ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Primary Hyperparathyroidism in Patients with Distal Forearm Fractures.

Zainab A Mahmood[1]*, Nizar Abdul-Lateef Jassim[2], Ahmed Abdulbari[3], and Mohanned Khalil Ahmed[4].

[1]FIBMS (Intern. Med.), FICMS (Rheum. and Med. Rehab.), Lecturer of Medicine, College of Medicine, University of Basra, Basra, Iraq.
[2]FIBMS (Intern. Med.), FICMS (Rheum. and Med. Rehab.), Consultant Rheumatologist, Professor of Medicine and Rheumatology, College of Medicine, University of Baghdad, Baghdad, Iraq.
[3]Senior specialist in Rheumatology and Rehabilitation, IbnSina Training Hospital, Baghdad, Iraq.
[4]MBChB, Diploma of Rheumatology, Baghdad Teaching Hospital, Baghdad, Iraq.

ABSTRACT

Primary hyperparathyroidism is a generalized disorder of calcium, phosphate, and bone metabolism due to an increased secretion of parathyroid hormone (PTH). The elevation of circulating hormone usually leads to hypercalcemia and hypophosphatemia. Since parathyroid hormone removes calcium from bones, all patients with a parathyroid problem will eventually develop thin bones. Bones with osteoporosis due to parathyroid problems can ache and hurt because the PTH is actively destroying the bone. We showed few cases of undiagnosed hyperparathyroidism in patients who presented with a distal forearm fracture. Aims: This study aims to discover the undiagnosed primary hyperparathyroidism in patients with distal forearm fracture and assessment of the prevalence of radiological changes associated with it. Also, it aims to assess serum calcium (Ca), phosphate (Po4), vitamin D and bone mineral density in those patients with a distal forearm fracture. Patients and methods: This is a prospective cross-sectional study conducted in Orthopedic Outpatient Unit in Al Fayhaa General Hospital, Basra, Iraq, and Al-Bari Medical center, Baghdad, from April 2017 till July 2018. Participants consent was taken for inclusion in the study. Forty patients were involved in this study. Those patients were men > 55 years and women > 50 years of age who presented with a distal forearm fracture. The fracture was diagnosed by using plain x-ray which was analyzed by an orthopedic surgeon. Blood samples were collected for measurement of serum level of parathyroid hormone (PTH), total Calcium, phosphate, vitamin D, and alkaline phosphatase (ALP). Bone mineral density was measured by lumbar DXA scan using Stratos densitometry and analyzed according to Turkish ethnicity. Results: Most of the patients included in the current study were women (82.5%). The mean age for all patients was 56.98±9.5 years. All patients had normal hands X-ray except one who had a subperiosteal reaction in the phalangeal bones. This patient also had high PTH (≥3 folds), and high ALP (≥2 folds) but normal S.Ca and S.Po4. There was no significant association between the level of PTH and history of previous fractures, vitamin D level, S. Po4, and bone status. Most of our patients were had normal S.Ca and ALP even in presence of very high PTH (≥3 folds) (p value= 0.037, 0.00 respectively). That means there is subclinical hyperparathyroidism. Conclusions: There are few undiagnosed cases of primary hyperparathyroidism (PHPT) which can be presented as distal forearm fracture. There was no significant association between the level of PTH and history of previous fractures, vitamin D level, S. Po4, and bone status. The biochemical changes are not common to occur in patients with primary hyperparathyroidism.

Keywords: distal forearm fracture, parathyroid hormone, hyperparathyroidism.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Parathyroid hormone:

The primary function of PTH is to maintain the extracellular fluid (ECF) calcium concentration within a narrow normal range. Any tendency toward hypocalcemia, as might be induced by calcium or vitamin D deficient diets, is counteracted by an increased secretion of PTH. This in turn (1) increases the rate of dissolution of bone mineral, thereby increasing the flow of calcium from bone into blood; (2) reduces the renal clearance of calcium, returning more of the calcium and phosphate filtered at the glomerulus into ECF; and (3) increases the efficiency of calcium absorption in the intestine by stimulating the production of 1,25(OH)2D. Immediate control of blood calcium is due to PTH effects on bone and, to a lesser extent, on renal calcium clearance. Continuous exposure to elevated PTH (as in hyperparathyroidism or long-term infusions in animals) leads to increased osteoclast-mediated bone resorption. However, the intermittent administration of PTH, elevating hormone levels for 1–2 h each day, leads to a net stimulation of bone formation rather than bone breakdown.[1]

Primary hyperparathyroidism:

Primary hyperparathyroidism (PHPT) is a generalized disorder of calcium, phosphate, and bone metabolism due to an increased secretion of PTH. The elevation of circulating hormone usually leads to hypercalcemia and hypophosphatemia.

Patients may present with multiple signs and symptoms, including recurrent nephrolithiasis, peptic ulcers, mental changes, and, less frequently, extensive bone resorption. The manifestations may be subtle, and the disease may have a benign course for many years or a lifetime. This milder form of the disease is usually termed asymptomatic hyperparathyroidism.[1]The diagnosis of hyperparathyroidism is made by documenting simultaneous elevations in the circulating levels of calcium and PTH in a patient with normal renal function. Patients with hyperparathyroidism also may have slightly low or low-normal serum phosphorus concentrations and mild hyperchloremic metabolic acidosis. Alkaline phosphatase levels may be elevated in patients with overt bone disease.[2] More recently, a newer presentation of PHPT has emerged, in which patients present with elevated PTH levels and consistently normal serum calcium. Patients with this phenotypical presentation, normocalcemic PHPT, are usually discovered during the evaluation for a metabolic bone disease. [3]

Radiographic changes:

Plain radiographic findings may include resorption and sclerosis of numerous sites in the skeletal system. Historically, osteitisfibrosacystica was used to describe the advanced skeletal disease in primary hyperparathyroidism. Bone findings were characterized by the osteoclasticresorption of bone, osteoblastic bone formation, and fibrous replacement of marrow, with radiographic findings of subperiostealresorption, brown tumors, bone cysts, and sclerosis. These days, the most common radiologic finding in primary hyperparathyroidism is osteopenia, which may be generalized or asymmetric. Fine trabeculations are initially lost, with resultant coarse and thickened trabeculae. About 30-50% of the bone density must be lost to show changes on radiographs. Although subperiosteal bone resorption can affect many sites, the most common site in hyperparathyroidism is the middle phalanges of the index and middle fingers, primarily on the radial aspect. [4]

Osteoporosis and Parathyroid Disease (Hyperparathyroidism):

Since parathyroid hormone (PTH) removes calcium from bones, all patients with a parathyroid problem will eventually develop thin bones. Bones with osteoporosis due to parathyroid problems can ache and hurt because the PTH is actively destroying the bone. While X-rays rarely show classical findings of PHPT, bone mass is typically reduced when it is measured by DXA. For many years, it was believed that the negative effects of PHPT on the skeleton were restricted to cortical bone. The densitometric profile of PHPT shows bone mineral density (BMD) reductions at the distal 1/3 forearm, a site composed primarily of cortical bone, with relative preservation of the lumbar spine, a predominantly trabecular site. [5] [6] The adverse effects of PHPT are likely to be mitigated by weight-bearing, since the radius, a nonweight-bearing site, is generally more affected than the tibia, a weight-bearing site. [7]

Patients and Method

Study design:

This is a prospective cross-sectional study conducted in an orthopedic outpatient unit in Al Fayhaa General Hospital, Basra, Iraq, and Al-Bari Medical Center, Baghdad, Iraq, from April 2017 till July 2018. Participants consent was taken for inclusion in the study.

Sample selection:

Forty patients were involved in this study. Those patients were men > 55 years and women > 50 years of age who presented with a distal forearm fracture. The fracture was diagnosed by using plain x-ray which was analyzed by orthopediacian. Exclusion criteria included those patients who have other secondary causes of fracture and osteoporosis like chronic rheumatic diseases and chronic kidney diseases.
Clinical and laboratory assessment:

Patients' clinical data were collected using interview. These data included: age, causes of fracture (falling vs direct trauma), history of previous fragility fracture, history of taking corticosteroids, previous or current attack of renal stone, menopausal history for women and history of chronic use of any medication. Blood samples were collected for measurement of serum level of PTH, total Ca, Po4, and alkaline phosphatase (ALP). The normal range are: ALP 40-125 U/l, total Ca 8.5-10.5 mg/dl, PTH 16-75 pg/ml and Po4 2.4-4.3 mg/dl. [8] Serum 25(OH) Vit D was measured using Electro-chemiluminescence immunoassay (ECLIA)-cobas. And the results were categorized into normal ≥ 30 ng/ml, insufficient 21-29 ng/ml, and deficient ≤ 20ng/ml. Bone mineral density was measured by lumbar DXA scan using Stratos densitometry and analyzed according to Turkish ethnicity. Osteopenia is defined as total T score -1 to -2.5, while osteoporosis as total T score <-2.5 or Z score <-2. [9]

Statistical Analysis: Normally distributed data presented using their mean and standard deviation, while non-normally distributed data presented as median and interquartile range. All data analyzed using SPSS version 21, graph Pad Prism and mintab version 18. P value were considered significant if less than 0.05.

RESULTS

The demographical features were represented in table 1. Most of our patients were women (82.5%). The mean age for all patients was 56.98±9.5 years.

Table 1: Demographical features

Variables	Values
Number	40 patients
Gender: No. (%)	
Man	7 (17.5%)
Woman	33 (82.5%)
Age: mean±SD (years)	56.98±9.582
Man	55.29±6.726
Woman	57.33±10.132
Causes of fracture: No. (%)	
Direct trauma	9 (22.5%)
Falling	31 (77.5%)
History of previous fracture: No. (%)	
No	35 (87.5%)
Yes	5 (12.5%)
Steroid use: No. (%)	
No	36 (90.0%)
Yes	4 (10.0%)
History of renal stone: No. (%)	
No	33 (82.5%)

ISSN: 0975-8585

Yes	7 (17.5%)
Preserved menstruation in women: No. (%)	
Yes	4 (12.2%)
No	29 (87.8%)
YSM: mean±SE (years)	9.9±1.911

SD; standard deviation, SE; standard error, YSM; year since menopause

Regarding the radiological findings; all patients had normal hands X-ray except one who had a subperiosteal reaction in the phalangeal bones (table 2). This patient also had high PTH (≥3 folds), and high ALP (≥2 folds) but normal S.Ca and S.Po4. Only 2 patients (5%) were had a very high level of PTH (≥3 folds) and 11 patients (27.5%) were had mild-moderate increased in PTH (<3 folds). The biochemical parameters were represented in table 2.

Table 2: Biochemical and Radiological characteristic

Variables	Number	%
X ray:		
Normal	39	97.5
Abnormal	1	2.5
Vitamin D:		
Normal	9	22.5
Insufficient	6	15.0
Deficient	25	62.5
PTH:		
Normal	27	67.5
Increased < 3 folds	11	27.5
Increased ≥ 3 folds	2	5.0
Serum Ca:		
Normal	34	85.0
High	2	5.0
Low	4	10.0
Serum Po4:		
Normal	36	90.0
High	2	5.0
Low	2	5.0
ALP:		
Normal	35	87.5
Increased < 2 folds	4	10.0
Increased ≥ 2 folds	1	2.5
Bone status:		
Normal	3	7.5
Osteopenia	17	42.5
Osteoporosis	20	50.0

ALP; alkaline phosphatase, Ca; calcium, PTH; parathyroid hormone, Po4; phosphorus.

Table 3 showed the association of different value of PTH with other clinical, biochemical and radiological parameters. The two patients who were with very high PTH (≥3 folds) all were had a history of renal stone, while 18.2% from patients with mild-moderate increased PTH (<3 folds) and 11.1% from patients with normal PTH were had a renal stone, the result was statistically significant (p value= 0.006).

There was no significant association between the level of PTH and history of previous fractures, vitamin D level, S.Po4 and bone status (p value= 0.171, 0.361, 0.818 and 0.519 respectively).

One of the two patients with very high PTH had normal S.Ca, and the other had high S.Ca. On the other hand, nine patients (81.8%) with mild-moderate increased PTH also had normal S.Ca (p value= 0.037) that means most of the cases with high PTH may have normal S.Ca. That also applicable for ALP level (p value= 0.00). The patient with very high PTH and ALP was had normal S. vitamin D, so we excluded secondary

ISSN: 0975-8585

hyperparathyroidism. All patients with mild-moderate increased PTH had normal ALP. One of the patients with very high PTH had osteopenia and the other had osteoporosis (table 3).

Table 3: Association of PTH with other variables

PTH / Variables	Normal		Increased <3 folds		Increased ≥3 folds		P value
	No.	%	No.	%	No.	%	
History of previous fractures:							
No	25	92.6	9	81.8	1	50.0	0.171
Yes	2	7.4	2	18.2	1	50.0	
Total	27	100.0	11	100.0	2	100.0	
Renal stone							
No	24	88.9	9	81.8	0	0.0	**0.006**
Yes	3	11.1	2	18.2	2	100.0	
Total	27	100.0	11	100.0	2	100.0	
Vitamin D:							
Normal	6	22.2	3	27.3	0	0.0	
Insufficient	5	18.5	0	0.0	1	50.0	0.361
Deficient	16	59.3	8	72.7	1	50.0	
Total	27	100.0	11	100.0	2	100.0	
Serum Ca:							
Normal	24	88.9	9	81.8	1	50.0	
High	1	3.7	0	0.0	1	50.0	**0.037**
Low	2	7.4	2	18.2	0	0.0	
Total	27	100.0	11	100.0	2	100.0	
Serum Po4:							
Normal	24	88.9	10	90.9	2	100.0	
High	1	3.7	1	9.1	0	0.0	0.818
Low	2	7.4	0	0.0	0	0.0	
Total	27	100.0	11	100.0	2	100.0	
ALP:							
Normal	23	85.2	11	100.0	1	50.0	
Increased <2 folds	4	14.8	0	0.0	0	0.0	0.00
Increased ≥2 folds	0	0.0	0	0.0	1	50.0	
Total	27	100.0	11	100.0	2	100.0	
Bone status:							
Normal	1	3.8	2	18.2	0	0.0	
Osteopenia	13	48.1	3	27.3	1	50.0	0.519
Osteoporosis	13	48.1	6	54.5	1	50.0	
Total	27	100.0	11	100.0	2	100.0	

ALP; alkaline phosphatase, Ca; calcium, PTH; parathyroid hormone, Po4; phosphorus

DISCUSSION

The presence of renal stone is the most common complication of PHPT. In our study, we showed that patients with high level of PTH commonly had a history of renal stones. This result is corresponding with studies done by Castellano E et al and Jane M. Suh et al.[10, 11] We found there were no significant associations between vitamin D and level of PTH. That was differ from the result of Marcella D. Walker et al [12] study, who found that vitamin D deficiency is associated with more severe PHPT as reflected by PTH levels but they also found that vitamin D status did not appear to significantly impact clinical presentation or bone density, however, we did not study the effect of vitamin D status in another parameter. This difference may be due to a small number of cases of high PTH that we found in our study. We measured total serum calcium level and it was not correlated with PTH level. Gregory S. Y. Ong et al [13] found that reliance on total Ca alone miss 45% with ionized hypercalcemia mainly in PHPT and measurement of ionized Ca is required to accurately assess calcium status and improve diagnostic accuracy. Rao et al. describe a biphasic chronology of PHPT

clinical development [14]. During the first phase, PTH levels are elevated but the serum calcium is normal. This first phase was a subclinical one because PTH levels were rarely measured when the serum calcium concentration was normal. The second phase is the one that has traditionally been recognized because of hypercalcemia symptoms. Normocalcemic primary hyperparathyroidism was first formally recognized at the time of the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008 [15]. We found that ALP level was not elevated in patients with high PTH. There was a case report published by BehzadEinollahi et al [16] who reported normal ALP in patients with PHPT.

In conclusion, there are few undiagnosed cases of PHPT which can be presented as distal forearm fracture. There is a case report which was published by Mayuko Kinoshita et al in 2017 [17] about a woman with nonunion forearm fracture discovered after 2 years to be a case of PHPT. There is also a study done by Hans Mallmin et al in 1991 involved 481 patients with a distal forearm fracture, from them 12 patients found to have PHPT.

There was no significant association between the level of PTH and history of previous fractures, vitamin D level, S. Po4, and bone status. The biochemical changes are not common to occur in patients with primary hyperparathyroidism.

REFERENCES

[1] F. Richard Bringhurst, Marie B. Demay,Stephen M. Krane, Henry M. Kronenberg. Bone and Mineral Metabolism in Health and Disease. In: Dennis L. Kasper, MD, Anthony S. Fauci, MD, et al editors. Harrisons Principles in Internal Medicine, 19th ed. McGraw-Hill Education. 2015. P: 2466-2470.

[2] John J. WysolmerskiAnd Karl L. Insogna. The Parathyroid Glands, Hypercalcemia, and Hypocalcemia. In: Lee Goldman, MD, Andrew I. Schafer, MD editor. Goldman's Cecil Medicine, 24th ed. Elsevier Inc. 2012. P: 1594, 1595.

[3] Francisco Bandeira, Natalie E. Cusano, Barbara C, et al. Bone disease in primary hyperparathyroidism. Arq Bras EndocrinolMetab vol.58 no.5 São Paulo July 2014

[4] GahierPenhoat M, Drui D, Ansquer C, Mirallie E, Maugars Y, Guillot P. Contribution of 18-FDG PET/CT to brown tumor detection in a patient with primary hyperparathyroidism. Joint Bone Spine. 2016 Oct 7.

[5] Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J ClinEndocrinolMetab. 2008;93(9):3462-70.

[6] Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the fourth international workshop. J ClinEndocrinolMetab 2014

[7] Hansen S, Beck Jensen JE, Rasmussen L, Hauge EM, Brixen K. Effects on bone geometry, density, and microarchitecture in the distal radius but not the tibia in women with primary hyperparathyroidism: a case-control study using HR-pQCT. J Bone Miner Res. 2010;25(9):1941-7.

[8] S.W.Walker. Laboratory Reference Ranges. In: Nicki R. Colledge, Brian R. Walker, Stuart H. Ralston editors. Davidson's Principles and Practice of Medicine, 22nd edition. Churchill Livingstone, Elsevier. 2014. P: 1309-1310.

[9] Czerwinski E, Badurski JE, Marcinowska-Suchowierska E, Osieleniec J. Current understanding of osteoporosis according to the position of the World Health Organization (WHO) and International Osteoporosis Foundation. OrtopTraumatolRehabil. 2007 Jul-Aug. 9(4):337-56.

[10] Castellano E, Attanasio R, Latina A, Visconti GL, Cassibba S, Borretta G. Nephrolithiasis In Primary Hyperparathyroidism: A Comparison Between Silent And Symptomatic Patients. EndocrPract. 2017 Feb;23(2):157-162.

[11] Jane M. Suh, John J. Cronan and Jack M. Monchik. Primary Hyperparathyroidism: Is There an Increased Prevalence of Renal Stone Disease? American Journal of Roentgenology. 2008;191: 908-911.

[12] Marcella D. Walker, Elaine Cong, James A. Lee, Anna Kepley, Chiyuan Zhang, Donald J. McMahon, and Shonni J. Silverberg. Vitamin D in Primary Hyperparathyroidism: Effects on Clinical, Biochemical, and Densitometric Presentation. J ClinEndocrinolMetab. 2015 Sep; 100(9): 3443–3451.

[13] Gregory S. Y. Ong John P. Walsh Bronwyn G. A. Stuckey Suzanne J. Brown Enrico Rossi Jennifer L. Ng, et al. The Importance of Measuring Ionized Calcium in Characterizing Calcium Status and Diagnosing Primary Hyperparathyroidism. The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 9, 1 September 2012, Pages 3138–3145.

[14] Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM. Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. J ClinEndocrinolMetab. 1988;67:1294–8.
[15] Bilezikian JP, Khan AA, Potts JT., Jr Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J ClinEndocrinolMetab. 2009;94:335–9.
[16] BehzadEinollahi, MehrdadTaghipour, Mohsen Motalebi, Mahdi Ramezani-Binabaj. Normal alkaline phosphatase level in a patient with primary hyperparathyroidism due to parathyroid adenoma. Journal of Parathyroid Disease. 2014,2(1),47–50.
[17] MayukoKinoshita,aKiyohitoNaito,a, KentaroAritomi,b Yoichi Sugiyama,a Nana Nagura,a Kenji Goto, et al. Forearm nonunion caused by hyperparathyroidism with 7 years follow up: A case report. Int J Surg Case Rep. 2017; 38: 158–162.