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# LESS KNOWN AND NEGLECTED RENAL COMPLICATION OF PRIMARY HYPERPARATHYROIDISM: RENAL CYSTS

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## Abstract

**Objectives:** Simple renal cysts are lesions that are epithelial in origin, with a prevalence changing between 5 to 15% in the normal population. In animal studies, it was shown that PTH might stimulate cyst formation via intracellular signaling systems triggering epithelial cell proliferation. Our primary aim was to detect the simple cyst prevalence in a large cohort of PHPT and compare it with sex and age-matched health individuals. The secondary aim was to detect determinants of cyst formation in PHPT.

**Materials and Methods:** A total of 307 PHPT patients and 112 healthy controls were enrolled in our study. PHPT group was compared with the control group regarding the biochemical parameters and presence, size and bilaterality of renal cysts in the US performed by a single experienced radiologist.

**Results:** Prevalence (43.65% vs 25%, p=0.020) and size [28.40 mm (min-max: 4-82) vs 12.20 mm (min-max: 3-94) (p=0.013)] of simple renal cysts were higher in the PHPT group compared to controls. The presence of renal cysts was correlated with age but not sex and positively correlated with the serum PTH level in regression analysis. Serum Ca, P, and 24-hour urinary Ca excretion were not found to be associated with cyst formation.

**Conclusion:** Simple renal cysts are a benign renal complication of PHPT that does not alter renal function significantly, and their presence is directly correlated with the hypersecretion of PTH.

**Keywords:** Simple renal cyst, parathyroid hormone, complication, primary hyperparathyroidism.

## Introduction

Simple renal cysts are lesions that are epithelial in origin with a thin wall and filled with fluid.[1] As reported before in different series, they occur in 5.20-15.20% of the population.[2] Simple kidney cysts are very common as people begin to age; up to half of all people, 50 years of age and older have at least one kidney cyst.[3,4] It is important to differentiate simple cysts from atypical or complex cysts, which may be cystic tumors and various infectious and inflammatory lesions.[5] Most of the time, they don't cause any symptoms and are diagnosed coincidentally by ultrasound ordered for an unrelated reason. Rarely may they become symptomatic if they rupture and cause bleeding.[6] Other rare complications are infections, mass effects on the other organs, and increased blood pressure.[7]

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is characterized by hypercalcemia and elevated or inappropriately normal serum levels of parathyroid hormone (PTH).[8] In recent years, most of the cases are asymptomatic with mild hypercalcemia detected during routine biochemistry tests. The common complications due to PHPT are osteoporosis, hypercalciuria, decreased renal function and nephrolithiasis.[9] There are also less pronounced complications such as the increased risk of cardiovascular disease, higher than normal frequency of diabetes and obesity, and hyperuricemia. [10,11]

In some in vitro and in vivo models, it is suggested that PTH plays a role in the development of renal cysts. In fact, PTH has been demonstrated to stimulate kidney cell proliferation in vitro by activating the mitogen-activated protein(MAP) kinase intracellular signaling.[12,13] In addition, PTH was demonstrated to activate the proliferation of the epithelial cells of the renal tubules harboring mutations of the PKD1 gene that takes part in autosomal dominant polycystic kidney disease.[13]

In this study, our primary outcome was to compare the renal cyst prevalence of PHPT patients who were recommended to undergo surgery regarding indications in the international guidelines and compare it with age and sex-matched healthy controls. Our secondary aim was to detect determinants of cyst formation in PHPT.

## Materials and Methods

A total of 307 patients with PHPT who were admitted to our outpatient clinics between the dates of May 2015-April 2020 with PHPT and evaluated in the multidisciplinary council, including the surgeons, nuclear medicine specialists and endocrinologists, having at least one indication for surgery, were enrolled in this study. Informed written consent was obtained from all subjects prior to their enrollment, and our local ethics committee approved the study protocol in accordance with the principles of the Declaration of Helsinki. Age

and sex-matched 112 healthy controls without any known previous kidney or endocrinologic disease were chosen as the control group. Patients who were under the age of 18, without a definitive diagnosis of PHPT and hypercalcemia, and taking drugs that may cause hypercalcemia, such as lithium or thiazide diuretics, were excluded. Diagnosis of PHPT was made by the concomitant presence of high serum levels of albumin-corrected calcium and elevated or inappropriately normal PTH levels. Familial hypocalciuric hypercalcemia was excluded in all patients by the measurements of 24 hours-urinary calcium excretion, fractionated calcium excretion and Ca SR inactivating mutations if required.

The normal range of calcium, according to our hospital's assay, was (8.80–10.20 mg/dL) (Roche Diagnostics, Manheim, Germany). Plasma intact PTH was measured using the Allegro immunoradiometric assay (Roche Diagnostics, Manheim, Germany). The detection limit of the assay was 1 pg/mL (normal range, 10–65 pg/mL), and the intra- and interassay coefficients of variation were 2% and 10%, respectively. In all individuals, we calculated albumin-adjusted calcium by using the following equation (Ca+(4-serum albumin) x0.80). Vitamin D was measured by liquid chromatography coupled with tandem mass spectrometry (Schimadzu-API LC-MSMS API 3200, Canada). The lower and upper detection limits were 4 and 150 $\mu$g/L, respectively.

Patients had an abdominal ultrasound (US) performed by a single experienced radiologist. Each US was performed with a low-to-medium frequency (3.50–5 MHz, depending on the physical characteristics of the subject) convex probe and the ultrasound scanner (Hitachi, Japan). Ultrasonography was performed in the supine, right and left lateral decubitus positions. The presence, number, and position of cysts and stones were evaluated.

BMD was performed using dual-energy X-ray absorptiometry (DXA) of the lumbar spine and the proximal femur in posteroanterior projection. At the time of the study, there was a Hologic DXA scanner within the center. The least significant change (LSC) used in the MBC was 4.50%, both for the spine and hip and distal radius.

*Statistics*

Descriptive statistics were defined as the number (n) and percentage (%) for categorical variables. For continuous variables, mean and standard deviation (SD) were used to describe normally distributed variables and median with minimum and maximum values were used for non-normal distributions. Participants were categorized as those with or without PHPT. Between-group differences in continuous variables were assessed by unpaired student's t-test or Mann-Whitney U test, as appropriate. Between-group comparisons in categorical variables were assessed by the $\chi 2$ test or Fischer's exact test. SPSS 23.0 for Windows (IBM Corp., Armonk, NY) was used for the analyses. Multivariate analysis was performed by multiple regression analysis for the factors influencing the presence of kidney cysts.

## Results

A total of 307 patients with PHPT and sex and age-matched 112 healthy controls were enrolled in the study. The median age of PHPT and control groups were 55 (26-78) and 56 (20-82) years, respectively (p=0.070). Number and percentage of female/male patients in PHPT and control groups were 274 (89.25%)/33(10.75%) and 99 (88.39%)/13 (11.61%), respectively. Number of patients with/without renal cysts in the PHPT group was 134 (43.65%)/173 (56.40%) vs 28 (25%)/84 (75%) in the control group (p=0.020). Among the patients with PHPT, 32 had unilateral, whereas 102 had bilateral cysts. In the control group, seven patients had unilateral, and 21 patients had bilateral simple renal cysts. There was no significant difference between the groups regarding bilaterality. The median size of the renal cysts was 28.40 mm (min-max:4-82) in the PHPT group, whereas it was 12.20 mm (min-max:3-94) in controls (p=0.013). Serum TSH and creatine were comparable between groups, whereas median Ca and PTH were significantly higher in PHPT compared to controls (p<0.001). Serum P was significantly lower in the PHPT group compared to controls (p=0.030) (Table1).

**Table 1.** Biochemical and clinical data of the patients with PHPT and healthy controls

| | PHPT (n=307) | Controls(n=112) | P value |
|---|---|---|---|
| Female/male (n/%) | 274(89.25%)/33(10.75%) | 99(88.39%)/13(11.61%) | 0.980 |
| Median age (min-max) (years) | 55 (26-78) | 56 (20-82) | 0.070 |
| Presence of renal cysts (n/%) | 134(43.65%) | 28 (25%) | 0.020 |
| Unilateral/bilateral cysts(n) | 32/102 | 7/21 | 0.940 |
| The median longest diameter of the cyst (min-max) | 28.40 (min-max:4-82) | 12.20 (min-max:3-94 | 0.013 |
| TSH (mean) | 2.23±1.56 | 1.89±0.90 | 0.023 |
| Ca mg/dl (mg/dl) | 11.47±1.08 | 9.08±0.84 | <0.001 |
| P mg/dl (mg/dl) | 2.74±1.12 | 3.73±0.95 | 0.030 |
| PTH pg/ml (median) | 225 (67-876) | 40(27-92) | <0.001 |
| Albumin g/L | 4.42±0.92 | 4.36±1.03 | 0.570 |
| Creatine mg/dl | 0.88±0.22 | 0.91±0.27 | 0.470 |

(Ca: Calcium, P: Phosphorus, PTH: Parathormone)

In the PHPT group, 298 (97%) of 307 patients underwent surgery in our center. Histopathology was reported as parathyroid adenoma in 293(98.30%), parathyroid hyperplasia in 3(1%) and parathyroid carcinoma in 2 (%0.70). Median Ca excretion in 24 hours urine collection was 357 mg/day (min-max;114-1216). Median P excretion was 740 mg/day (min-max;1-2160) (Table 2).

BMD was documented for everyone in the PHPT group but not in the control group. Of 307 PHPT patients, 54 had osteopenia, 77 had osteoporosis, and 176 had normal T scores at one of three sites in DEXA. Kidney stones were detected in 70 of 307 PHPT patients and in 4 of 112 control individuals. The difference between the two

groups was statistically significant (p<0.001). The presence of renal cysts in PHPT patients with or without nephrolithiasis was similar ( p=0.475)

In the regression analysis, parameters associated with the presence of renal cysts were found to be age and serum PTH level. Neither serum calcium nor urinary Ca excretion was not associated with cyst formation (Table 3).

**Table 2.** Renal and bone-related parameters and prevalence of complications in PHPT group

| | |
|---|---|
| 24 hours urinary Ca (mg/day) | 357 (114-1216) |
| 24 hours urinary P (mg/day) | 740(1-2160) |
| Osteoporosis (n/%)<br>Osteopenia (n/%)<br>Normal T score(n/%) | 54 (17.59%)<br>77 (25.08%)<br>176(57.33%) |
| Nephrolithiasis present/absent(n/%) | 70 (22.80%)/237(78.20%) |

(Ca: Calcium, P: Phosphorus)

**Table 3.** Multiple regression analysis for the detection of risk factors for the presence of simple renal cysts

| | P value | Odds Ratio |
|---|---|---|
| Age | <0.001 | 0.270 |
| Serum total Ca | 0.580 | 0.044 |
| Serum PTH | <0,001 | 0.310 |
| Serum P | 0.570 | -0.016 |
| 24 hours urinary Ca | 0.693 | 0.032 |
| 24 hours urinary P | 0.815 | -0.410 |
| Sex | 0.720 | - |

(Ca: Calcium, P: Phosphorus, PTH: Parathormone)

## Discussion

PHPT is a common endocrine disease that occurs because of the autonomous secretion of PTH and resultant high Ca levels and lack of feedback inhibition due to a reduced number of calcium-sensing receptors (CaSR). The prevalence is 7 per 1000 people, and it is 3-4 times more frequent in females than males.[14] In the last decade, the vast majority of PHPT cases have been admitted to outpatient clinics with mild or nonspecific symptoms.[15] In our study %42 PHPT patients had either osteopenia or osteoporosis, and %22 had symptomatic or asymptomatic nephrolithiasis detected with US.

In this study, we detected that the renal cyst prevalence was significantly higher in PHPT patients compared to healthy controls. It was also detected that the main determinants of cyst formation were age and PTH level. Although renal cysts are benign, harmless lesions in most cases, they may lead to serious complications such as rupture and bleeding rarely and can be accepted as end-organ damage of primary hyperparathyroidism, according to our results.

The major renal manifestations of PHPT are hypercalciuria related to impaired renal function and nephrocalcinosis. Symptomatic kidney stones were reported to occur in %20 of the cases, whereas nephrocalcinosis is rare.[16] In asymptomatic PHPT presence of asymptomatic kidney stones detected with conventional imaging such as US or non-contrast CT is considered an indication for surgery. Therefore, it is recommended in the guidelines to screen all PHPT patients with US.[17]

Herein the present study, our aim was to reveal another unpronounced renal complication that may be related to PHPT, which is a "simple renal cyst". To our knowledge, there is only one study without a control group in the literature.[12] In our study, we detected that the prevalence and the size of the simple renal cysts were significantly higher than the age and sex-matched healthy individuals. In the previous study, renal cyst prevalence was found to be 34.90% in PHPT patients, which was slightly higher than our population, which might be due to older mean age.[12] The limitation of the mentioned study was its retrospective nature, including US examinations by different operators and the lack of a control group.

In our study presence of simple cysts was not associated with gender in the PHPT group in contrast with the general population, where male gender is a well-known risk factor.[4] In our study number of female patients was eight times higher than males, which means increased PTH is a risk factor for the formation of simple cysts regardless of sex.

In the regression analysis, determinants of cyst formation in the PHPT group were age and serum PTH but not serum Ca, P, or 24 hours urinary excretion of Ca. In addition to that, prevalence did not differ in patients with or without kidney stones. PTH activates the intracellular pathways by binding to transmembrane Gs/adenylyl cyclase and Gq/phospholipase C and in the proximal tubule-like opossum kidney cell line. In addition to that, PTH causes PKC- and PKA-dependent inhibition of Na-dependent phosphate (Na/Pi) transport.[13] Adding to its well-described regulation of renal transport function, several findings suggest that PTH may regulate MAPK in target tissues.[18] In one study, PTH caused time- and concentration-dependent increases in MAPK activity that resulted in increased proliferation of mesangial and tubular epithelial cells.[19] In light of those findings, we can conclude that PTH is responsible for cyst formation by increasing the cellular growth of epithelial cells in the kidneys. In our study, the median largest diameter of the cysts was higher in PHPT compared to controls supporting the findings of Corbetta et al.[12]

In the PHPT group, all cysts were reported as simple cysts. That finding supports this possible complication of PHPT is relatively benign and can cause less morbidity when compared to other renal complications such as stones, reduced GFR and nephrocalcinosis. However, several observational studies have reported that the incidence and prevalence of hypertension are higher in patients with simple renal cysts, which means that benign complications may worsen cardiovascular outcomes and renal functions in PHPT patients. [20,21,22]

There are a few limitations in our study. We included only PHPT patients with surgery indications since their information was recorded in the database of the multidisciplinary council. PHPT patients with an asymptomatic and mild form of the disease without any indication for surgery were not included. Since patients with an indication for surgery might have more severe diseases, that may have caused a bias. Another limitation is the relatively smaller sample size of the control group, which is nearly 1/3 of the patient group. That was due to difficulty in finding age-matched healthy individuals undergoing renal ultrasonography.

In conclusion, simple renal cysts are benign renal complications of PHPT that do not alter renal function significantly, and their presence is directly correlated with the hypersecretion of PTH. They can rarely cause complications and lead to misdiagnosis of hereditary polycystic kidney disease.

**Ethical Considerations:** Approval was obtained from Ankara Yildirim Beyazit University Faculty of Medicine Clinical Research Ethics Committee for the study (Decision number: 32 Date: 17.03.2021).

**Conflict of Interest:** The authors declare no conflict of interest.

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