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Biochemical spectrum of parathyroid hormone disorders in patients attending Tribhuvan University Teaching Hospital, Kathmandu, Nepal

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Abstract

Objectives: This study intends to determine the association of parathormone with vitamin D and other biochemical parameters (calcium and phosphate) and evaluate the relationship between low vitamin D and parathormone levels.

Methods: A hospital-based cross-sectional study was conducted among 310 study participants over the period of 1 year. Patients who underwent laboratory investigations for vitamin D, parathormone, calcium, and phosphate in the Clinical Biochemistry Laboratory at the Institute of Medicine, Tribhuvan University Teaching Hospital were included. Serum intact parathyroid hormone, vitamin D, calcium, and phosphate were measured in Abbott Architect (ci4100) integrated system autoanalyzer.

Results: Among the 310 study participants, 177 (57%) were males and 43% were females. The mean age of the patient was 47.09 ± 19.01 years. High intact parathyroid hormone (>68 pg/ml) was observed in 73% of the patients. Low vitamin D (<20 ng/ml) was present in 30.2% of the patients. The findings from our study depict that there is a negative significant correlation between intact parathyroid hormone levels, vitamin D, and calcium levels and a positive correlation between intact parathyroid hormone and phosphate levels ($p < 0.001$).

Conclusions: The findings from our study illustrate that there is a swapping drift in the profile of hyperparathyroidism in the Nepalese population. We report the presence of hyperparathyroidism in the middle age group than in the older age group contradictory to that reported in the literature.

Keywords

Parathyroid, vitamin D, spectrum, calcium, phosphate

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Introduction

Parathyroid gland disorders are considered a common endocrine problem as the disease is evolving rapidly these days.[1] The disorders cover a wide range of clinical findings with varied forms of clinical as well as laboratory presentation.[1] The disease includes primary disorders of parathyroid secretion comprising an intrinsic defect of the parathyroid gland, leading to primary hyperparathyroidism or hypoparathyroidism, or it can be secondary and tertiary disorders in which increased or decreased parathyroid levels are an adjustment to another pathophysiological process within the body. Hypovitaminosis D is also considered one of the causes of hyperparathyroidism.[1] There have been cases of functional hypoparathyroidism with vitamin D deficiency without secondary hyperparathyroidism (SHPT).[1,2]

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Vitamin D is a fat-soluble vitamin, an integral component of the "calcium–vitamin D–parathyroid hormone" endocrine axis, thereby playing a crucial role in calcium homeostasis.[3] Vitamin D has both skeletal and extra-skeletal functions. It affects intestinal calcium absorption and supports skeleton formation and continuity.[4] Vitamin D deficiency is frequently seen in adults,[5] and causes osteomalacia and osteoporotic fractures.[6]

Inadequate serum vitamin D is associated with SHPT, increased bone turnover, and bone loss, which increase fracture risk.[7] Vitamin D also plays an important role as an immunomodulator and has shown antiproliferative and anti-inflammatory features.[8] Serum 25-hydroxyvitamin D concentration [25 (OH)D] for the assessment of vitamin D status depicts a high proportion of patients with vitamin D deficiency.

The prevalence of vitamin D deficiency ranges from 50% to 90% as reported in the general population of both developed and developing nations.[3,9] To date, an ideal serum 25-OH vitamin D grade is not established. But we generally consider levels above 30 ng/ml as adequate, 20–30 ng/ml as insufficient, and levels under 20 ng/ml as deficient.[9,10] In case there are no primary parathyroid pathologies, evidence suggests that vitamin D deficiency leads to SHPT. Hence, a high value of parathormone (PTH) can also be used as a representative marker for determining vitamin D deficiency.[11]

As the normal range of vitamin D in the Asian population is not ideal as in the case of the well-established range of the Western population, there is no definite margin to address the blunted PTH response in hypovitaminosis D status in the Nepalese population. As reported in a study, despite having a subnormal vitamin D level, hypocalcemia-induced hyperparathyroidism might not be triggered in the population as anticipated.[12]

Thus, this research study is intended to determine the relationship between PTH, vitamin D, and other biochemical parameters (calcium (Ca), alkaline phosphatase (ALP), phosphate (P), and creatinine (Cr)).

Methods

A hospital-based observational (descriptive) cross-sectional study was conducted in the Department of Clinical Biochemistry Laboratory at the Institute of Medicine, Tribhuvan University Teaching Hospital (TUTH). Non-probability (purposive sampling) method was used for recruiting patients who came for laboratory investigations for vitamin D, PTH, calcium, and phosphate in the Clinical Biochemistry Laboratory at the Institute of Medicine, TUTH. Pregnant females, patients on regular calcium supplements, and other medications affecting bone mineral status as well as those with inadequate clinical information were excluded from the study. The sample size was calculated using Cochrane's formula ($n = z^2P(1-P)/d^2$,[13] where the prevalence was 28% taken for SHPT in chronic kidney disease (CKD) patients).[14]

With a prevalence rate (p) of 28%, a z value of 1.96, and an allowable error (d) of 5%, we calculated the minimum sample size of 310 for this study. A total of 310 participants were included in the study over the period of 1 year from December 2021 to November 2022.

Five milliliters of venous blood samples was collected in a gel separator tube and transported to the Clinical Biochemistry Laboratory where the sample was centrifuged and the serum was separated and analyzed. Serum intact parathyroid hormone (iPTH) and vitamin D were measured using chemiluminescence immunoassay in Abbott Architect (ci4100) integrated system. Serum calcium was measured by the Arsenazo III method, serum phosphate by the phosphomolybdate method, and albumin by the bromocresol green method in Abbott Architect (ci4100) integrated system.

The reference ranges used in our study are mentioned as follows:

Parameter	Method	Reference range	Unit
Total calcium	Arsenazo III	2.1–2.6	mmol/l
Inorganic phosphorus	Phosphomolybdate	2.5–4.8	mg/dl
25-Hydroxy Vitamin D*	CMIA**	30–100	ng/ml
iPTH	CMIA**	15–68	pg/ml
ALP	Para-nitrophenyl phosphate	44–147	IU/l
Urea	Enzymatic	2.1–7.1	mmol/l
Creatinine	Jaffe/enzymatic	80–115 (male) 53–97 (female)	µmol/l

*Here all the measured vitamin D parameters indicate 25-hydroxy vitamin D.
**Chemiluminiscent Microparticle Immunoassay.

Statistical analysis

Data were entered in MS Excel 2010 and analyzed with Statistical Package for Social Sciences (SPSS version 22.0) Chicago, Inc. The normality of the data was checked using the Kolmogorov–Smirnov test. Descriptive and inferential statistics were applied accordingly. For descriptive statistics, mean, standard deviation, percentage, and range were calculated. Chi-square test was used to analyze the categorical variables. For parametric variables, the students' "t" test, and for nonparametric variables, the Mann–Whitney U test was used. The correlation between patient age, serum vitamin D, PTH, calcium, and phosphate was determined using Spearman's correlation coefficient. p Value $\leqslant 0.05$ was considered statistically significant.

Results

Demographic profile

This hospital-based observational (descriptive) cross-sectional study done among 310 study participants depicted the mean age of the study population as 47.09 ± 19.01 years with 57% being the male participants (Table 1). Among them, 29 individuals were excluded due to the unavailability of complete data in the database for analysis.

The biochemical parameters in the study population are illustrated in Table 2. The study population exhibited high values of iPTH along with lower vitamin D and calcium levels, respectively. Normally distributed data are expressed in mean ± SD while non-normal data are expressed in median (interquartile range).

PTH levels were subdivided into three groups (i.e., <15 pg/ml, 15–68 pg/ml, and >68 pg/ml) which showed that 73% of the study population had iPTH values >68 pg/ml as shown in Table 3, respectively.

The majority (41.3%) of the study population surprisingly had sufficient levels of vitamin D, that is, 30–100 ng/ml as depicted in Table 4. Among all, four individuals comprising 1.4% had hypervitaminosis D.

The comparison of biochemical parameters in male and female study populations depicted that median creatinine level was significantly higher in males compared to females ($p < 0.05$) as shown in Table 5.

We correlated the median values of iPTH, calcium, and phosphate in the study population revealing that median iPTH levels were negatively correlated with serum vitamin D and calcium and positively correlated with serum phosphate levels, respectively as shown in Table 6 ($p < 0.05$).

Table 1. Demographic profile of the study population ($n = 310$).

Variables	Values ($n = 310$)
Age (years)	47.09 ± 19.01
Gender	
Male	177 (57%)
Female	133 (43%)

Table 2. Biochemical parameters in the study population.

Variables	Values
iPTH (pg/ml)	168.30 (59.50, 366.10)
Vitamin D (ng/ml)	26.50 (18.70, 40.75)
Calcium (mmol/l)	1.90 (1.70, 2.1)
Phosphorus (mg/dl)	5.1 (3.75, 6.2)
ALP (U/l)	133.08 ± 78.13
Uric acid (μmol/l)	357.84 ± 147.64
Urea (mmol/l)	16.55 (7.60, 24.17)
Creatinine (μmol/l)	321.00 (167.00, 693.25)
Albumin (g/l)	37.74 ± 7.29

Table 3. Status of parathyroid hormone in the study population.

Group	Proportion
PTH (<15 pg/ml)	6 (2%)
PTH (15–68 pg/ml)	78 (25%)
PTH (>68 pg/ml)	226 (73%)

Table 4. Vitamin D status in the study population.

Vitamin D	Proportion
<20 ng/ml	94 (30.2%)
20–30 ng/ml	84 (27.0%)
30–100 ng/ml	128 (41.3%)
>100 ng/ml	4 (1.4%)

Discussion

This hospital-based cross-sectional study was conducted in the Clinical Biochemistry Laboratory at the Institute of Medicine, TUTH. The study findings depict that among the parathyroid disorders, the most common was SHPT (73%) with hypoparathyroidism being less common (<2%) respectively. The mean age of the patient was 47.09 ± 19.01 years similar to the study reported in India[15] and Pakistan.[14] SHPT is commonly seen in CKD patients undergoing hemodialysis.[16] Low vitamin D and other hypocalcemic conditions could also lead to raised PTH but are less extensively studied.[17] This laboratory-based study focused on the spectrum of PTH disorders, not only on CKD patients. Our study found that increased PTH was predominantly seen in males (59.8%) compared to females (40.2%) but the mean difference was not statistically significant. Similar findings were reported in a study done in Pakistan by Khan et al.[14] Out of 281 patients, only six patients (2%) had hypoparathyroidism which was highest in males (66.7%). There is no adequate data on hypoparathyroidism in the literature, specifically from the Nepalese population.

Hypoparathyroidism is one of the postoperative complications after thyroid surgery and is usually accompanied by decreased calcium levels, increased serum phosphate levels, and low or incongruously normal plasma levels of iPTH levels.[18–21]

The role of iPTH is to increase the serum calcium level is done by increasing the renal tubular calcium reabsorption and stimulating the osteoclastic bone resorption to raise the serum calcium levels; the synthesis of 1,25-dihydroxy vitamin D in the kidneys is enhanced, which ultimately aids in the absorption of calcium from the intestine. Hence, the decreased parathyroid hormone impairs these functions and results in hypocalcemia. There is a need for lifelong calcium supplementation in patients with permanent hypoparathyroidism. Moreover, hypoparathyroidism also necessitates supplementation of 1,25-dihydroxy vitamin D for optimum maintenance of normal calcium levels.[22,23]

Table 5. Comparison of biochemical parameters in male and female study population ($n = 310$).

Variables	Males ($n = 161$)	Females ($n = 120$)	Total ($n = 281$)	p Value
Age	50.00 (31.00, 66.00)	43.50 (31.25, 58.75)	48 (31, 64)	0.03*
Vitamin D	26.20 (18.85, 45.70)	27.25 (18.22, 37.65)	26.50 (18.70, 40.75)	0.32
iPTH	189.00 (70.95, 357.85)	138.40 (54.40, 388.57)	168.30 (59.50, 366.10)	0.62
Calcium	1.90 (1.70, 2.06)	1.90 (1.70, 2.10)	1.90 (1.70, 2.1)	0.32
Phosphate	5.20 (3.70, 6.30)	4.80 (3.80, 6.17)	5.1 (3.75, 6.2)	0.72
Albumin	36.00 (32.00, 43.00)	39.00 (33.00, 45.00)	38.00 (32.50, 43.00)	0.44
Creatinine	400.050 (177.50, 742.00)	227.50 (96.25, 425.00)	321.00 (167.00, 693.25)	0.03*
Uric acid	357.00 (265.00, 463.50)	318.00 (255.25, 454.25)	335.00 (260.00, 463.00)	0.44

*p Value < 0.05 is considered to be statistically significant.

Table 6. Correlation of iPTH, calcium, and phosphate in the study population.

Variables	iPTH	Vitamin D	Calcium	Phosphorous	ALP
iPTH	–	$r = -0.224$**	$r = -0.350$**	$r = 0.522$**	$r = 0.128$
		$p = <0.001$	$p = <0.001$	$p = <0.001$	$p = 0.550$
Vitamin D	$= -0.224$**	–	$r = 0.253$**	$r = -0.173$**	$r = -0.182$
	$p = <0.001$		$p = <0.001$	$p = 0.004$	$p = 0.394$
Calcium	$r = -0.350$**	$r = 0.253$**	–	$r = -0.378$**	$r = -0.385$*
	$p = <0.001$	$p = <0.001$		$p = <0.001$	$p = 0.05$
Phosphorous	$r = 0.522$**	$r = -0.173$**	$r = -0.378$**	–	$r = 0.085$
	$p = <0.001$	$p = 0.004$	$p = <0.001$		$p = 0.693$

*p Value < 0.05 is considered to be statistically significant.

Another major finding from the study is the high proportion of patients with hypovitaminosis D (vitamin D < 20 ng/ml) which was seen in 30% of the total study population. The median vitamin D level was 26.50 (18.70, 40.75) and the serum calcium level was 1.90 (1.70, 2.1), respectively. Low vitamin D has been seen in the general Nepalese population with the prevalence ranging from 57%[24] to 73.6%[25] conducted in hospital-based and community settings. The present laboratory-based study supports a similar finding with vitamin D deficiency (<20 ng/ml) in 30.2% and insufficient (20–30 ng/ml) in 27% of the study population. Our finding shows a slightly lower prevalence of hypovitaminosis D which might be due to vitamin D supplementation or general public awareness. In contrast, among all, four individuals comprising 1.4% had hypervitaminosis D which may be attributed to the probable cause of oral contraceptive uses in females, insidious granulomatous diseases which are not full-blown, etc.[26,27]

The correlation of calcium phosphate products with iPTH and vitamin D revealed that iPTH was negatively correlated with vitamin D and calcium levels ($p < 0.001$). There is a significant impact of hypovitaminosis D on iPTH levels. SHPT characterized by elevated serum PTH levels is associated with serum 25(OH) levels lower than 30 ng/ml and/or serum calcium levels lower than 8.5 mg/dl. Our study shows that SHPT was seen in 73% of the study population which is similar to the studies reported from Bangladesh,[28] Iran,[29] India,[30] and the United States,[31] respectively. All of these studies support the inverse relationship between iPTH and vitamin D levels, but the exact inflection point of 25(OH)D above which iPTH level rises is still not clear.

Our finding delineates that there is a significant correlation between iPTH levels and phosphate levels ($p < 0.001$). The altered metabolism of calcium, phosphate, and iPTH has commonly seen in chronic kidney disease patients.[32,33] The severity of hyperphosphatemia and hyperparathyroidism rises with the increasing severity of CKD, and both are linked with increased cardiovascular disease (CVD) events.[30] Hyperphosphatemia is associated with increased risk for death, CVD events, and vascular calcification among patients with and without kidney disease and high iPTH is associated with CVD events even in CKD stages 3 and 4.[34,35] While 25-(OH) D and iPTH are measured in our study, it is advocated state relation between renal function parameters with bioactive whole PTH and 1,25 $(OH)_2$ D as well in future works associated with CKD. Dietary regulation was not monitored in the study population which might have affected the levels of calcium which is one of the limitations of this study. There is a direct correlation between hypomagnesemia and hypocalcemia which has not been explored in our study; however, it can also be studied in further research.

Conclusion

The findings from our study illustrate that there is a swapping drift in the profile of hyperparathyroidism in the Nepalese population. We report the presence of hyperparathyroidism in the middle age group than in the older age group as reported in the literature. Also, the increasing burden of chronic kidney disease might have contributed to a rise in SHPT in Nepal. A large prospective cohort study can be done in the future taking the findings from this study for a weighed conclusion.

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Authors' Contributions

Conceived and designed the experiments: Apeksha Niraula and Naresh Parajuli; performed the experiments: Apeksha Niraula, Sujata Baidya, and Eans Tara Tuladhar; analyzed the data: Apeksha Niraula, Aseem Bhattarai, and Raju Kumar Dubey; and wrote and edited the manuscript: Apeksha Niraula, Vijay Kumar Sharma, Mithileshwer Raut, Eans Tara Tuladhar, Raju Kumar Dubey, Aseem Bhattarai, and Naresh Parajuli. All authors read and approved the final manuscript.

Declaration of conflicting interests

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Ethics approval

The protocol of this study for the subject recruitment process and participation in the study adhered to the Declaration of Helsinki's guidelines and an ethical approval letter was obtained from the Institutional Review Committee of the Institute of Medicine, Maharajgunj Medical Campus with reference No. 322(6-11) E2 078/079. Written informed consent was obtained from all the study participants. For those below 18 years old, informed consent was obtained from their parents.

Informed consent

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Trial registration

Not applicable.

Data availability statement

Data supporting the conclusions of this article are within the manuscript and are available on reasonable request from the principal investigators due to ethical reasons.

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