RESEARCH ARTICLE

Biochemical spectrum of parathyroid disorders diagnosed at a tertiary care setting

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Abstract

Objective: To determine the clinical and biochemical pattern of parathyroid disorders in a tertiary care setting.

Methods: The cross-sectional study was conducted at the Armed Forces Institute of Pathology, Rawalpindi, Pakistan, from September 2017 to February 2018, and comprised patients with suspected parathyroid disorders. A panel of biochemical tests were used for diagnosis of parathyroid disorders, which included parathyroid hormone levels, total calcium, ionized calcium, inorganic phosphorus, alkaline phosphatase, magnesium, total vitamin D and urinary calcium-to-creatinine ratio. SPSS 24 was used for data analysis.

Results: Of the 384 subjects, 248(65%) were male and 136(35%) were female. Overall mean age was 48±19years. Of the total, 302(786%) had parathyroid issues, with 244(81%) having secondary hyperparathyroidism. Mean serum total calcium, phosphorus, ionized calcium, magnesium and total vitamin D were 8.98±1.52 mg/dl, 4.0±1.30 mg/dl, 4.65±0.52 mg/dl, 2.11±0.27 mg/dl and 20.5±8.52 ngml respectively. Of the patients diagnosed with secondary hyperparathyroidism, 72.2% patients had chronic kidney disease and 20.2% had isolated vitamin D deficiency.

Conclusion: Parathyroid disorders had significant impact on bone health. Moreover, secondary hyperparathyroidism was seen to be emerging as a major endocrine problem, especially in chronic kidney disease patients and vitamin D-deficient individuals.

Keywords: Parathyroid disorders, Serum calcium, Inorganic phosphorus, Urine calcium creatinine ratio. (JPMA 70: 243; 2020) **https://doi.org/10.5455/JPMA.302643153**

Introduction

Parathyroid disorders are evolving as a common endocrine problem and may sometimes present as a diagnostic dilemma to the treating endocrinologist or physician. These are characterised by a wide spectrum of clinical disorders, reflecting a diverse clinical and biochemical presentation. This includes primary disorders of secretion comprising an intrinsic defect of the parathyroid gland, leading to primary hyperparathyroidism or hypo-parathyroidism, or secondary and tertiary disorders in which increased or decreased parathyroid levels are an adjustment to another pathophysiological process within the body. Recently, there has been an evolution of newer phenotypes, like functional hypo-parathyroidism in which vitamin D deficiency is not accompanied by secondary hyperparathyroidism (SHPT), whereas some patients demonstrate hypercalcemia along with inappropriately normal parathyroid hormone (PTH) levels.[1] Pseudohypo-parathyroidism is a rare entity which comprises a group of rare and heterogeneous disorders due to end organ resistance to parathyroid hormone action.[2]

PTH is the principal regulator of calcium homeostasis in human body, ultimately affecting all organs due to the importance of calcium physiology.[3] PTH acts by increasing tubular reabsorption of calcium in the kidneys, increasing bone resorption, up-regulating 1-α-hydroxylase leading to increased 1,25-dihydroxy vitamin D (1,25[OH]2D) production and increased intestinal reabsorption of calcium.[4] Calcium sensing receptors (CaSR), located in chief cells of parathyroid gland and renal tubules, play a pivotal role in calcium regulation, by controlling the secretion of parathyroid hormone and renal reabsorption of calcium in response to the extracellular ionized calcium levels; thus maintaining the serum calcium levels within the normal physiological range.[5] It also plays an important role in controlling urinary calcium excretion independent of its effect on PTH secretion.[6] CaSR defects are further divided into gain of function mutations, causing autosomal dominant hypo-parathyroidism and loss of function mutations causing familial hypo-calciuric hypercalcemia and neonatal severe primary hyperparathyroidism, as well as hypercalcemia in the face of normal intact PTH (iPTH)

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levels.

Primary hyperparathyroidism is a common endocrine problem worldwide, showing prevalence of one to seven cases per thousand adults.[7] Secondary hyperparathyroidism and mineral dysfunction is an important feature and adaptation in the setting of established chronic kidney disease (CKD), with the process having started even before the symptomatology of CKD appears. PTH levels start to increase in early stages of kidney failure and are later directly related to the degree of kidney dysfunction.[8] Across Europe and Australia, the prevalence of SHPT within dialysis patients is estimated to be around 30-49%, whereas in Asia, the prevalence estimate was 28% for India and 11.5% for Japan.[9] Taking into account this relatively high prevalence of SHPT, it is necessary to screen all CKD patients for hyperparathyroidism regardless of cost.[10]

Disorders of PTH are responsible for affecting the bone mineral status of an individual with the most common symptomatology being generalised body weakness, joint pains, paraesthesias, renal stones and headache. Non-specificity of symptoms is usually a diagnostic challenge so parathyroid disorders are mostly diagnosed as part of routine testing for other disorders; biochemical markers being an important tool for investigation in such cases. Simultaneous testing with bone health profile markers gives an overall broader picture of the disease status and paves the way for prompt diagnosis and interpretation of such disorders.

There are not many studies in Pakistan indicating the prevalence and risk factors for parathyroid disorders and utilizing the wide panel of biochemical tests to diagnose these disorders, which can be missed on routine screening. The current study was planned to determine the clinical and biochemical pattern of parathyroid disorders in a tertiary care setting. The study will help to open a pathway for the diagnosis of various parathyroid disorders in a developing country like Pakistan, where more attention is paid to infectious and nutritional disorders due to limited resources. The study will also shed light on the variation in these disorders and also the level of care available for such patients.

Material and Methods

The cross-sectional study was conducted at the Endocrine clinic of the Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan, from September 2017 to February 2018, and comprised patients with suspected parathyroid disorders. The study was approved by the institutional review board. The sample size was calculated using given formula of World Health Organisation (WHO) sample size estimation [$n= z^2P(1-P)/d^2$],[11] taking prevalence of secondary hyperparathyroidism to be 28% in CKD patients.[9] The sample was raised using non-probability convenient sampling technique after taking informed consent from each subject. Most of the patients had been referred from Nephrology and Urology departments. A panel of biochemical tests was used, including serum total calcium, phosphorus, albumin, alkaline phosphatase (ALP), ionized calcium, magnesium, total vitamin D, plasma iPTH, urine calcium-to-creatinine ratio and fractional excretion of calcium. A self-generated questionnaire was used to assess demographic data, co-morbidities, like diabetes and hypertension (HTN), family history and history of calcium intake and other medications. Standard height was measured using a scale to the nearest 0.5cm, and body weight was measured on a weighing scale to the nearest 0.5kg.

All patients visiting the AFIP Endocrine clinic for PTH profiling and suspected of having a parathyroid disorder were selected irrespective of age and gender.

Those excluded were pregnant females, all patients on regular calcium supplements and other medications affecting bone mineral status as well as those with inadequate clinical information.

Venous blood samples were collected after overnight fasting (10-12 hours) to standardise sample collection and to cater for diurnal variation and dietary effects, especially in the case of hormones. About 10ml blood was collected in serum gel separator tube, lithium heparin tube and ethylenediamine tetraacetic acid (EDTA) tube. Potassium EDTA tubes were used for sampling of plasma iPTH levels, and the samples were transported to the laboratory in ice-pack. Refrigerated centrifugation was carried out and the samples were analysed within 20-30 minutes of collection. Serum calcium, phosphorus, ALP, albumin, magnesium and urine calcium-to-creatinine ratio were analysed on fully automated random access discrete chemistry analyser (ADVIA 1800, Siemens Healthcare Diagnostics Inc. New York, United States [USA]). Serum ionized calcium levels were done on blood gas analyser (Cobasb221, Roche Diagnostics USA). Plasma iPTH was carried out by fully automated random access two-site chemilluminescent enzyme labelled immunoassay (Immulite 2000, Siemens Healthcare Diagnostics Inc. New York, USA) with an intra-assay precision of 4.2-5.7% and inter-assay precision of 6.3-8.8%, linearity of 263 pmol/L and detection limit of 0.3 pmo/L (kit lot number 323 and 324). Total Vitamin D quantification was performed by competitive chemilluminescence immunoassay (Advia Centaur, Siemens Healthcare Diagnostics Inc. New York, USA), with an inter-assay precision of 3.0-5.3% and intra-

assay precision of 4.2-11.9%, linearity of 374 nmol/L and detection limit of 8.0 nmol/L. Manufacturer-provided controls were run for all analytes in each batch of analysis for internal quality control. Serum corrected calcium was used instead of serum total calcium in case of low albumin levels (<40 g/L) by using the formula measured calcium + 0.02 (40-albumin).[12]

Data was analysed using SPSS 24. Frequencies and percentages were computed for qualitative variables, like gender, co-morbidities, clinical presentation and aetiology, whereas means and standard deviation (SD) were computed for quantitative variables, like age and biochemical parameters. Age stratification was done to quantify disorders with each age group.

Result

Of the 384 subjects, 248(65%) were male and 136(35%) were female. Overall mean age was 48±19 years. Of the total, 219(57%) individuals were from rural areas and 165(43%) were from urban areas. A total of 302(78.6%) patients were diagnosed with various parathyroid disorders, while the rest showed a normal biochemical profile (Table-1). The disorders were more dominant in males, whereas hypo-parathyroidism was more common in females (Figure-1).

Overall, 134(35%) patients were diabetic, with male-to-female ratio being 7:3; 157(41%) patients were hypertensive,115(73%) males and 42(27%) females; and 137(36%) were suffering from CKD, with males getting affected 4 times more than females. Vitamin D deficiency was found in 54(14%) patients, and vitamin D insufficiency in 307(80%). SHPT aetiology revealed that

Table-1: Baseline characteristics.

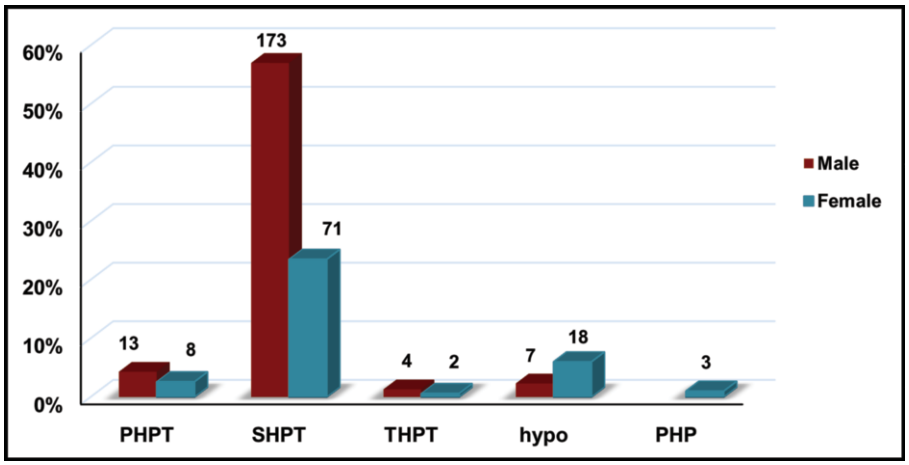
Study Variables	Descriptive (Mean ±SD)
Age (years)	48 ± 19
Weight (Kg)	60.3 ± 10.8
Height (cm)	160.8 ± 25.9
Total calcium (mg/dl)	8.98 ± 1.52
Phosphorus (mg/dl)	4.0 ± 1.30
Ionized Calcium (mg/dl)	4.65 ± 0.52
Albumin (g/l)	41 ± 4
Urinary Calcium to Creatinine Excretion	0.23 ± 0.43
Fractional Excretion of calcium	3.4 ± 7.60
Alkaline Phosphatase (IU/L)	Median= 120 IQR= (179-88)
PTH (pmol/L)	Median= 11.8 IQR= (30-5)
Vitamin D (ng/ml)	20.5 ± 8.52
Magnesium (mg/dl)	2.11 ± 0.27

SD: Standard deviation.
PTH: Parathyroid hormone.

176(72%) patients had CKD, 49(20%) had isolated vitamin D deficiency or insufficiency, 19 (8%) had no definite cause of SHPT. Out of the CKD population, 86(63%) were on dialysis and 51(37%) were not on dialysis.

A total of 126(33%) patients were diagnosed with magnesium deficiency; 114(91%) of them in the SHPT group, and 6(5%) in the hypo-parathyroid group (Figure-2).

The most prevalent symptoms were body aches 169(44%), headache 80(21%), renal stones 73(19%), paraesthesias 46(12%) and others 15(4%).

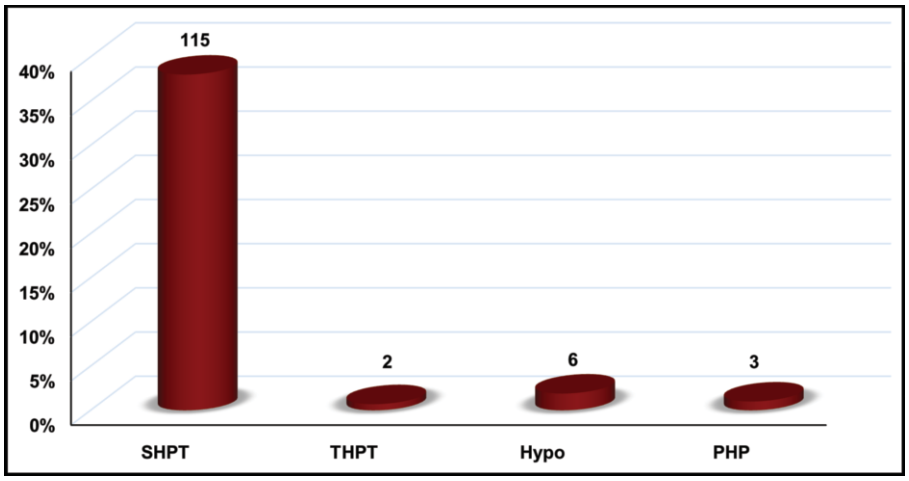


(PHPT= Primary Hyperparathyroidism, SHPT= Secondary Hyperparathyroidism, THPT= Tertiary Hyperparathyroidism, Hypo= Hypoparathyroidism, PHP= Pseudohypoparathyroidism)

Figure-1: Gender-wise distribution of Parathyroid disorders.

Most common parathyroid disorder was SHPT 244(81%), followed by hypoparathyroidism 25(8.0%), primary hyperparathyroidism 21(7.0%), tertiary hyperparathyroidism 6(2.0%), pseudo-hypoparathyroidism 3(1%), CaSR defects 2(0.7%) and humoral-hypercalcemia of malignancy 1(0.3%). Patients with CaSR defects showed inappropriately normal PTH levels with high serum calcium levels and low urinary calcium-to-creatinine ratio. Out of the patients presenting with hypo-parathyroidism, 20(80%) had undergone thyroid surgery. Only 5(20%) presented with hypo-parathyroidism due to other causes.

There were 31(8%) patients aged 1-20 years, 102(26.6%) aged 21-40



SHPT: Secondary Hyperparathyroidism
THPT: Tertiary Hyperparathyroidism
Hypo: Hypoparathyroidism
PHP: Pseudohypoparathyroidism

Figure-2: Magnesium deficiency in Parathyroid disorders.

years, 145(37.9%) aged 41-60 years, and 106(27.5%) aged >60 years.

SHPT showed bimodal distribution, with most patients aged 20-40 years, or were >60 years, whereas primary hyperparathyroidism presented mostly in those aged 1-20 years. Only 3(1%) patients showed biochemical picture of pseudo-hypoparathyroidism, all being females aged 1-20 years. CaSR defects were seen in 2(0.07%) patients, both presenting in childhood and were labelled as familial hypo-calciuric hypercalcemia.

Discussion

The study showed that the highest disease frequency in parathyroid disorders was SHPT, while the rest of the disorders represented a very small portion of the spectrum.

SHPT has been studied extensively in CKD and haemodialysis patients in the past. Our study was not exclusively for CKD patients, but still showed comparative results to previous studies that focused on CKD and haemodialysis patients.[8,10,13] A 2014 study[8] reported the frequency of SHPT in CKD patients to be 77.5% in Amman, Jordan, which is quite close to the frequency noted in the current study. We observed that SHPT was more dominant in males, a finding consistent with previous studies, mainly due to male predominance in CKD population.[13] On the other hand, majority of the patients diagnosed with hypoparathyroidism were females and comprised postsurgical status in our study; another finding concurrent with international studies.[14] Unfortunately, there is not much literature on the prevalence of hypo-parathyroidism locally.

Primary hyperparathyroidism, on the contrary, has been reviewed in detail over the past few years, both internationally and locally, considering its surgical management and association with pregnancy and other high risk conditions. It is more commonly present in females but our study showed a male preponderance.[15] Another retrospective study[16] depicted young age as the main group affected. In another community-based, non-referral study[17] in the USA, the frequency of primary hyperparathyroidism and hypo-parathyroidism was 3.1% and 1.9% respectively; our study showed slightly higher frequency due to hospital-based settings.

Vitamin D deficiency is another important aspect studied extensively in association with parathyroid disorders in the past. In a study conducted[1] in Karachi, the frequency of Vitamin D deficiency leading to SHPT was 17.7% which was in close proximity to the frequency reported in our study (20%). Even though the definition and cut-off for vitamin D deficiency differs geographically, with separate methodology used for vitamin D estimation, and different extent of sunlight exposure, it still presents as an important cause of SHPT in almost all parts of the world.[18-20]

The presentation of parathyroid disorders is non-specific and should always be suspected in case of other co-morbidities, like DM and HTN that are established risk factors for CKD.[9] PTH is a uraemic toxin and can have multiple systemic effects with adverse outcomes on quality of life in CKD and haemodialysis patients.[21] There is no definite screening programme in our country but such patients are recommended to get their parathyroid profile done every 3-6 months. Parathyroid disorders are also associated with various genetic aspects which still require further research and evaluation in our setup and can widen the horizon for diagnosis of these disorders.[4] Furthermore, some rare diseases of the gland like calcium sensing receptor defects and humoral hypercalcemia of malignancy still need further workup at our institution.

There are certain limitations of the current study. We did not include radiological and histopathological findings as part of the diagnostic workup. Parathyroid disorders require a long-term follow-up to assess the outcomes and management of these disorders, along with prognosis. There is a need to conduct population based studies to give a better overview of the disease prevalence.

Conclusion

Parathyroid disorders are not rare and have significant impact on bone health. SHPT is emerging as a major endocrine problem, especially in CKD patients and individuals presenting with low vitamin D status. Simultaneous testing with a panel of biochemical markers would definitely improve the diagnostic yield in case of parathyroid disorders.

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Conflict of Interest: None.

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