EP146

Serum calcium to phosphorous ratio (Ca/P) as a simple, inexpensive screening tool in the diagnosis of primary hyperparathyroidism (PHPT)

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Background: Primary hyperparathyroidism (PHPT) remains often overlooked and underdiagnosed. Several strategies, including biochemical markers used alone or combined in complex algorithms, have been investigated in the past to identify tools useful to easily diagnose or screen PHPT. At present, however, the diagnosis of PHPT remains challenging, especially in asymptomatic patients. As serum calcium (Ca) and phosphorous (P) are inversely related in PHPT, the Ca/P ratio might be considered a good candidate tool in the diagnosis of PHPT. Surprisingly, no data on Ca/P ratio are available in literature, despite they are very simple biochemical measurements largely available in any clinical laboratory setting.

The aim of the study was to investigate the diagnostic value of the Ca/P ratio in the diagnosis of PHPT.

Material and Methods: From 2005 to the end of December 2015, data retrospectively obtained from review charts of 97 patients with documented PHPT (69 females; 28 males) were compared with those of 96 controls (C) (44 females; 52 males). Exclusion criteria: age younger than 18 or older than 90 years; severe renal and liver diseases; active metabolic bone disease (Paget's disease of the bone, osteomalacia, rickets, etc); any type of cancer; malnutrition; severe obesity; gastrointestinal malabsorption; sarcoidosis; endocrinological disorders such as hypercortisolism, diabetes insipidus, hyperthyroidism, pseudohypoparathyroidism; familial hypocalciuric hypercalcemia; hypophosphoremia not due to PHPT (e.g. genetic causes); patients treated with steroid, lithium, active forms of vitamin D (calcitriol, ergocalciferol, etc), thiazide diuretics, lithium, cinacalcet, bisphosphonates (or at least four weeks whash out from oral bisphosphonates). Biochemical measurements included serum PTH, Vitamin D, Ca, P, albumin, and creatinine. Serum Intact PTH was determined by a Beckman Coulter UniCelDxI 600 Synchron Access (Beckman Coulter Italy, Cassina de' Pecchi, Milan, Italy). Serum 25OH-Vitamin D was measured by chemiluminescence with the LIASON® XL 1,25OH-Vitamin D assay (DiaSorin, Stillwater, MN). Serum calcium and phosphorous were detected using Beckman Coulter UniCel DxC AU 680 (Beckman Coulter Italy, Cassina de' Pecchi, Milan, Italy). Normal ranges were 15-88 pg/mL, 8.5-11, and 2.5-5.1 mg/dl for PTH, Ca, and P, respectively.

Statistical analysis: The nonparametric Mann-Whitney U test was used for comparisons due to the fact that most of the variables were not normally distributed as assessed by Kolmogorov-Smirnov test. All the data are shown as median and minimum-maximum. The diagnostic accuracy of each examined parameter was investigated using receiver operator characteristics (ROC) curves in order to define cutoff points that better identify affected patients, according to their biochemical profile. ROC cutoffs were calculated by the Youden's index. Statistical analyses were performed using SPSS software for Windows (version 19.0; SPSS Inc, Chicago, IL) or Sigma Plot (version 11.00; Systat Software Inc, San Jose, CA). For all comparisons, P<0.05 was considered statistically significant.

Figure 1. ROC curves of Ca/P and Corrected-Ca/P ratios in all enrolled subjects

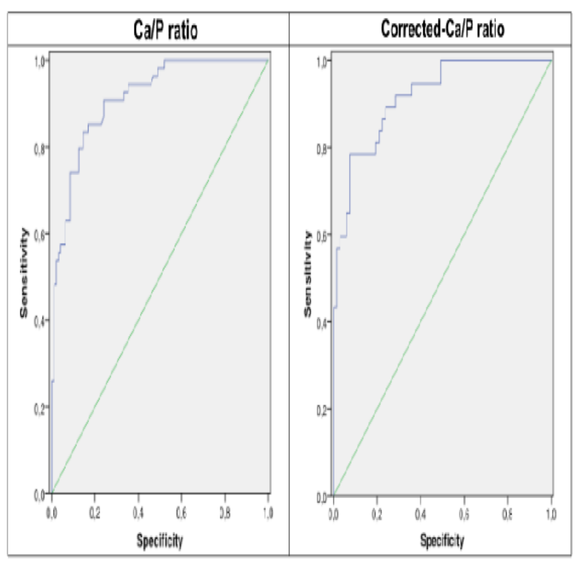
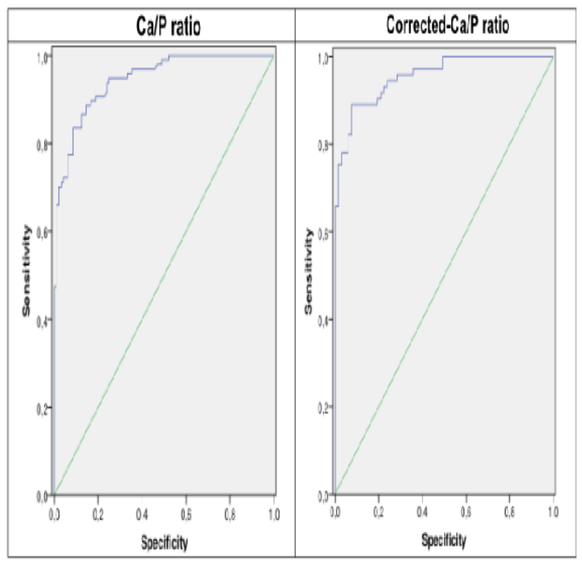


Figure 2. ROC curves of Ca/P and Corrected-Ca/P ratios in NCPHPT patients and control subjects



NCPHPT:normocalcemic hyperparathyroidsm; PTH: parathyroid hormone

Results: Characteristics of both controls and patients with PHPT are shown in Table 1. Ca and Ca corrected by albumin (Corrected-Ca) was significantly higher in PHPT than C (p<0.0001). P was significantly lower in PHPT than C (p<0.0001). PTH was significantly higher in PHPT than C (p<0.0001). Ca/P and Corrected-Ca/P ratios were both significantly higher in PHPT than C (Table 2). Table 3 shows the diagnostic value of each serum parameter and/or ratios. ROC curves analyses identified a cutoff of 3.5 for both Ca/P ratio and Corrected-Ca/P ratio. The sensitivity and specificity were 86% and 87%, respectively for Ca/P ratio and 89% and 93%, respectively for corrected Ca/P ratio (p<0.0001) (Table 3; Figure 1). The diagnostic value of Ca/P ratio was significantly higher if compared with PTH and Ca used alone or in combination, especially in the subgroup of patients with normocalcemic PHPT (NCPHPT) (Table 4; Figure 2).

Table 1. Demographic and clinical characteristic of all study partecipants

Subjects	n (%)
Controls (n 96)	
Sex	
Females	44 (45,36%)
Males	52 (54,63%)
PHPT (n 97)	
Sex	
Females	69 (71,13%)
Males	28 (28,87%)
PHPT pattern	
Hypercalcemic	43 (44,3%)
NCPHPT*	54 (55,7%)
Morphological evidence of hyperfunctioning parathyroid	
Histological evidence at parathyroidectomy (n 56)	54 (55,6%)
Ultrasound evicence (n 97)	89 (91,7%)
Cytological evicence (n 50)	11 (11,3%)
PTH in washing fluid of fine needle aspiration biopsy (n 48)	36 (37,1%)
Scintigraphic evicence (n 57)	35 (36,1%)

PHPT: primary hyperparathyroidsm; NCPHPT:normocalcemic hyperparathyroidsm ; PTH: parathyroid hormone

Table 2. Age, biochemical and hormonal differences between patients with PHPT and controls

	Normal range	PHPT n=97	Controls n=96	P-value
Age (yrs)	18-90*	63 (23-90)	58,5 (20-89)	0,34
Serum ca (mg/dl)	8,5-11	11 (9.4-15,5)	9,4 (8,3-10,2)	<0.0001
Serum P (mg/dl)	2,5-5,1	2,4 (1,4-3,9)	3,5 (2,1-4,5)	<0.0001
Ca to P Ratio	-	4,6 (2,7-8,8)	2,7 (2,0-4,6)	<0.0001
Serum PTH (pg/ml)	15-88	135,2 (57,6-1748)	32.1 (14-80,7)	<0.0001
Serum 25-OH vitamin D (ng/ml)	30-100	17,25 (4-44,1)	20.35 (4-41,3)	0.008
Serum creatinine (mg/dl)	0,5-1,4	0,8 (0,5-1,5)	0,8 (0,5-1,7)	0.454
Serum albumin (g/dl)**	3,5-5	4,3 (2,7-4,8)	4,1 (2,6-5)	0,01
Serum corrected ca (mg/dl)**	-	11 (9.3-15,9)	9,2 (8,4-10,7)	<0.0001
Corrected-Ca/P Ratio**	-	4,6 (2,7-8,8)	2,6 (2,1-4,4)	<0.0001

*Measurement are expressed as median (mininum-maximum). * age range for enrolment in this study; **available in 73 PHPT patients (72,25%) and 67 controls (69,8%). Ca: calcium, P: phosphorus*

Table 3. Diagnostic value of each biochemical parameter in all enrolled subjects.

	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Ca/P	3,5	86,5	87,5	87.5	86,6	87,0
Corrected-Ca/P Ratio	3,5	89,0	91,0	91.5	88,4	90,0
Serum PTH	88	85,6	100	100	87,3	92,7
Serum Ca (>11)	11	44,3	100	100	64,0	72,0
Serum Corrected-Ca	11	46,6	100	100	63,2	72,1
Serum P	2,5	52,6	92,7	87.9	65,9	72,5

PPV: positive predictive value; NPV: negative predictive value.

Table 4. Diagnostic value of each biochemical parameter in aNCPHPT patients and control subjects

	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Ca/P	3.5	79,6	87,5	78,2	88,4	84,7
Corrected-Ca/P Ratio	3.5	78,4	91,0	82,9	88,4	86,5
Serum PTH	88	85,2	100	100,0	92,3	94,7
Serum Ca (>11)	11	0,0	100	0,0	64,0	64,0
Serum Corrected-Ca	11	2,7	100	100,0	65,0	65,4
Serum P	2.5	38,9	92,7	75,0	72,9	73,3

Conclusions: Ca/P ratio is a valuable highly sensitive, highly specific tool for the diagnosis of PHPT. In case of NCPHPT, Ca/P ratio identifies patients with PHPT better than Ca alone. Considering that Ca/P is simple to obtain, easily accessible in every clinical and laboratory setting worldwide and inexpensive even when used in large sample size of patients, this diagnostic tool could be useful for screening PHPT, especially in patients accessing emergency rooms or in the general practitioner setting.

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