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WHAT ARE THE PARAMETERS THAT PREDICT THE DEVELOPMENT OF NEPHROLITHIASIS AND OSTEOPOROSIS IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM?

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Abstract

Objectives: Primary hyperparathyroidism (PHPT) is associated with an increased risk of nephrolithiasis and osteoporosis, and predicting the development of these diseases will reduce PHP-related morbidities.

Materials and Methods: A total of 311 patients with PHPT due to parathyroid adenoma were evaluated retrospectively. The patients were divided into groups, as patients with and without nephrolithiasis and those with and without osteoporosis. Demographic and biochemical variables that could predict the development of nephrolithiasis and osteoporosis in these groups were examined.

Results: Nephrolithiasis was observed in 24.44% of 311 PHPT patients. Serum creatinine (Cr), serum calcium (Ca), adjusted Ca (adj Ca), albumin and 24-hour urinary phosphorus (24h uP) levels were higher, and serum P-value was significantly lower in patients with nephrolithiasis than those without nephrolithiasis. In the Receiver Operating Characteristic (ROC) analysis, serum Cr ≥0.66 mg/dl, adj Ca ≥10.72 mg/dl, serum P ≤2.71 mg/dl and 24h uP ≥635 mg/day cut-off values were found to have high sensitivity and low specificity values on the risk of developing nephrolithiasis. Of all patients, 43.09% had osteoporosis, and it was determined that only ≥50.50 years (sensitivity 81.34%, specificity 49.51%) and intact parathyroid hormone ≥ 201.50 pg/mL (sensitivity 75.14%, specificity 41.04%) values could predict osteoporosis (Area Under the ROC curve ranged from 0.57 to 0.67).

Conclusion: While biochemical parameters are useful in predicting nephrolithiasis in patients with PHPT, the development of osteoporosis seems to be less related to biochemical parameters.

Keywords: Primary hyperparathyroidism, nephrolithiasis, osteoporosis.

Introduction

Primary hyperparathyroidism (PHPT) is one of the common endocrine diseases, and it was diagnosed with various clinical findings such as significant hypercalcemia, fractures, nephrolithiasis and pancreatitis in the past, but today it is diagnosed with minimal or no symptoms owing to the routine measurement of serum calcium (Ca) levels.[1,2]

Even asymptomatic, PHPT often causes bone loss, and patients with PHPT have an increased risk of silent fractures in the cortical and trabecular regions.[3-5] Therefore, bone mineral density (BMD) measurement and vertebral fracture analysis are recommended for patients with PHPT at the time of diagnosis and periodically thereafter.[2]

The risk of nephrolithiasis is increased in PHPT, and the prevalence of silent kidney stones in asymptomatic PHPT(aPHPT) patients is up to 35%.[6,7] Renal imaging and 24-hour urinary Ca (24-h uCa) measurement are recommended for all patients, and it is stated that the biochemical urinary stone risk profile should be evaluated when 24-h uCa excretion exceeds 400 mg.[8,9]

The aim of this study was to determine the factors that predict the development of osteoporosis and nephrolithiasis in patients with PHPT, and thus predict the development of nephrolithiasis or osteoporosis in these patients.

Materials and Methods

Patients

The records of 390 patients followed for PHPT were reviewed, and 311 patients with PHPT due to parathyroid adenoma were included in the study. Patients with parathyroid carcinoma, parathyroid hyperplasia, normocalcemic HPT, hypercalcemia due to malignancy or bone metastases, and those using thiazide diuretics or lithium were not included in the study. In addition, patients with PHPT who also had gastrointestinal, hematological, rheumatological or other endocrinological diseases that could cause osteoporosis were not included in the study. The diagnosis of PHPT was made in the presence of hypercalcemia with the presence of elevated or normal intact PTH (iPTH).

Patients' demographic characteristics, a history of nephrolithiasis and fractures, laboratory [serum Ca, albumin, serum phosphorus (P), iPTH, alkaline phosphatase (ALP), 25-hydroxyvitamin D, creatinine (Cr) and 24-h uCa and 24-h urinary P (uP)], renal imaging and BMD results were recorded. The patients were divided

into groups as patients with and without nephrolithiasis, and those with and without osteoporosis, and demographic characteristics and laboratory findings were compared among the patients.

Biochemistry and Imaging

Serum Ca, albumin, serum P, Mg, ALP, Cr, 24-h uCa and 24-h uP were measured by standard laboratory methods. Adjusted Ca (Adj Ca) levels were calculated [Adj Ca= Serum Ca + [0.8 x (normal albumin – patient albumin)]]. Allegro IRMA (Roche Diagnostics) was used to detect plasma iPTH (normal range, 15–60 pg/mL). The detection limit was set at 1 pg/mL, with intra-assay and inter-assay coefficients of variation of 2% and 10%, respectively. Liquid chromatography with tandem mass spectrometry was used to determine 25-hydroxyvitamin D levels (Shimadzu-API LC-MS-MS API 3200, Canada), and the normal range was 20–80 µg/L.

Renal ultrasonography (US) or abdominal computed tomography (CT) was used to evaluate nephrolithiasis. Patients with a history of renal stone disease and patients with renal stones/calcifications on imaging were included in the nephrolithiasis group. BMD was evaluated with dual-energy X-ray absorptiometry (DEXA) (QDR-4500, Hologic Inc, Waltham, MA). DEXA measurements were made from the lumbar vertebra, femur and forearm (distal 1/3 radius). BMD was expressed as T-score or Z-score. In the diagnosis of osteoporosis, the region with the lowest T score in the lumbar spine, femoral neck and forearm was considered. The results were classified as normal, osteopenia and osteoporosis according to the criteria defined by WHO.

Statistical analysis

All statistical analyses were performed on IBM SPSS Statistics Version 21.0 for Windows (IBM Corp. Released 2012. Armonk, NY), and the statistical significance value was accepted at <0.05. The continuous variables were summarized as median (Quartile 1-Quartile 3) after examining the normality. The sex was given as frequency and percentage. The Yates Chi-Square or Fisher's exact test was used to analyze categorical variables. The comparisons between patients with versus without the condition (nephrolithiasis, osteoporosis) were analyzed by the Mann-Whitney U test. The Odds ratio was calculated from the univariate logistic regression model to obtain significant differences. When a significant difference was found between groups, the Area Under the Receiver Operating Characteristic (ROC) was calculated to decide whether to determine the cut-off value(s) to discriminate between patients with and without the condition. The Area Under the ROC curve (AUC) takes values between 0 and 1. To interpret the AUC values, we use the following rule of thumb given by Hosmer et. al: 0.50: no discrimination, 0.51-0.70: Poor, 0.71-0.80: Acceptable, 0.81-0.90: Excellent, >0.91: outstanding discrimination.[10]

Results

Of the 311 patients, 34 (10.93%) were male, 277 (89.07%) were female, and the median age was 54 years.

Nephrolithiasis

Nephrolithiasis was found in 24.44% (n=76) of the patients with PHPT. Gender and age distribution were similar in patients with and without nephrolithiasis. Nephrolithiasis was observed in 32.35% of male and 23.47% of female patients. Serum Cr, serum Ca, adj Ca, albumin, and 24-h uP levels were higher, and serum P-value was significantly lower in patients with nephrolithiasis than those without nephrolithiasis. There was no significant difference between the groups in terms of ALP, iPTH, 25 (OH)D and 24-h uCa level (Table 1).

Table 1. The Comparison of Patients with Nephrolithiasis and Those without Nephrolithiasis

Variables	Without Nephrolithiasis	With Nephrolithiasis	p*	OR (95% CI lower - upper)	AUC (95% CI lower-upper)
Sex (Male/Female)	23 (67.65) / 212 (76.53)	11 (32.35) / 65 (23.47)	0.354		
Age (years)	54 (47-61)	53.50 (46-59)	0.414		
Serum Cr (mg/dL)	0.67 (0.59-0.80)	0.74 (0.64-0.89)	**0.006**	16.336 (2.856 – 93.451)	0.636 (0.543 – 0.728)
Serum Ca (mg/dL)	11.19 (10.80-11.60)	11.53 (10.90-12.10)	**<0.001**	1.698 (1.280 – 2.252)	0.639 (0.565 – 0.713)
Adj Ca (mg/dL)	10.80 (10.41-11.28)	11.19 (10.65-11.76)	**0.002**	1.522 (1.161 – 1.996)	0.619 (0.543 – 0.694)
Serum P (mg/dL)	2.60 (2.30-2.94)	2.42 (2.10-2.82)	**0.012**	1.838 (1.105 – 3.059)	0.596 (0.523 – 0.668)
Albumin (g/L)	4.43 (4.20-4.61)	4.55 (4.23-4.80)	**0.027**	2.251 (1.085 – 4.670)	0.584 (0.506 – 0.662)
ALP (U/L)	96 (78-132)	94.50 (78.25-128.75)	0.745		
iPTH (pg/mL)	151 (102-214)	177.50 (112.25-287.75)	0.069		
25 (OH) D (µg/L)	16.10 (10.10-25.55)	15.38 (9.40-24.35)	0.388		
24-h uCa (mg/day)	357.20 (249.50-491)	397.50 (306.25-519.50)	0.106		
24-h uP (mg/day)	720 (532-973)	820 (680-1030)	**0.017**	1.001 (1.000-1.001) p>0.05	0.592 (0.522-0.662)

Abbreviations: Cr: Creatinine, Ca: Calcium, Adj Ca: Adjusted calcium, P: Phosphorus, ALP: Alkaline phosphatase, iPTH: intact parathyroid hormone, CI: confidence Interval, AUC: Area Under the Curve, OR: Odds ratio obtained univariate logistic regression.
Data were summarized as median (quartile 1-quartile 3) or frequency (percentage) according to variable type.
**Continuity Correction Chi_Square test for sex, Mann Whitney U test results for quantitative variables.*
The limits for interpretation of the AUC: 0.50:no discrimination, 0.51-0.70:Poor, 0.71-0.80:Acceptable, 0.81-0.90:Excellent, >0.91: outstanding discrimination.

As a result of the ROC analysis performed to determine the cut-off point on the risk of nephrolithiasis, it was determined that AUC values caused poor discrimination. Serum Cr ≥0.66 mg/dl, adj Ca ≥10.72 mg/dl, serum P ≤2.71 mg/dl and 24h uP ≥635 mg/day cut-off values were found to have high sensitivity and low specificity values on the risk of developing nephrolithiasis (Table 2).

Osteoporosis

Osteoporosis was found in 43.09% (n=134), osteopenia in 33.76% (n=105) and normal BMD in 23.15% (n=72) of the patients with PHPT. In addition, forearm BMD values were compatible with osteoporosis in 40.7% of the patients and osteopenia in 33.3%. The median age of patients with osteoporosis was significantly higher than those without osteoporosis (p<0.001). While the median iPTH was 159.50 (Q1:110.50-Q3:277.43) pg/mL in patients with osteoporosis, the median iPTH was 152 (Q1:100.85-Q3:201.50) pg/mL in patients without osteoporosis, and a borderline significance was determined between the two groups (p=0.049). There was no significant difference between the groups with and without osteoporosis in terms of serum Cr, serum Ca, adj Ca, serum P, albumin, ALP, 25 (OH) D, 24-h uCa and 24-h uP levels (Table 3).

As a result of the ROC analysis performed to determine the cut-off point on the risk of osteoporosis, it was observed that the risk of osteoporosis increased at ≥ 50.50 years (sensitivity 81.34%, specificity 49.51%) and iPTH ≥ 201.50 pg/mL (sensitivity 75.14%, specificity 41.04%) (Table 2).

Table 2. The Cut-Off Values for Variables That Show a Statistically Significant Difference Between Groups

Variables	AUC (95% CI lower-upper)	Cut off value	Sensitivity (%)	Specificity (%)
For Nephrolithiasis				
Serum Cr (mg/dL)	0.636 (0.543 – 0.728)	≥0.66	73.91	45.52
Serum Ca (mg/dL)	0.639 (0.565 – 0.713)	≥11.09	71.50	44.68
Adj Ca (mg/dL)	0.619 (0.543 – 0.694)	≥10.72	72.37	45.30
Serum P (mg/dL)	0.596 (0.523 – 0.668)	≤2.71	71.50	40.43
Albumin (g/L)	0.584 (0.506 – 0.662)	≥4.40	69.74	43.16
24-h uP (mg/day)	0.592 (0.522-0.662)	≥635	80.01	40.61
For Osteoporosis				
Age (years)	0.672 (0.611 – 0.733)	≥50.50	81.34	49.51
iPTH (pg/mL)	0.565 (0.500-0.631)	≥201.50	75.14	41.04

Abbreviations: Cr: Creatinine, Ca: Calcium, Adj Ca: Adjusted calcium, P: Phosphorus, iPTH: intact parathyroid hormone, CI: confidence Interval, AUC: Area Under the Curve. The limits for interpretation of the AUC: 0.50:no discrimination, 0.51-0.70:Poor, 0.71-0.80:Acceptable, 0.81-0.90:Excellent, >0.91: outstanding discrimination.

Table 3. The Comparison of Patients with Osteoporosis and Those without Osteoporosis

Variables	Without Osteoporosis	With Osteoporosis	p*	OR (95% CI lower-upper)	AUC (95% CI lower-upper)
Sex (Male/Female)	22 (64.71) / 155 (55.95)	12 (35.29) / 122 (44.05)	0.430		
Age (years)	51 (44-57)	56 (52-64)	**<0.001**	1.051 (1.027-1.076)	0.672 (0.611 – 0.733)
Serum Cr (mg/dL)	0.70 (0.60-0.86)	0.67 (0.59-0.79)	0.203		
Serum Ca (mg/dL)	11.20 (10.85-11.79)	11.28 (10.89-11.90)	0.595		
Adj Ca (mg/dL)	10.79 (10.42-11.42)	10.92 (10.46-11.49)	0.638		
Serum P (mg/dL)	2.60 (2.20-3.05)	2.50 (2.28-2.84)	0.330		
Albumin (g/L)	4.48 (4.18-4.70)	4.43 (4.20-4.67)	0.991		
ALP (U/L)	87 (76-128)	99 (81.75-133.25)	0.080		
iPTH (pg/mL)	152 (100.85-201.50)	159.50 (110.50-277.43)	**0.049**	1.002 (1.001 – 1.004)	0.565 (0.500-0.631)
25 (OH) D (µg/L)	15.60 (10-24.70)	16.71 (10.09-25.83)	0.585		
24-h uCa (mg/day)	361.50 (247.85-479.75)	385 (264-517.50)	0.392		
24-h uP (mg/day)	755 (560-980)	725 (531-980)	0.566		

Abbreviations: Cr: Creatinine, Ca: Calcium, Adj Ca: Adjusted calcium, P: Phosphorus, ALP: Alkaline phosphatase, iPTH: intact parathyroid hormone, CI: confidence Interval, AUC: Area Under the Curve, OR: Odds ratio obtained univariate logistic regression.
Data were summarized as median (quartile 1-quartile 3) or frequency (percentage) according to variable type.
**Continuity Correction Chi_Square test for sex, Mann Whitney U test results for quantitative variables.*
The limits for interpretation of the AUC: 0.50:no discrimination, 0.51-0.70:Poor, 0.71-0.80:Acceptable, 0.81-0.90:Excellent, >0.91: outstanding discrimination.

Discussion

In this study, the factors that may predict the development of nephrolithiasis and osteoporosis in patients with PHPT were evaluated. Serum Cr ≥0.66 mg/dl, adj Ca ≥10.72 mg/dl, serum P ≤2.71 mg/dl and 24-h uP ≥635 mg/day values were found to predict the development of nephrolithiasis; and age ≥50.50 years and iPTH ≥201.50 pg/ml values to predict the development of osteoporosis with high sensitivity, low specificity and weak strength.

Today, the main renal manifestations of PHPT are hypercalciuria and nephrolithiasis.[11] Symptomatic nephrolithiasis is present in approximately 10-20% of patients.[11,12] The prevalence actually appears to be much higher when asymptomatic patients are screened for nephrolithiasis.[7,8,11] While younger age and male gender have been shown as risk factors for nephrolithiasis, less consistent relationships have been observed between

the degree of hypercalcemia and hypercalciuria, PTH levels, and other urinary factors and nephrolithiasis.[9,11] In a study by Reid et al., nephrolithiasis was found in 13.9% of 611 patients with PHPT, and only younger age and male sex were found to be independently associated with nephrolithiasis. The authors attributed this to the hypothesis that younger individuals are at higher risk of nephrolithiasis due to greater renal activation of 1,25-dihydroxy vitamin D, greater intestinal Ca absorption and, consequently, greater calciuria.[13,14]

Saponaro et al. detected nephrolithiasis in 21.6% of 176 aPHPT patients, and hypercalciuria was reported to be a predictor for nephrolithiasis.[15] In a case-control study of 617 PHP patients, 23% of the patients had renal calcification (12% nephrolithiasis, 12% nephrocalcinosis, both 1%), with most being mild.[16] Cipriani et al. reported the prevalence of nephrolithiasis as 35.5% in 76 patients with aPHPT.[7] In our study, the prevalence of nephrolithiasis was found as 24.44%. Differences in the prevalence of nephrolithiasis in patients with aPHPT may be due to the retrospective, prospective, or observational study design, the use of different imaging modalities, or patient selection. We included only patients with parathyroid adenoma in our study. We did not include patients with parathyroid carcinoma with higher serum Ca levels and more complications. The prevalence of nephrolithiasis may be higher in studies including these patients.

Current guidelines recommend a value of 24-h uCa >400 mg/day to define hypercalciuria. However, it has been stated in the literature that this cut-off value for hypercalciuria is found in approximately one-third of patients with aPHPT, indicating a very low positive predictive value.[15,17] Saponaro et al. reported that the cut-off values of 250 mg/day for women and 300 mg/day for men showed higher sensitivity as a predictor of nephrolithiasis, but the specificity was lower than >400 mg/day. In the same study, it was reported that the sensitivity of the cut-off value of 231 mg/day obtained after ROC analysis was high, but the specificity was low.[15] Tay et al. reported that a threshold of >211 mg/day in patients with aPHPT had a sensitivity of 84.2% and a specificity of 55.3% for nephrolithiasis.[17] In another study evaluating the relationship between nephrolithiasis and hypercalcemia, it was shown that the risk increases at the upper limit of normal even if the 24-h uCa level is within the normal range.[18] In our study, although 24-h uCa was higher in patients with nephrolithiasis than in those without nephrolithiasis, this difference was not statistically significant, and therefore, the 24-h uCa value that could predict nephrolithiasis could not be calculated. This finding suggests that other urinary factors associated or not associated with hypercalciuria may also play a role in the development of nephrolithiasis. There are limited and conflicting results regarding the potential role of high 24-h urinary oxalate and low citrate in patients with PHPT.[9,11] However, these variables were not evaluated in our study. Changes in serum albumin levels affect total serum Ca levels. Therefore, it is important to use the adj Ca level in the analysis. In our study, serum albumin levels and accordingly adj Ca levels were found to be higher in patients with nephrolithiasis, and this is consistent with an increased risk of nephrolithiasis. On the other hand, there are studies in the literature in which serum albumin levels are similar in patients with and without nephrolithiasis.[19]

On DEXA performed in PHPT patients, BMD loss is greater in cortical regions such as the distal one-third of the forearm than cancellous sites such as the lumbar spine, reflecting the catabolic or anabolic effects of PTH on different skeletal parts.[20] However, epidemiological data suggest an increased risk of both vertebral and peripheral fractures in PHPT.[4] New technologies for noninvasively imaging skeletal microarchitectures, such as high-resolution peripheral quantitative CT (HRpQCT) and trabecular bone score (TBS), demonstrate that trabecular deterioration occurs both in the spine and in the radius and tibia.[21,22] Using these technologies, studies have shown that the risk of vertebral fracture (VF) is increased in PHPT compared to age- and sex-matched controls and many PHPT patients have silent Vfs.[3,23]

The prevalence of osteoporosis in PHPT differs among studies (39-62.9%).[7,24,25] Mean T scores are in the osteopenic range in most studies.[24,25] In a study by Reid et al., osteoporosis was observed in 48.4% of the cases, osteopenia in 39.9% and normal BMD was in 11.7% with DEXA, and greater age, lower body mass index, and lower Cr level were reported to be independently associated with osteoporosis.[13] Liu et al., investigated the risk factors associated with VF in PHPT, and found the prevalence of osteoporosis at 54.7% and the prevalence of VF at 12.8%. The authors stated that VF was associated with age, osteoporosis at the hip, prior fractures, osteoporosis treatment, and poorer renal function, but these risk factors were similar to those in patients without PHPT, and there was no association between VF and TBS, spine BMD, or biochemical severity of PHPT.[5] Unlike the study of Liu et al., different studies have shown that TBS was associated with common VFs in PHPT.[26,27] In our study, 33.76% of our patients had osteopenia, 43.09% had osteoporosis, and 23.15% had normal BMD. Age and serum iPTH levels were found to be associated with the development of osteoporosis. However, since our study was retrospective, HRpQCT and TBS measurements were not available in our study population, and the risk of VF could not be evaluated.

This study has some limitations. First, only patients who were operated for PHPT and were found to have parathyroid adenoma were included in the study. Patients who did not meet the surgical indications and were followed up and patients with parathyroid carcinoma who had a higher risk of complications such as severe hypercalcemia, nephrolithiasis and osteoporosis were not included in the study. Second, urinary stone risk factors other than 24-h uCa could not be evaluated to assess the risk of nephrolithiasis. Finally, VF risk assessment could not be performed in our study group.

In conclusion; the factors that may predict the development of nephrolithiasis and osteoporosis in patients with PHPT were evaluated, and serum Cr, adj Ca, serum P, and 24-h uP values were found to predict the development of nephrolithiasis; and age and iPTH values to predict the development of osteoporosis with high sensitivity and low specificity. However, the low AUC values indicate that the predictive power of these parameters is weak. The exclusion of cases with parathyroid carcinoma in the study may have reduced the

power of the cut-off point for these variables. In addition, increasing the number of patients included in further studies might change these rates.

Ethical Considerations: Local ethical committee approval was obtained according to the ethical standards of the Helsinki declaration (Approval date and number: 2021/21-2080).

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

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