, might occur in about 5% of PHPT patients (15), though the proportion reduces to less than 1% when PHPT patients treated with thiazide are excluded. True low 24-h urine calcium excretion in patients with PHPT raised concern for familial hypocalciuric hypercalcaemia (FHH).

Effects of parathyroidectomy (PTX) on hypercalciuria

Hypercalciuria is expected to resolve after successful PTX, contributing to reduce the risk of kidney stones recurrence. Indeed, Palmieri *et al.* reported that hypercalciuria persisted after surgery in about 40% of hypercalciuric PHPT patients (13). Persistent renal calcium leak was associated with surgically diagnosed parathyroid hyperplasia (50% vs 22% in PHPT patients without renal calcium leak). Moreover, patients with persistent renal calcium leak did not experience improved bone mineral density at the spine, total femur and femoral neck. Therefore, it would be expected that about

Figure 1

Alterations of the renal calcium, oxalate and phosphate handlings in PHPT patients. The spectrum of calcium handling alterations occurring in PHPT patients are represented; relative hyperoxaluria and hyperphosphaturia might provide further risk factors for calcium oxalate and calcium phosphate stones development. Dash lines indicate factors poorly investigated in PHPT patients. In the boxes at the bottom, conditions able to modify the entity of calcium leak are reported. *(3).

30% of PHPT patients experience persistent hypercalciuria after PTX, and this condition, if not corrected, affects the expected gain in bone mineral density (13).

Effects of cinacalcet on hypercalciuria

Cinacalcet HCl, the agonist of the calcium-sensing receptor (CASR) currently available for the control of hypercalcaemia in PHPT patients with a wide range of disease severity, reduces circulating PTH levels, normalizes serum calcium, and reduces fasting urine calcium excretion though 24-h urine calcium levels are unaffected (16, 17). CASR molecules are expressed throughout the different segments of the nephron (18): CASR is mainly expressed in the thick ascending loop of Henle, where it functions as a major determinant of urinary calcium excretion. In other regions, the CASR acts to fine tune and integrate multiple stimuli that derive from sodium, pH and mineral ion metabolism, setting the sensitivity threshold for several cAMP-coupled hormones to extracellular calcium. The inhibitory effect of cinacalcet on calcium tubular reabsorption (evaluated as fasting calcium–creatinine ratio) has been supposed to be mediated by a shift in the dose–response curve of PTH on tubular calcium reabsorption or by a direct effect of cinacalcet on the CASR in the thick ascending loop (19). Calcium excretion in 24-h urine is in part determined by the intestinal calcium absorption, a component that might overcome the reduction of calcium tubular reabsorption. Nonetheless, this unexpected lack of effect of cinacalcet on urine calcium excretion, as well as on urine output and acidification, remains to be fully understood (18).

Effects of cholecalciferol supplementation on hypercalciuria

Few data are available on the effect of vitamin D repletion in PHPT patients; increase in urinary calcium excretion has been reported, though with no evidence of kidney stones development (20, 21, 22). A recent interventional study in PHPT patients with coexistent vitamin D deficiency showed that vitamin D replacement increases serum 25-hydroxyvitamin D levels and reduces serum PTH without causing hypercalcaemia and hypercalciuria (23). A randomized, placebo-controlled, double-blind study evaluated the effect of vitamin D₃ supplementation (2800 IU daily for 26 weeks) in PHPT patients: no increase in urinary calcium excretion has been detected (24). A daily dose of cholecalciferol (600–1000 IU) is considered

as sufficient in most cases to reach the target of serum 25OHD concentration >20 ng/mL (50 nmol/L).

Effects of thiazide diuretics on hypercalciuria

Thiazides increase renal tubular reabsorption of calcium resulting in reduced urine calcium excretion; serum calcium concentrations are increased independently of PTH levels. Thiazides significantly decrease 24-h urine calcium excretion, yet neither increase serum Ca nor influence PTH levels in patients with PHPT (25). Therefore, discontinuing thiazides is crucial for a correct calcium/creatinine clearance ratio calculation to preoperatively rule out familial HHC. Besides, it should be considered that Griebeler *et al.* estimate that 71% of patients with thiazide-associated hypercalcaemia may have underlying PHPT based on continued hypercalcaemia after stopping thiazides (26).

Kidney function in PHPT patients

PHPT has been recognized as a risk factor for impaired renal function, though the specific relationship between PHPT and this condition is not completely understood. Prolonged hypercalcaemia was considered to impair kidney function, and a reduced glomerular filtration rate was common in advanced severe PHPT (27, 28). Supporting the connection between PHPT and renal impairment, in the PEARS cohort of 1424 asymptomatic PHPT patients and 7120 controls, serum creatinine at diagnosis is predictive of mortality at a 3-year term, the

Figure 2

CKD and its related risk factors in PHPT patients. Specific local and systemic conditions known to affect kidney function in PHPT patients are illustrated. ↑, increased; ↓, decreased.

risks of kidney failure and kidney stones are increased with hazard rates of 13.8 and 5.1 respectively (29, 30, 31).

PHPT patients display a number of risk factors for kidney function impairment (Fig. 2):

1. *Age*: The incidence of PHPT peaks is in women aged 50–70 years (32, 33). Though kidney function physiologically declines with age, the KDIGO panel of experts recommends to consider an eGFR <60mL/min as reflecting a deterioration of kidney function at any age from 20 to 90 years (1);
2. *Dehydration*: Dehydration secondary to osmotic diuresis induced by massive hypercalciuria or other osmotic agents or concomitant morbidities, increased serum creatine levels;
3. *Kidney stones*: Stones are considered the cause of primary kidney disease determining tubulointerstitial chronic kidney disease (CKD). Recent studies demonstrated that prolonged activation of the intrarenal inflammasome is responsible for the loss of kidney function in oxalate crystal nephropathy (34), which frequently occurs in PHPT patients (3, 35);
4. *Kidney cysts*: Multiple kidney cysts are frequent in patients with PHPT occurring in about one-fifth of patients (36);
5. *Chronic elevated PTH levels*: Emerging evidence shows that increased PTH accelerates endothelial injury and subsequent organ fibrosis, and PTHR1 is expressed in glomerular endothelial cells and in proximal tubular cells (37);
6. *Insulin resistance*: PHPT is associated with increased insulin resistance (38);
7. *Obesity*: Severely obese PHPT patients have larger parathyroid tumour weight, higher pre- and post-operative PTH, and greater symptoms (39);
8. *Arterial blood hypertension*: A higher prevalence of obesity, hypertension, hyperlipidaemia, type 2 diabetes mellitus and coronary heart disease has been reported in PHPT patients compared with the general New Jersey population and to the age-, sex- and BMI-matched

goitre patients (40). However, such findings were not confirmed in an Italian PHPT series (41).

CKD is defined as having more than 3 months of decreased glomerular filtration rate (GFR) or evidence of kidney damage (1). Markers of kidney damage include albuminuria, urine sediment abnormalities, electrolyte abnormalities related to tubular disorders, or structural abnormalities detected by histology or imaging. CKD is staged by cause and severity of abnormal kidney measures, with more severe stages corresponding to poorer prognosis. Serum creatinine by itself should not be relied on to assess kidney function. When serum creatinine is measured, estimated GFR (eGFRcr) should be calculated (1). A GFR of less than 60 mL/min/1.73 m² is considered as moderately decreased for adults of any age.

Assessing GFR with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine levels (Table 1), CKD, defined as an eGFRcr <60 mL/min/1.73 m², was diagnosed in a proportion of PHPT patients aged 30–80 years ranging from 13% to 19% in the different series (Table 2). Most PHPT patients with CKD were diagnosed with a stage 3, and only 1–2% of PHPT patients had an eGFRcr lower than 30 mL/min/1.73 m² (G4 stage). Estimated GFR was associated with age, hypertension, antihypertensive medication use, fasting glucose and 25-hydroxyvitamin D (42). Patients with CKD were older, had higher 25-hydroxyvitamin D levels and lower 1,25-dihydroxyvitamin D levels, and were more likely to be hypertensive than those without CKD (42, 43). Traditional risk factors, rather than clinical or biochemical indices of PHPT, are associated with lower eGFR in mild PHPT (42, 43). Evaluation of kidney function in PHPT patients by measurement of cystatin C, a low-molecular-weight protein secreted by nearly all cells, freely filtered at renal glomerular level and then metabolized by the proximal tubule, which is considered a more reliable tool to assess GFR than serum creatinine, showed that the most evident determinant of circulating cystatin C

Table 1 KDIGO definition and diagnostic criteria of CKD (1).

Definition	Abnormalities of kidney structure or function with implications for health
Duration	>3 months
Marker of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g (≥3 mg/mmol)) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 mL/min/1.73 m ²

Table 2 GFR categories.

GFR category	GFR (mL/min/1.73 m ²)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

CKD, chronic kidney disease; GFR, glomerular filtration rate.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfil the criteria for CKD.

levels was ionized calcium, suggesting that severity of PHPT might contribute to kidney function impairment. Cystatin C measurement diagnoses preclinical kidney disease in about one-sixth of PHPT patients, which showed an unfavourable cardiometabolic profile, characterized by higher BMI, insulin resistance, arterial blood hypertension and dyslipidaemia. In the general population (44), the preclinical or mild kidney disease was associated with increased risk for development of established CKD and with increased risk of mortality, cardiovascular and non-cardiovascular outcomes.

The impact of renal function on the biochemical expression of PHPT has been well documented (45, 46, 47, 48, 49). Several studies clearly identify a correlation between PTH levels and degree of renal impairment in PHPT (50), but the eGFR threshold in PHPT, below which a significant stimulus elevates PTH levels, has not been established. Currently, the most convincing data come from a study of 294 patients with PHPT, where serum PTH levels were significantly higher in patients with eGFR <30 mL/min/1.73 m². Therefore, up to now no convincing evidence support the threshold of eGFR <60 mL/min/1.73 m² (CKD stage 3) below which PTH elevation occurs in PHPT. Besides, PHPT may worsen existing renal failure (50).

PHPT patients with reduced kidney function have an increased risk of experiencing life-threatening complications due to metabolic acidosis often precipitated by concomitant acute events, such as infections or cardiovascular accidents. Due to bone calcium mobilization and efflux, metabolic acidosis might dramatically worsen hypercalcaemia, which induced neurologic and cardiologic symptoms (51).

Effects of parathyroidectomy (PTX) on kidney function

Guidelines on the management of asymptomatic PHPT confirmed impaired eGFR among surgical criteria,

indicating the threshold of 60 mL/min/1.73 m². Indeed, definite data about a beneficial effect of PTX on existing renal disease are still lacking (50). Previous randomized controlled trials conducted primarily in mild asymptomatic PHPT patients showed no effect of PTX on renal function (52, 53, 54). No changes in eGFR were detected after PTX at the follow-up of about 5 years (11). More recently, PTX has been shown to prevent further deterioration of renal function in PHPT patients with a coexisting renal impairment (55). This is not the case in patients with a baseline eGFR, estimated by the CKD-EPI equation, above 60 mL/min/1.73 m². In this study, presurgical eGFR and systolic blood pressure are significantly and independently associated with the variation in eGFR after PTX. By contrast, in a prospective study on 62 PHPT patients, where renal function, evaluated as serum creatinine and eGFR levels, was reduced day 1 and at follow-up after successful PTX (56).

Effects of cinacalcet on kidney function

Cinacalcet does not affect creatinine and eGFR levels in PHPT patients (16, 17).

Effects of colecalciferol supplementation on kidney function

In female patients with PHPT, circulating 25-hydroxyvitamin D (25OHD) levels were inversely correlated with eGFR (57), more likely reflecting the effect of concomitant metabolic alterations rather than a direct effect of 25OHD on kidney function. Moreover, serum 25OHD levels were higher in the patients with kidney stones, though any significant difference in renal calcium excretion could be detected (42). However, data from intervention studies are lacking.

Effects of bisphosphonates on kidney function

Alendronate has been shown to increase BMD in patients with PHPT (58, 59, 60) and therefore it is suggested as treatment for osteopenia/osteoporosis in PHPT patients (10). The use of alendronate in PHPT patients has not been reported to be associated with impairment of the kidney function. Nonetheless, it should be kept in mind that intravenous zoledronic acid, a therapeutic option for acute symptomatic hypercalcaemic crisis, is not recommended when eGFR is below 30 mL/min. Denosumab might represent an alternative to bisphosphonates in controlling severe hypercalcaemia as

reported in cases of parathyroid carcinomas (61, 62). Bisphosphonates can be safe and beneficial for patients with a glomerular filtration rate of 30 mL/min or higher, but prescribing bisphosphonates in advanced CKD requires caution because of the increased possibility of low bone turnover disorders such as osteomalacia, mixed uraemic osteodystrophy and adynamic bone, even aggravating hyperparathyroidism. Bisphosphonates treatment can improve both bone mineral density and vascular calcification in patients with stage 1–2 CKD and osteoporosis (63).

Kidney involvement in particular forms of PHPT

1. *MEN1-related PHPT*: patients with MEN1-related PHPT experienced high frequency of early-onset kidney stones before 30 years of age (up to 86.2%) (64), while in an Italian series kidney stones occurred in MEN1-related PHPT patients with similar frequency compared with sporadic PHPT patients (65). Different degrees of renal insufficiency were reported in 19.4% of MEN1-related PHPT patients (66).
2. *Parathyroid carcinoma-related PHPT*: parathyroid carcinoma is an extremely rare tumour with an incidence of 1.25 per 10 000 000 per year. Most PHPT patients with parathyroid carcinoma experience serum calcium and PTH levels significantly higher than those detected in PHPT with benign parathyroid tumours; nonetheless, median 24-h urinary calcium excretion did not differ in PHPT patients with parathyroid carcinomas compared with PHPT patients with benign parathyroid tumours (67). About 46% of PHPT patients with parathyroid carcinoma had serum creatinine levels >1.1 mg/dL (eGFR <60 mL/min/1.73 m²), while renal symptoms (kidney colics, kidney stones, nephrocalcinosis) could be detected in 26.8% of patients (68).
3. *PHPT during pregnancy*: PHPT is rare during pregnancy; among maternal complications of PHPT, kidney stones with renal function deterioration and hypercalcaemic crisis with acute neurological disturbances have been reported (69). In a recent series of 74 mild PHPT women aged 20–40 years who experienced pregnancy, kidney stones were reported in 12% of patients (70).

Molecular aspects

Variations of the biological activity of the key molecules involved in the renal calcium, phosphate and electrolytes

Figure 3

Molecules involved in the calcium, oxalate and phosphate handlings at the distal convoluted (DCT) and connecting tubules levels. CASR, calcium-sensing receptor; PTHR1, PTH receptor-1; NCX1, sodium/calcium exchanger protein; PMCA1b, ATPase plasma membrane Ca²⁺ transporting 1; SLC26A6, solute carrier family 26 member 6; NaPt2, sodium-dependent phosphate transport protein 2A; TRPV5, transient receptor potential cation channel subfamily V member 5.

handling might contribute to pathogenesis of PHPT or might modulate its clinical presentation (Fig. 3).

Glial cell missing 2 (GCM2)

GCM2 is a parathyroid-specific embryonic transcription factor, whose inactivating mutations are associated with familial isolated hypoparathyroidism (OMIM#146200). The 282D polymorphic variant has been demonstrated to be linked to PHPT in a combined cohort of 510 PHPT Italian patients and to display GCM2 enhanced transcriptional activity; nonetheless, any significant correlation with kidney stones or kidney function was detected (71).

PTH receptor (PTHR1)

Data about the role of *PTHR1* gene variants in PHPT are not available.

TRPV5

PTH stimulates renal calcium reabsorption through the coordinated expression of renal transcellular calcium transport proteins. The PTH-induced stimulation is enhanced by the magnitude of the calcium influx

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Table 3 Prevalence of reduced kidney function in PHPT patients.

	Patients (n)	Period	Origin	Kidney stones (%)	Equation	eGFR (mL/min/1.73 m ²)				Ref.
						>90	89–60	30–59	<30	
Walker 2012	138	1984–1991	USA	16	MDRD#	84%		15%	1%	(102)
Walker 2014	114	2005–2013	USA	10	MDRD#	85%		15%	0%	(101)
Walker 2014	114	2005–2013	USA	10	CKD-EPI*	81%		19%	0%	(101)
Tassone 2009	294	1993–2007	Italian	nr	MDRD#	52%	31%	15%	2%	(99)
Tassone 2015	109	1995–2012	Italian	nr	CKD-EPI*	87%		13%		(100)
Ermetici 2015	190	2005–2010	Italian	54	CKD-EPI**	47%	39%	13%	1%	(43)

#MDRD equation (103); *CKD-EPI creatinine equation 2009 (104); **CKD-EPI creatinine–cystatin C equation 2012 (105); nr, not reported.

through the gatekeeper TRPV5, which in turn facilitates the expression of the downstream calcium transport proteins. Therefore, the renal transcellular transport proteins, including TRPV5, could contribute to the pathogenesis of PTH-related disorders (72). Mice lacking *TRPV5* develop severe hyperparathyroidism associated with hypercalciuria (73). *TRPV5* polymorphism (rs4236480) was observed to be associated with stone multiplicity of calcium nephrolithiasis in patients with idiopathic calcium stone formation (74). It would be of interest to investigate the effect of the *TRPV5* gene variant in PHPT patients.

Calcium-sensing receptor (CASR)

Inactivating mutations of the *CASR* gene are usually associated with hypocalciuria (calcium clearance <0.01) in the type 1 familial hypocalciuric hypercalcaemia (HHC1, OMIN#145980) and neonatal severe primary hyperparathyroidism (NSHPT, OMIM#239200). Fasting urinary calcium excretion was significantly higher in

patients with PHPT than in those with HHC, though most of the individual values measured in patients with HHC were in the same range as those measured in patients with PHPT (75). Indeed, in some patients harbouring germline inactivating mutations of the *CASR* gene, located in the cytoplasmic tail of the receptor protein, hypercalciuria has been diagnosed (76, 77). *CASR* protein is expressed and active in kidney cells, where its activation by extracellular calcium inhibits the PTH-induced calcium reabsorption. Therefore, common variants of the *CASR* gene modulate the effect of PTH-related hypercalcaemia on renal calcium handling (Table 4). The 990G allele, located in the cytoplasmic tail of the receptor protein, has been associated with increased renal calcium excretion in PHPT Italian patients (78, 79). Two further single nucleotide polymorphisms (SNPs), located in the regulatory region of the *CASR* gene, rs7652589 and rs1501899, are associated with kidney stones occurrence in PHPT patients (80). The rs1501899 likely determines a reduction of the *CASR* expression, while the 990G causes a gain of function of the *CASR*

Table 4 Effects of single nucleotide polymorphisms (SNPs) of the calcium-sensing receptor (*CASR*) gene on kidney disease in PHPT patients. nd, not determined; ↓, reduced; ↑, increased.

CASR SNP	Accession Number	Substitution	Minor Allele			Associated PHPT-related kidney phenotype	Refs
			Type	Activity	Frequency		
A986S	rs1801725	G>T	S	nd	40.0% vs 30.0% 38.0% vs 34.0% 26.4% vs 19.6% 40.0% vs 28.0%	None	(92) (78) (79) (97)
R990G	rs1042636	A>G	G	↑	12.0% vs 6.5% 4.0% vs 5.0% 8.0% vs 13.7% 5.8% vs 8.8%	Kidney stones	(78) (79) (97) (98)
Q1011E	rs1801726	C>G	E	nd	5.0% vs 10.0% 3.0% vs 3.5% 14% vs 9.0% 2.0% vs 5.5%	None	(78) (79) (97) (98)
NCRR (5'-UTR)	rs7652589	G>A	A	↓	32.2% vs 33.4%	Kidney stones	(80)
NCCR (intron 1)	rs1501899	G>A	A	↓	32.1% vs 31.5%	Kidney stones	(80)

protein. The combinatory effect of these two SNPs have been investigated in PHPT patients: patients carrying one or two copies of the minor allele at both rs1501899 and 990G displayed a 8-fold increased risk of experience kidney stones, compared with patients homozygous for the wild-type allele at both SNPs (81) (Table 3). *In vitro* study in HEK293 cells stably transfected with the wild-type CASR and the 990G variant demonstrated that the 990G allele is associated with high sensitivity to the calcimimetic compound R-568 (82), in terms of the effect of CASR activation on both intracellular calcium oscillations and p44/42-ERK phosphorylation. Similar increased sensitivity has been reported *in vivo* in a small cohort of patients with CKD-related hyperparathyroidism, where patients harbouring the 990G allele of the CASR gene responded with higher sensitivity to cinacalcet and exhibited a higher risk of calcium stone formation (83). By contrast, in a small cohort of MEN1-related PHPT patients, the presence of the 990G allele did not influence the efficacy profile of cinacalcet (84).

Lastly, recent data highlighted the role of proinflammatory cytokine like IL-1 β and IL-6 in regulating the expression levels of CASR on kidney cells. Proinflammatory cytokines interleukin-1 β and interleukin-6 upregulate CASR expression in parathyroid and kidney and do this through defined response elements in the CASR gene promoters. This results in decreased serum PTH, 1,25-dihydroxyvitamin D and calcium levels. Besides, elevated levels of calcium acting via the CASR can function as a danger signal that stimulates assembly of myeloid cell cytosolic multiprotein inflammasomes resulting in maturation of the proinflammatory cytokine IL-1 β by caspase-1 (85).

AP2S1 and GNA11

The FHH/HHC phenotype can also be associated with loss-of-function mutations of *AP2S1* and *GNA11*, encoding the σ -2 subunit of the adaptor-related protein complex 2, and G α_{11} proteins respectively. Inactivating mutations of the *AP2S1* gene have been identified as the cause of HHC3 (OMIM#600740), while inactivating mutations of the *GNA11* gene determine HHC2 (OMIM#145981). AP2 σ 2 is involved in the clathrin-mediated endocytosis of plasma membrane proteins such as CASR and G α_{11} couples CASR to intracellular signalling (86, 87). Estimated glomerular filtration rate and urinary calcium concentrations were similar in HHC1 and HHC3 patients (75), though patients with

HHC3 have higher plasma calcium concentration than patients with HHC1, indicating that the rate of renal tubular absorption of filtered calcium was higher in HHC3 than in HHC1 patients.

SLC12A1

Hypercalciuria associated with kidney stones and PHPT in the neonatal period has been recently described in a family harbouring two heterozygous mutations in the *SLC12A1* gene, encoding the sodium-potassium-chloride cotransporter-2 (NKCC2), which was previously implicated in antenatal type 1 Bartter syndrome (OMIM#601678) (88).

Claudin 14

The *CLDN14* gene encodes a protein involved in the regulation of paracellular permeability of ion transport at epithelial tight junctions in the nephron. The C allele of the rs219780 SNP of *CLDN14* has been associated with kidney stones, high levels of PTH and with low bone mineral density in healthy women; however, no difference in the frequency of kidney stones between the genotype groups in PHPT patients could be found (89).

SCL26A6

Urine oxalate has been indicated as a risk factor for kidney stones in PHPT patients (3). With the exception of the rare genetically determined conditions, increased urine oxalate excretion is due to increased intestinal absorption. *SLC26A6*, the gene coding for a sulphate transporter, is expressed in the human distal segments of the proximal tubules where it mediates oxalate-dependent NaCl absorption. The 206M polymorphic variant of the *SLC26A6* gene, whose encoded protein exhibits reduced activity, is not associated with kidney stones in PHPT patients, though it has been shown to be associated with less severe hypercalciuria in PHPT patients with stone formation, suggesting a role of SCL26A6 as contributor in kidney stone development in PHPT patients (35).

Phosphate handling

Patients with PHPT showed persistent hypophosphataemia without evidence of salt wasting; chronic

hyperparathyroidism in PTH-D1 transgenic mice, a model of primary hyperparathyroidism induced by parathyroid-specific overexpression of cyclin D1 gene under the control of PTH promoter, *Slc34a1* mRNA and protein expression was reduced by 50% relative to control mice, while *Slc9a3r1/NHERF-1* and *Pthr1* were unchanged, suggesting that *Slc34a1* has a predominant role in determination of renal phosphate handling and a persistent regulation by PTH (90). It would be of interest to investigate the role of *Slc34a1* gene variants in PHPT patients.

Vitamin D receptor (VDR)

Though VDR polymorphic variants are associated with kidney stones in the general population (91), VDR variants are not associated with PHPT and with PHPT clinical presentation in different cohorts (92, 93, 94).

From a clinical practice point of view, clinicians should consider that:

1. The high number of molecules, with the common variants or rare mutations of their coding genes, involved in renal calcium handling determines the great variability in clinical presentation; therefore, careful clinical, biochemical and hormone workout often needs more than one evaluation;
2. Though genetic analysis of the genes involved in renal calcium handling might define the risk of kidney stones development in PHPT patients, data from controlled study are not yet available;
3. At present, genetic analysis is recommended only for the *CASR* gene mutations in all patients with calcium-creatinine clearance ratio less than 0.02, as it can help to distinguish FHH from PHPT (9).

Specific items that should be considered for the clinical management of kidney disease in PHPT patients

Surgical management

1. Symptomatic PHPT patients for kidney stones should not experience delay in the diagnosis and surgical treatment of PHPT (2);
2. Asymptomatic PHPT patients are recommended to receive an extensive diagnostic workout aimed to define kidney involvement (2);
3. Asymptomatic PHPT patients with eGFR below 60 mL/min/1.73 m² should be subject to surgery as

part of the therapeutic goal aimed to remove all the factors associated with the further decline in eGFR;

4. Careful monitoring of the kidney performance after parathyroid surgery should be considered for PHPT patients with CKD.

Medical management

1. Diagnosis and treatment of all the concomitant risk factors of CKD should be considered in PHPT patients: age, hypertension, obesity, diabetes/insulin resistance and previous kidney damages.
2. eGFR is associated with arterial blood hypertension in PHPT patients as well as in general population. Therefore, hypertension monitor and treatment should be considered in the PHPT management. In a large multi-ethnic, community-based cohort, it has been demonstrated that higher serum aldosterone concentration is associated with higher serum PTH concentration, and that the use of renin-angiotensin-aldosterone system (RAAS) inhibitors is associated with lower PTH concentration (95). RAAS inhibitors might be considered and tested for the control of hypertension in PHPT patients also. By contrast, treatment with eplerenone, an antagonist of aldosterone, failed in reducing PTH levels in PHPT patients, though it was effective in controlling blood pressure (96).
3. Modification of lithogenic profile of PHPT urine: controversies about the diagnosis of urine lithogenic profile in PHPT patients have been raised by the Panels of the last Consensus Conference (2), as studies demonstrating the capacity of a biochemical urine profile to predict the kidney stones risk in PHPT patients are lacking. Moreover, evidence about the efficacy of nutritional or medical interventions on the urine lithogenic profile or on the risk to develop kidney stones are derived from studies in the general population, while studies have not been performed in PHPT patients.
4. Monitoring and management of PHPT patients with established CKD can be a challenge as CKD-related biochemical and clinical alterations alter the classic clinical presentation of PHPT (namely, lack of hypophosphataemia, further increased levels of PTH, multiglandular involvement and impaired bone mineral density by concomitant CKD-related bone disease) and the indication for the currently recommended drugs for the control of hypercalcaemia (bisphosphonates).

Conclusions

Kidney involvement, though mainly asymptomatic, frequently occurs in current PHPT patients. The impact on the health conditions of the PHPT patients as well as the progression of the kidney disease are far from being elucidated and the guidelines for the management of kidney disease in asymptomatic PHPT are largely based on evidence derived from the general population than from studies in PHPT patients. Nonetheless, available evidence highlights the need to approach kidney disease in PHPT patients with careful attention on mild preclinical kidney disease as well as established CKD.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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