Influence of Serum Biochemistry on Bone and Kidney Phenotypes in Subjects With Symptomatic Primary Hyperparathyroidism

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Research Article

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Abstract

OBJECTIVE

To analyze the abnormalities in serum parathormone (PTH)-25-hydroxy-vitamin D (25-OHD) axis and calcium phosphate homeostasis in symptomatic PHPT patients having bone disease, nephrolithiasis and impaired renal function (IRF) at diagnosis.

METHODS

Consecutive adults (>18 years) with diagnosed symptomatic PHPT were enrolled in the retrospective study. Relevant clinical, biochemical and imaging parameters were recorded.

RESULTS

Adult patients with symptomatic PHPT were identified (N=60, age 45.2±14.4 years, 45 females). Predominant phenotypes were bone disease (osteoporosis and/or clinical fractures, n=42, 70%) and nephrolithiasis (n=24, 40%). Compared to patients with nephrolithiasis only (subgroup C, n=7) and simultaneous bone disease/nephrolithiasis (subgroup D, n=17), patients with isolated bone disease phenotype (subgroup B, n=25) had significantly higher alkaline phosphatase (AlP) and lower 25-OHD levels at presentation. Patient subgroups with nephrolithiasis had higher serum calcium levels and lower effective glomerular filtration rate (eGFR) at presentation. PTH was not significantly different among these subgroups. Patients with IRF (eGFR <60 ml/min per 1.73 m^2, n=17) in our cohort had significantly higher serum calcium, phosphate, PTH levels and nephrolithiasis rates. Presence of nephrolithiasis, higher calcium x phosphate product (IRF: 36.2 ± 10.7 versus no IRF: 26.2 ± 5.7 mg^2/dl^2) and increased PTH levels were independently associated with IRF at diagnosis.

CONCLUSIONS

While PHPT patients with isolated bone disease were found to have lower 25-OHD and higher AlP levels independent of PTH levels; PTH was found to be an independent predictor of impaired renal function at diagnosis.

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder biochemically characterized by hypercalcaemia with either raised or inappropriately normal serum concentrations of parathyroid hormone (PTH). While asymptomatic PHPT has become the predominant form of presentation in high income countries, *symptomatic* presentations of PHPT in form of bone and kidney disease still predominate in India owing to absence of routine serum calcium monitoring [1].

It has long been accepted that chronic 25-hydroxy-vitamin D (25-OHD) deficiency can lead to parathyroid adenoma growth, higher PTH level and substantial skeletal involvement [2]. Interestingly, Walker *et. al*.

suggested that 25-OHD deficiency might affect cortical bone mineral density via a direct PTH independent action on bones [3]. While 25-OHD was not found to be significantly lower in PHPT patients with fractures, patients with nephrolithiasis showed significantly higher 25-OHD levels compared to others in the same cohort [3]. Hypercalciuria is often considered as an important risk factor of nephrolithiasis in PHPT [4]. However, in one recent study, patients with nephrolithiasis were more likely to be normocalcemic and 47.3% of them were found to have normal urinary calcium levels [5]. It has indeed been suggested that serum biochemical variables might be unreliable in the prediction of renal stones in PHPT [6]. Patients with asymptomatic PHPT typically tend to have laboratory values similar to, but somewhat milder, than those with *symptomatic* PHPT and they often do not meet the criteria for surgical intervention other than the biochemical criterion [7]. Since many patients with *symptomatic* PHPT might have simultaneous bone disease and nephrolithiasis on initial presentation, the precise impact of biochemical parameters on different *symptomatic* phenotypes is difficult to assess and remain unclear.

Impaired renal function, another known complication of PHPT, is associated with disease severity and higher risk of mortality [8]. Relatively few studies have looked into the association of PHPT with renal function [9–11]. Effective glomerular filtration rate (eGFR) was found to have an inverse correlation with both calcium and PTH levels in one recent study, suggesting that PHPT severity might have a significant impact on renal function of patients at presentation [9]. On contrary, one previous study did not find any association of calcium or PTH levels with renal dysfunction in PHPT, thereby challenging the rationale of including the eGFR threshold (< 60 ml/min/m^2) as a criterion for surgical intervention in PHPT [11]. Low eGFR might also be responsible for increased PTH levels in blood, further complicating the scenario. However, secondary elevation of PTH has not been consistently reported at the aforementioned eGFR threshold (< 60 ml/min/m^2) in PHPT [10, 12].

The present study was undertaken to elucidate the potential differences in serum abnormalities of parathormone-25-OHD axis and calcium-phosphate homeostasis among the subgroups of *symptomatic* PHPT patients presenting with isolated bone disease (osteoporosis and/or clinical fractures), isolated nephrolithiasis and simultaneous bone disease/kidney stones. Furthermore, we aimed to find out whether any biochemical marker of PHPT severity was independently associated with impaired renal function (eGFR < 60 ml/min/m^2) at initial presentation in our cohort of *symptomatic* PHPT patients.

Materials And Methods

Patient selection

This was a single center retrospective observational cross sectional study approved by institutional ethics committee. Consecutive cases of documented symptomatic primary hyperparathyroidism (PHPT) were identified from June 2014 to December 2020 in our tertiary care center. Diagnosis of PHPT was based on persistent elevation of serum adjusted calcium above the upper limit of normal range (8.5–10.4 mg/dl) and increased or inappropriately normal serum intact PTH (upper limit of normal range 72 pg/L) after excluding other demonstrable causes of hypercalcemia. Asymptomatic PHPT was defined as

unequivocal primary hyperparathyroidism, established by laboratory testing, who display no overt signs of the disease or target organ manifestations other than hypercalcaemia [13]. Patients with asymptomatic PHPT, suggestion of multiple endocrine neoplasia (MEN), pre-existing renal disease unrelated to PHPT and patients on vitamin D supplementation at the time of presentation were excluded from the analysis in our study. Records of these patients were retrospectively reviewed for age, gender, menstrual status, presenting signs and symptoms, routine biochemical investigations.

Laboratory methods

Serum biochemical parameters, including, creatinine, calcium, albumin, inorganic phosphate, alkaline phosphatase, intact PTH, and 25-OHD were performed by standard methods. Values of eGFR were calculated from serum creatinine level using the MDRD equation as recommended by the third International Workshop on Asymptomatic PHPT [14, 15]. Serum calcium, phosphate and alkaline phosphatase were done by spectrophotometry. Serum calcium values were adjusted for serum albumin concentrations using the formula, adjusted calcium = total serum calcium (mg/dl) + 0.8 [4 - serum albumin (mg/dl)]. The reference ranges for adjusted calcium, phosphate, and alkaline phosphate were 8.5–10.4 mg/dl, 2.5–4.5 mg/dl, and 20–140 IU/L, respectively. Intact PTH was done by chemiluminescent immunometric assay on immunoassay analyser Immulite 1000 (Siemens Healthcare, Erlangen, Germany). Inter-assay coefficients of variation overall was 3.1–10.6% for PTH concentrations ranging from approximately 12 to 1400 pg/ml. The normal reference range for PTH was 14–72 pg/ml. 25-OHD was measured by chemiluminescent immunoassay method on Euroimmun analyser I-2P (EUROIMMUN, Germany). Inter-assay coefficients of variation were 6.9% and 7.8% at mean values of 24.6 ng/ml and 16.6 ng/ml respectively. Cut-offs for 25-OHD deficiency and insufficiency were taken as 20 ng/ml and 30 ng/ml respectively.

Imaging

Ultrasonography (USG) findings of whole abdomen were noted. Relevant radiological survey of long bones and dorsolumbar spine were done. Bone mineral density (BMD) testing was done by dual energy X-ray absorptiometry (DXA-Lunar) [enCore-based X-ray bone Densitometer, Prodigy advance, version 17.0, GE Healthcare Lunar, LU43616EN, GE Medical Systems, Madison, WI, USA] using the standard protocol.

Identifying symptomatic phenotypes at diagnosis

Criteria for diagnosis of symptomatic bone disease included presence of osteoporosis ± clinical fractures (long bone or vertebral) ± osteitis fibrosa cystica (OFC) at presentation. ‘Clinical vertebral fracture’ was defined by presence of definitive symptoms or clinical signs (including back pain, spinal tenderness on examination, kyphosis and/or history suggestive of height loss) corroborated by radiological evidence. OFC was defined on the basis of radiology characterised by lytic lesions of varying size and shapes (usually round to oval). Patients were diagnosed to have osteoporosis on basis of BMD T score <-2.5 (Z score <-2.5 for premenopausal women and men aged < 50 years) at any of three sites, including lumbar spine (L1-L4), femoral neck and distal 1/3rd radius. Patients with USG evidence nephrolithiasis (including microlithiasis) were identified. We divided the entire population of symptomatic PHPT into four

subgroups for analysis (group A: no bone disease and kidney stones, group B: bone disease only, group C: kidney stones only, group D: bone disease and kidney stones). Patients with impaired renal function (IRF) were identified on the basis of low eGFR (< 60 ml/min per 1.73 m^2) at presentation.

Statistical methods

SPSS 22 (statistical Package for Social Sciences 22, USA) was used for data analysis. The data with normal distribution were expressed as mean ± SD; data that did not have a normal distribution were expressed as median (inter-quartile range). Correlations were analyzed by the Spearman test. Difference in proportions between two groups was tested by chi-square test. Student's *t* test or Mann–Whitney *U* test (for skewed data) was applied for comparing two groups. One-way analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test was used to the test for difference between the means/medians of four subgroups. Post-hoc analysis was performed with correction for multiple testing (Bonferroni) to detect inter-subgroup difference of means/medians. To determine independent predictors of impaired renal function at diagnosis, forward conditional multivariate binary logistic regression analysis was done after including parameters that were found significant on univariate analysis. A two tailed *p* value of < 0.05 was considered statistically significant.

Results

Baseline characteristics and clinical presentation

Total 64 consecutive patients with PHPT were identified and 60 patients (15 males, 45 females) with symptomatic PHPT were enrolled after excluding patients with asymptomatic presentation (n = 4). The mean age was 45 ± 14 years with 38 patients (63.3%) presenting before 50 years of age. Female preponderance was noted (female:male ratio of 3:1). The median body mass index was 23.9 kg/m^2.

Symptomatic bone disease (presence of osteoporosis ± clinical fractures ± OFC) was present in majority of patients (n = 42, 70%) followed by nephrolithiasis (n = 24, 40%: bilateral, n = 7). Clinical fractures were present in 25% patients (n = 15; vertebral, n = 5). Nephrocalcinosis was detected in 13 patients and 11 patients out of them had concomitant nephrolithisis. Four subgroups of patients were identified: no bone disease/kidney stones (subgroup A, n = 11), isolated bone disease phenotype (subgroup B, n = 25), kidney stones only (subgroup C, n = 7) and simultaneous bone disease/kidney stones (subgroup D, n = 17). Total 17 patients (28.3%) at diagnosis had impaired renal function (IRF) i.e. eGFR below 60 ml/min per 1.73 m^2, the recommended threshold of surgery for PHPT. Out of them, 6 patients had eGFR below 30 ml/min per 1.73 m^2.

Gastrointestinal disease was the predominant mode of presentation in PHPT patients without bone disease or kidney stones. Total 12% cases (n = 7; recurrent, n = 5) presented with pancreatitis in our cohort. Cholelithiasis was documented in 12% cases (n = 7), with majority being asymptomatic (n = 5). Other gastrointestinal symptoms were nausea and vomiting (n = 14, 23%), anorexia (n = 19, 32%), constipation (n = 13, 22%). However, commonest clinical symptom reported overall was generalised

weakness and fatigability (n = 35, 58%). Neuropsychiatric symptoms, such as anxiety, depression, confusion, memory loss, irritability and difficulty in concentration were present in 15% cases.

Influence of demographic profile on clinical phenotypes

All patients, who presented with clinical fractures in our cohort (n = 15), were females. Out of them, 60% (n = 9) of them were above 50 years of age (chi-square test, $p < 0.05$) and 80% (n = 12) were postmenopausal. Females had similar osteoporosis rates compared to males (n = 28/41, 68% versus n = 10/15, 66%). Proportion of males was significantly higher in IRF than females (47% versus 16%, p = .01). This may be due to presence of higher nephrolithiasis rates in males compared to that in females, albeit not statistically significant (60% versus 34%, p = 0.06).

Biochemical profile and impact on phenotypes

Biochemical parameters of total population (N = 60) are given in Table 1. Mean serum calcium and phosphate levels were 11.8 mg/dl and 2.4 mg/dl respectively. 25-OHD insufficiency was present in 75% patients (n = 45) and 25-OHD deficiency was present in 51% patients (n = 31) at diagnosis. While PTH did not have a significant correlation with 25-OHD or alkaline phosphatase (ALP) or serum phosphate, a trend towards statistically significant correlation was noted with calcium (rho 0.251, p = 0.053) and eGFR (rho − .233, p = 0.07). ALP had a significant negative correlation with serum 25-OHD level (rho − .334, p < 0.01). 25-OHD had a modest positive correlation with serum calcium levels (rho .276, p = 0.03).

Table 1
Parameters in PHPT patients across categories of symptomatic phenotypes

Parameter	Total (N = 60)	A: No bone disease & kidney stones (n = 11)	B: Bone disease only (n = 25)	C: Kidney stones only (n = 7)	D: Bone disease & kidney stones (n = 17)	*p value*
Age (years)	45.2 ± 14.4	43.7 ± 14.2	44.9 ± 16.5	45 ± 14.5	46.7 ± 12.3	.93
Gender (Female/male)	45/15	9/2	21/4	4/3	11/6	-
BMI (Kg/m^2)	23.9 ± 3.6	24.3 ± 2.8	23.1 ± 2.1	22.3 ± 4.1	25.6 ± 4.9	.81
eGFR (ml/min per 1.73 m^2)	79.6 ± 32.7	96.9 ± 23.1	90.5 ± 29.1*$	49.1 ± 29.2	61.9 ± 28.6^	.001
Calcium (mg/dl)	11.8 ± 1.4	11.4 ± 0.8	11.6 ± 1.7*$	12.5 ± 1.3	12.2 ± 0.8^	.01
Phosphate (mg/dl)	2.4 ± 0.6	2.4 ± 0.3	2.3 ± 0.6	2.6 ± 0.9	2.6 ± 0.7	.34
Ca-P (mg^2/dl^2)	28.9 ± 8.6	27.6 ± 1.6	27.1 ± 10.1	31.7 ± 8.6	31.9 ± 8.8	.06
AlP (i.u./l)	219 (143–432)	213 (158–433)	385 (216.5–501) *$	130 (90–170)	187 (146 -294.5)	.009
PTH (pg/ml)	339 (166.8–845)	335 (156–564)	243 (155 -1168.5)	875 (129–2275)	544 (170-784.5)	.813
25-OHD (ng/ml)	20.9 ± 8.6	24.8 ± 12.8	15.7 ± 6*$#	28.6 ± 4.9	22.6 ± 5.5	.000

Normally distributed data presented as mean ± standard deviation; Non-parametric data presented as median (inter-quartile range). Difference across four categories was analysed with one-way *ANOVA* test or Kruskal-Wallis test as applicable. *p value* < 0.05 was considered significant.

Post-hoc analysis, * $p < 0.05$ (subgroup B versus C), $ $p < 0.05$ (subgroup B versus D), # $p < 0.05$ (subgroup B versus A), ^ $p < 0.05$ (subgroup D versus A).

BMI, body mass index; eGFR, estimated glomerular filtration rate; Ca-P, calcium x phosphate product; AlP, alkaline phosphatase; PTH, parathormone; 25-OHD, 25-hydroxy-vitamin D.

ALP, 25-OHD, calcium and eGFR levels were significantly different among four subgroups of patients in symptomatic PHPT cohort. On post-hoc analysis, compared to patients with nephrolithiasis only (subgroup C) and simultaneous bone disease/kidney stones (subgroup D), patients with isolated bone disease phenotype (subgroup B) had significantly higher ALP, lower 25-OHD levels, lower calcium levels and higher eGFR at presentation (Table 1, Fig. 1). Serum 25-OHD was also significantly lower in isolated bone disease (subgroup B) compared to patients with no bone disease/kidney stones (subgroup A). PTH was not significantly different among these subgroups (Table 1, Fig. 1).

In the group of IRF (eGFR below 60 ml/min per 1.73 m^2, n = 17), nephrolithiasis was significantly higher than in others (76% versus 26%, p = 0.01). Significantly higher calcium, higher phosphate, higher calcium x phosphate (Ca-P) product and PTH levels were also noted in this group (Table 2). On subgroup analysis among IRF group, only phosphate and Ca-P product levels were significantly higher in eGFR subgroup (< 30 ml/min per 1.73 m^2, n = 6) compared to patients with eGFR 30–59 ml/min per 1.73 m^2 (n = 11). Univariate analysis showed significant association ($p < 0.05$) of male gender, presence of nephrolithisis, calcium, phosphate, calcium x phosphate product and PTH levels with IRF (eGFR < 60 ml/min per 1.73 m^2); whereas no significant association with systolic or diastolic blood pressure, BMI and vitamin D levels were found. A forward conditional multivariate binary logistic regression analysis was performed involving parameters ($p < 0.05$ on univariate analysis) and the best model revealed three independent predictors of IRF. These were presence of nephrolithiasis (adjusted odds ratio 9.7 [95% C.I. 1.7–55.1], p = 0.01), higher calcium x phosphate product (adjusted odds ratio 1.17 [95% C.I. 1.03–1.34], p = 0.01) and higher PTH levels (adjusted odds ratio 1.002 [95% C.I. 1.001–1.003], p = .02).

Table 2
Parameters in PHPT patients with impaired renal function (IRF) at diagnosis

Parameters	IRF: eGFR < 60 ml/min per 1.73 m^2		*p*
	No (n = 43)	Yes (n = 17)	
Age (years)	43.7 ± 13.8	49 ± 15.6	.20
Age > 50 years (n = 22)	15 (35%)	7 (41%)	.64
Male gender (n = 15)	7 (16%)	8 (47%)	**.01**
BMI (kg/m^2)	24.5 ± 3.7	22.8 ± 2.9	.07
Hemoglobin (gm/dl)	10.9 ± 1.8	10.5 ± 2.5	.42
Calcium (mg/dl)	11.5 ± 0.8	12.7 ± 1.9	**.01**
Phosphate (mg/dl)	2.3 ± 0.5	2.8 ± 0.7	**.00**
Ca-P (mg^2/dl^2)	26.2 ± 5.7	36.2 ± 10.7	**.00**
AlP (IU/L)	284.5 [157–433]	173 [133.5–250]	.08
PTH (pg/ml)	241.5 [153–566]	812 [584–1391]	**.00**
25-OHD (ng/ml)	19.6 ± 8.1	24.2 ± 9.5	.08
Nephrolithiasis (n = 24)	11 (26%)	13 (76%)	**.00**

Categorical data presented as n (%); Normally distributed data presented as mean ± standard deviation; Non-parametric data presented as median [inter-quartile range]. Difference between two groups was analysed with Student t test or Mann-whitney test as applicable. Difference in proportions of categorical variables was measured using chi-square test.

p value < 0.05 was considered significant. BMI, body mass index; eGFR, estimated glomerular filtration rate; Ca-P, calcium x phosphate product; AlP, alkaline phosphatase; PTH, parathormone; 25-OHD, 25-hydroxy-vitamin D.

Discussion

In our cohort, asymptomatic PHPT was uncommon due to various reasons, including, lack of awareness regarding the disease in the primary health care facilities, lack of routine calcium screening and prevalent vitamin D deficiency in our country. Moreover, 75% of our cohort were vitamin D insufficient. Suboptimal vitamin D nutrition stimulates parathyroid adenoma growth and calcaemic response to PTH [2]. Apart from the predominance of severe symptomatic presentations, this may also explain the earlier presentation of PHPT in our study compared to that reported in western countries.

Among symptomatic phenotypes in west, overt nephrolithiasis usually occurs in less than 20% of patients with PHPT and radiologically evident bone disease is found to be even less common [16]. Our cohort had 40% cases of nephrolithiasis and 25% cases of clinical fractures at presentation. Age and

female gender were earlier found to be significant predictors of fractures in PHPT [17]. In support of this finding, all patients presenting with clinical fractures in our cohort were females and majority (80%) of them were postmenopausal. All patients who had clinical vertebral fractures at presentation (n = 5), were postmenopausal. Although trabecular bone is relatively preserved compared to the cortical bone in patients with PHPT, fracture risk is increased at both non-vertebral (predominantly cortical) and vertebral (trabecular) sites [18]. The higher prevalence of fractures (especially vertebral) in postmenopausal females can be explained by the typical postmenopausal bone loss (particularly in trabecular bone) due to estrogen deficiency.

In our study 25-OHD had a significant negative correlation with ALP, but no correlation with PTH levels was seen. This observation is in contrast to one study done among 100 Caucasian patients that found a significant correlation of lower 25-OHD levels with some (PTH, r= -0.42; 1,25-$(OH)_2D$, r = -0.27; phosphate, r = 0.31), but not all (serum or urine calcium) indicators of PHPT severity [3]. PTH can stimulate the renal 1α-hydroxylase with subsequent reduction in 25-OHD via increased 1,25-$(OH)_2D$ biosynthesis; and increased 1,25-$(OH)_2D$ can in turn accelerate 25-OHD catabolism. Due to lack of consistently significant inverse correlation between 25-OHD and 1,25-$(OH)_2D$ in PHPT, 25-OHD deficiency has long been believed to be the reason behind increased parathyroid gland weight and higher PTH level [2]. However, adenomatous transformation following parathyroid hyperplasia may lead to increased set point of the calcium sensing receptor (CaSR) and resetting of serum calcium levels at a higher level [19]. This abnormal calcium or 1, 25-$(OH)_2D$ sensing in tumours along with autonomous PTH secretion can explain the lack of correlation between PTH and 25-OHD in our cohort. Impaired calcium sensing in parathyroid tumours was indeed observed in one subset of patients with severe bone mineral density deficit [20].

Patients with isolated bone disease phenotype in our cohort had significantly higher ALP levels (not PTH levels) and lower 25-OHD levels compared to other subgroups. In this regard, 25-OHD was found to be an independent predictor (effect not mediated by higher PTH) of cortical bone mineral density in PHPT [3]. In another study, 25-OHD deficiency was associated with lower cortical width on bone biopsy, whereas PTH levels failed to show any association [21]. Although PTH was similar between *symptomatic* PHPT subgroups in our study, higher ALP levels indeed suggest increased bone turnover in patients with isolated bone disease. The pulsatile secretion of intact PTH account for about 50% of its total secretion even in patients with PHPT [22]. This could explain the lack of correlation between PTH and ALP levels in our cohort. Serum ALP demonstrates a lower variability, thereby may be a more suitable marker of bone turnover.

Younger age and male gender have been found to be independently associated with presence of nephrolithiasis in previous studies [6, 9, 23]. A trend towards significant association with male gender was observed in our study. Serum calcium was significantly higher in patients with nephrolithiasis similar to previous studies [9, 24, 25]. As in our cohort of *symptomatic* PHPT, 25-OHD was found to be significantly higher in nephrolithiasis in one study [3]. In contrast, another study reported lower level of 25-

OHD in nephrolithiasis at diagnosis than their counterparts [23]. Several other studies did not find any association between serum biochemistry and renal stones [6, 26–28].

Patients with IRF (eGFR < 60 ml/min/m^2) in our cohort had significantly higher calcium, phosphate, PTH levels and nephrolithiasis rates. Reduced glomerular filtration leading to higher phosphate levels, as seen in our study, has been reported in one previous study [29]. Long standing nephrolithiasis or hypercalcemia in PHPT can lead to decrease in eGFR [8]. Few previous studies however did not find higher nephrolithiasis rates in IRF [9, 11, 30], thereby suggesting that urinary obstruction might not be common in PHPT with renal stones. With the exception of few studies [9, 30], neither calcium levels [10, 11, 29, 31] nor PTH levels [11, 29, 31] have consistently been found to be higher in IRF. It has therefore been suggested that secondary elevation of PTH might not occur at the eGFR threshold of 60 ml/min per 1.73 m^2 [12]. Nonetheless, Tassone *et al.* observed that PTH levels increase further in PHPT only when eGFR goes below 30 ml/min per 1.73 m^2 [10]. The conflicting evidence with regards to PTH elevation in IRF may be due to variable proportion of severe renal dysfunction in the IRF group. Although 35% of patients with IRF (n = 6/17) in our study had eGFR below 30 ml/min per 1.73 m^2, PTH was *not* found to be significantly higher in these patients when compared to subgroup with eGFR 30–60 ml/min per 1.73 m^2 despite a *higher* phosphate level (an important stimulus for PTH secretion). Underlying 25-OHD deficiency could also be an important determinant of eGFR threshold at which significant PTH elevation occurs. However, a trend towards higher 25-OHD in IRF nullifies this possibility in our study.

Thereafter we did a logistic regression analysis and showed that PTH was an independent biochemical predictor of IRF in our symptomatic PHPT cohort. Amongst several reasons of PHPT related kidney dysfunction, direct effect of PTH in accentuating endothelial injury and organ fibrosis in the kidneys with high expression of PTH receptors has also been suggested [32]. The causal effect of CaxP on renal dysfunction is difficult to establish. Nonetheless, elevated admission CaxP has previously been found to be an independent predictor of decline in renal function in hospitalized patients [33]. As phosphate levels increase with decline in eGFR in a background of persistent hypercalcemia as in PHPT, precipitation of calcium phosphate crystals is more likely to occur and that may lead to injuries in the distal tubules and collecting ducts.

Our study has certain limitations. First, there was a lack of information regarding sun exposure, hydration status, dietary calcium and vitamin D intake in majority of our patients. Second, gold standard LC-MS/MS assay for 25-OHD measurement was not available.

Conclusion

Predominant phenotypes in our PHPT cohort were bone disease (osteoporosis and/or clinical fractures) and nephrolithiasis. Compared to patients with kidney stones only and simultaneous bone disease/kidney stones, patients with isolated bone disease phenotype had significantly higher ALP and lower 25-OHD levels (not higher PTH levels). Patient subgroups with nephrolithiasis had higher serum calcium levels and lower eGFR at presentation. Patients with eGFR < 60 ml/min/m^2 in our cohort had

significantly higher serum calcium, phosphate, PTH levels and nephrolithiasis rates. Presence of nephrolithiasis, higher calcium x phosphate product and increased PTH levels were independently associated with impaired renal function at diagnosis. Further large scale studies are needed to validate this preliminary observation.

Declarations

Funding – None

Conflicts of interest/Competing interests – None to declare

Ethics approval – The study was approved by institutional ethic committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent – Written consent was obtained from every study participant.

Authors' contributions – MB is the primary author. JA had helped in data extraction and statistical analysis. SC had edited the manuscript. SM is the corresponding author, had supervised and edited the manuscript. All the authors approved the final version of the manuscript.

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Figures

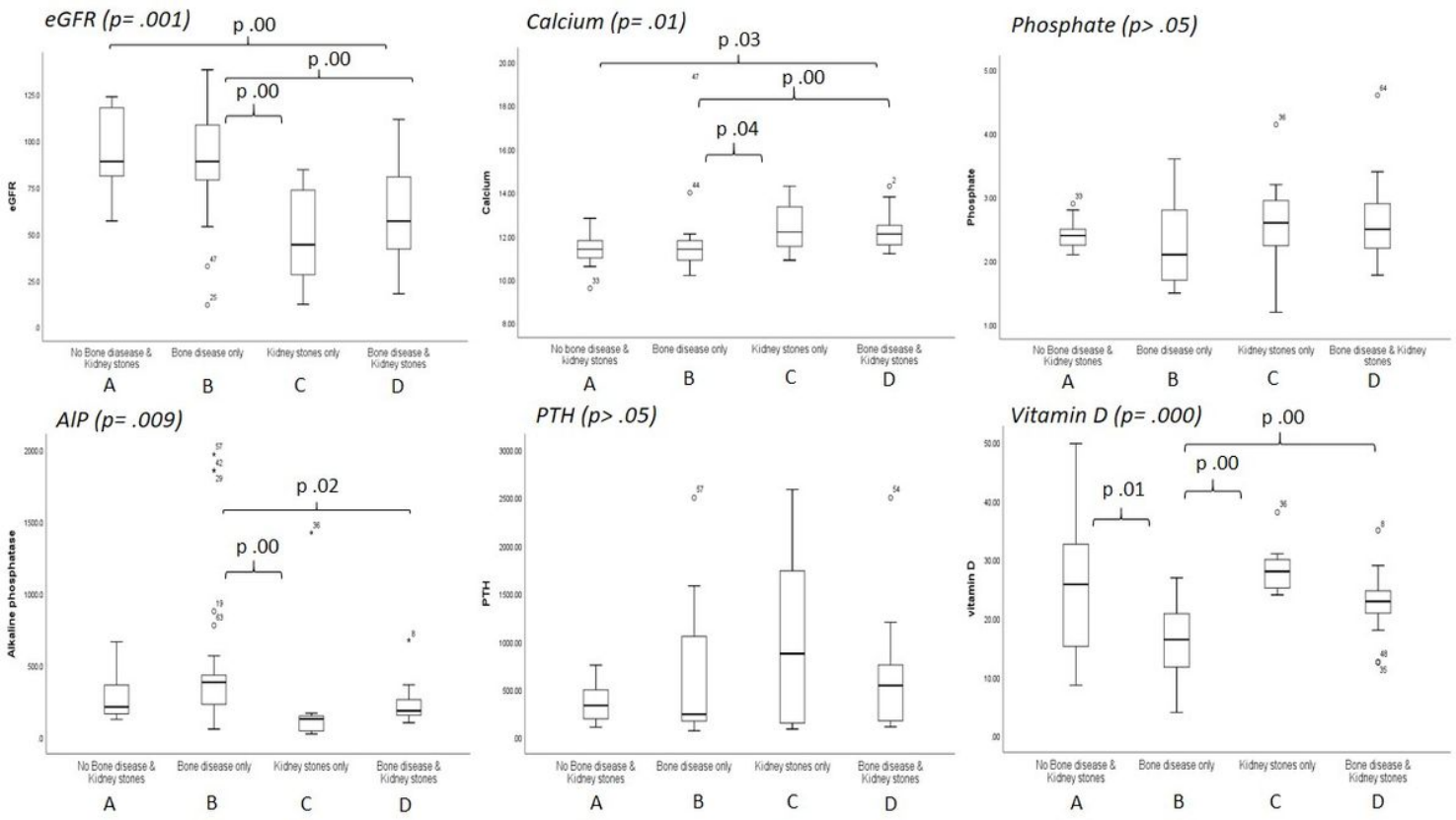

Figure 1

Box plot showing biochemical parameters across categories of symptomatic PHPT phenotypes p values shown for one-way ANOVA test or Kruskal-Wallis test and inter-group differences in mean/median on post-hoc analysis; p <0.05 was considered significant. Symptomatic PHPT groups: (A) No bone disease & kidney stones, (B) Isolated bone disease, (C) Kidney stones only, (D) Simultaneous bone disease & kidney stones.