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Reevaluating surgical indications for asymptomatic hyperparathyroidism: hypercalciuria is not a urinary stone risk

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Introduction

The latest guideline for asymptomatic primary hyperparathyroidism (PHPT) recommends surgery for female patients with 24-hour urinary calcium (Ca) >250 mg/day and male patients with >300 mg/day, as they are at risk for urinary stones (US), but the evidence remains unclear. To determine whether the urinary Ca excretion criterion was appropriate as a surgical indication, we conducted a retrospective survey of a study population of PHPT patients with asymptomatic or symptomatic US and without US.

Materials and methods

746 sporadic PHPT patients operated between 2004 and 2020 at Tokyo Women's Medical University
The inclusion criteria: Preoperative 24-hour urinary data on Ca, phosphorus (P), creatinine (Cr), and normal intact parathyroid hormone (i-PTH) levels after parathyroidectomy are available.
The exclusion criteria: Reoperation, multiple endocrine neoplasms, and preoperative bisphosphonate or calcimimetic

Symptomatic US: US with symptoms such as stone attack, hematuria, hydronephrosis, or other conditions requiring treatments
Asymptomatic US: US identified based on imaging findings (KUB, if necessary, ultrasound or CT)

Evaluation of the appropriateness of the 24-hour urinary Ca thresholds

1. The sensitivity and specificity were calculated using cut-off values of >250 mg/day for female and >300 mg/day for male.
2. Receiver operating characteristic (ROC) curve analysis was conducted, and the area under the curve (AUC), sensitivity, specificity, and optimal cut-off value using the highest Youden index were calculated.

Search for other risk factors
A logistic regression model was used to calculate the adjusted odds ratio (OR) with 95% confidence interval (CI) .
All values in the groups are expressed as the median and interquartile range. Statistical significance was set at a p-value of <0.05.

Results

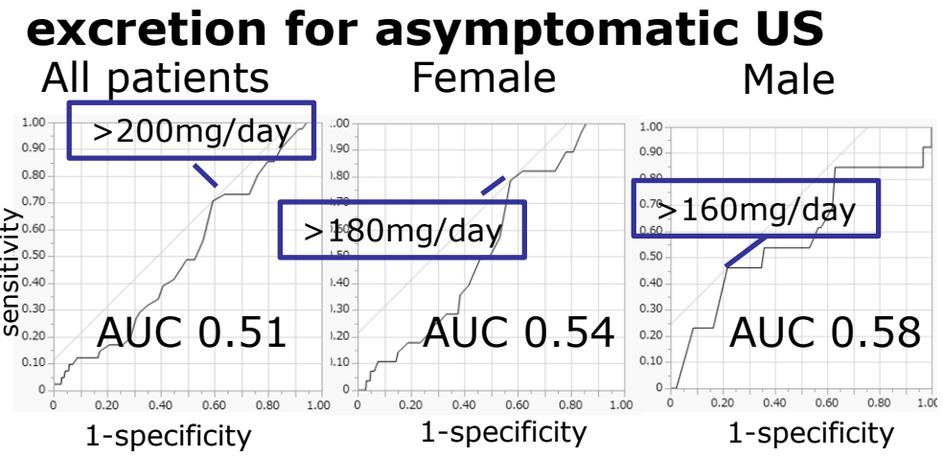
746 PHPT patients

Characteristics of patients

(Reference range)	No US n=466	Asymptomatic US n=41	Symptomatic US n=239	P value
Sex (Female/Male)	370/96	28/13	144/95*	**<0.001**
Age (years)	61 (17)	60 (19.5)	55 (21) *#	**<0.001**
Blood test				
Ca (8.5 - 9.9 mg/dL)	10.8 (1.1)	11.2 (1.15)	10.9 (1.2)	0.35
P (2.5 - 4.3 mg/dL)	2.55 (0.6)	2.5 (0.65)	2.5 (0.6)**	**0.034**
ALP (38 -113 U/L)	104(67.7)	110 (60.4)	107 (57.7)	0.85
Cr (0.48-0.79 mg/dL)	0.64(0.25)	0.74 (0.3)	0.71 (0.25) *	**<0.001**
eGFR (ml/min/1.73 m^2)	76.7(28.9)	76.1(29.13)	77.1 (32.06)	0.23
i-PTH (16-65 pg/mL)	161 (122)	171 (146.5)	170 (117)	0.39
24-h urinary test				
Ca(100-300 mg/day)	230 (160)	220 (140)	250 (140)	0.56
P (500-2000 mg/day)	590 (255)	610 (270)	660 (270) *	**<0.001**
Cr(1000-2000 mg/day)	795(370)	830(430)	910(460)*	**<0.001**

*p<0.01, ** p<0.05 compared to patients without US
# p<0.05 compared to patients with asymptomatic US

ROC curve of 24-hour urinary Ca excretion for asymptomatic US



Sensitivity and specificity of various cut-off values for asymptomatic US

24-h urinary Ca	Cut-off value (mg/day)	Sensitivity (%)	Specificity (%)
All	>200	70.7	40.6
Female	>250	**39.2**	58.4
	>180	78.6	42.7
Male	>300	**15.4**	64.6
	>160	46.2	79.2

Results of univariable and multivariable analysis (asymptomatic and symptomatic US included)

	Univariable analysis		Multivariable analysis	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
Male	2.42 (1.74-3.36)	<0.001	1.78 (1.18-2.51)	**0.005**
Age <52*	2.36 (1.70-3.28)	<0.001	1.98 (1.41-2.79)	**<0.001**
24-h urinary Ca >210 mg/day*	1.15 (0.85-1.56)	0.35	0.86 (0.61-1.21)	0.40
24-h urinary P >720 mg/day*	1.96 (1.41-2.72)	<0.001	1.36(0.91-2.01)	0.13
24-h urinary Cr >780 mg/day*	2.16 (1.58-2.95)	<0.001	1.39 (0.95-2.05)	0.092

*Cut-off values determined by ROC curve analysis

Discussion

Urinary Ca levels did not affect the occurrence of US in patients with PHPT. The mechanism underlying US occurrence is complex and cannot be unequivocally determined by urinary calcium excretion. ROC analysis assuming hypercalciuria as a risk factor showed an AUC of about 0.5 for urinary Ca excretion, with slightly better results after sex separation. Sensitivity remained below 40% with cutoff values of 250 mg/day for females and 300 mg/day for males, indicating the cut-off value is too high.

This study found no predictive risk factors for asymptomatic US in PHPT patients. The analysis of asymptomatic US may be less likely to show significant differences due to the small sample size. Young age and male sex have been associated with an increased risk of US. Patients with these factors are predisposed to high serum uric acid and creatinine levels that may affect stone formation.

Conclusion

Hypercalciuria should not be considered a reliable criterion for surgery in asymptomatic PHPT cases, as it was not found to be a significant risk factor for urinary stones. Instead, male sex and younger age were identified as risk factors for urinary stones.