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Hyperparathyroidism and Associated Factors in Chronic Kidney Disease

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ABSTRACT

Background: **The normal axis of calcium, phosphorus, vitamin D, and intact parathyroid hormone (iPTH) come under stress when chronic kidney disease (CKD) progresses beyond stage 3(GFR<30 ml/kg/1.73^2). This results in increased secretion of iPTH which is known as secondary hyperparathyroidism. This exacerbates further if simultaneous deficiency of nutritional vitamin D (Cholecalciferol) is also found. Secondary hyperparathyroidism results in vascular calcification and increases cardiac mortality. Early intervention in form of dietary modification (low phosphorus, low potassium), correcting vitamin D deficiency along with the addition of active vitamin D (calcitriol) would help in alleviating patients' suffering and saving costs as well.**

Material and method: **This study was conducted from Jan 2017 to Jan 2018 at The Indus Hospital, Karachi with the age group ≥14 years of either gender who were suffering from chronic kidney disease (CKD). Patients on dialysis, chronic liver disease, and vitamin D supplementation were excluded. Their history, demographic, BMI, Calcium, Phosphorus, Alkaline Phosphatase, 25-Hyydorxyvitamin D, albumin, and intact parathyroid hormone (iPTH) were all noted.**

Results: **265 patients were enrolled for final analysis in this data with a male to female ratio of 1:1.03 (146/121). Hyperparathyroidism (iPTH> 68 pg/ml) was seen in 190 (71.2%) patients. Mean values of all quantitative variables were not statistically significant when compared hyper parathyroid with normal parathyroid. Hyperparathyroidism was found significant in late CKD in comparison to early CKD (P-value <.001), While vitamin D deficiency was significantly associated with hyperparathyroidism in early CKD but not in late CKD.**

Conclusion: **Hyperparathyroidism is significantly present in CKD which is contributed by CKD progression and vitamin D deficiency.**

Keywords: Chronic Kidney Disease, hyperparathyroidism, intact Parathyroid hormone, vitamin D.

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I. Introduction

The toll of Chronic Kidney disease is increasing like other chronic diseases because of increasing health care facilities to more people and increasing life expectancy in the world. The prevalence of Chronic Kidney disease (CKD) in Pakistan is around 12.5% [1]. There is complex derangement of calcium, phosphorus, vitamin D, and parathyroid hormone with the progression of CKD which gives rise to a variety of bone diseases [2], [3]. The common bone disease of them is osteitis fibrosa cystica which is also known as a high bone turnover disease. Intact parathyroid hormone (iPTH) is always found raised (secondary hyperparathyroidism) [4]. The parathyroid gland in this condition usually undergoes diffuse hyperplasia. This is differentiated from tertiary hyperparathyroidism in CKD in which there is the typical nodular formation of the parathyroid gland due to long-standing and often untreated or undertreated secondary hyperparathyroidism [5], [6].

The optimal parathyroid hormone level in CKD is still in debate. According to K/DOQI, the optimal level of iPTH ranges as 35–70 pg/ml for stage 3 CKD, 70–110 pg/ml for stage 4, and 150–300 pg/ml for stage 5 and dialysis [7]. K-DIGO, on the other hand, emphasizes more on keeping calcium and phosphorus levels in the normal range in all CKD stages without commenting on iPTH until the patient requires dialysis therapy where iPTH levels have been maintained between 2 to 9 times of normal iPTH range [8]. The mineral bone axis remains more or less intact in CKD until the glomerular function rate (GFR) declines below 60 ml/kg/1.73^2. Nephrologists start intervening at this stage with a diet modification i.e. low phosphorus and potassium diet. Next to this is usually correction of vitamin D deficiency with the administration of nutritional vitamin D

(Cholecalciferol or Ergocalciferol) and addition of active vitamin D (Calcitriol) is usually suggested when iPTH is persistently above normal. In certain cases of secondary hyperparathyroidism, where serum calcium remains high then calcimimetics can be added along with other described measures. Tertiary hyperparathyroidism is the phenomenon of untreated/undertreated secondary hyperparathyroidism in which the parathyroid gland is no more responding to normal feedback mechanisms [9].

The Suffering of the patients increases many folds with the development of secondary hyperparathyroidism especially when it remains uncontrolled. The complications related with this are calcification of tissues leading to cardiovascular disease and bone fracture [10]-[13]. These complications can be prevented with timely recognition and intervention i.e. Diet modification, phosphate binding agents, correction of nutritional vitamin D deficiency, and addition of active vitamin D (Calcitriol) would help in reducing patients' suffering. Other than patient's suffering, a lot of cost can be saved when incidence of cardiovascular disease, bone disease would be declined.

II. Materials and Method

This observational study was conducted at the Indus Hospital, Karachi campus from Jan 2017 to Jan 2018. All the adults (age >14 years) of either gender with established chronic kidney disease (pre-dialysis) on regular follow-up consenting to participate in the study were included. All those patients were excluded who were taking vitamin D or calcium treatment and not requiring dialysis and not suffering from chronic liver disease. This was followed by detailed history and general physical examination and demographic details were documented.

Routine investigations i.e. serum creatinine (mg/dl), calcium (mg/dl), phosphorus (mg/dl), alkaline phosphatase, intact parathyroid hormone (iPTH) level (pg. /ml), vitamin D level (ng/ml), albumin (mg/dl) were carried out as per standard method used in biochemistry laboratory of The Indus Hospital and Health network. Parathyroid status was further categorized into three on basis of iPTH level as <150, 150 to 300, and >300 pg/ml to see how it is influenced by bone mineral profile (calcium, phosphorus, alkaline phosphatase, vitamin D, and albumin) after dividing them as normal, low and high.

Estimated glomerular filtration rate (GFR) was calculated using the four-variable modification of diet and renal disease (MDRD) equation. On basis of GFR, patients were categorized into five CKD stages, i.e.
CKD stage 1 (GFR>90ml/kg/1.732),
CKD stage 2 (GFR<90>60ml/kg/1.732),
CKD stage 3 (GFR<60>30ml/kg/1.732),
CKD stage 4 (GFR<30>15ml/kg/1.732),
CKD stage5 (GFR<15ml/kg/1.732). They were further classified as early CKD (CKD stage 1, 2, 3), and Late CKD (CKD stage 4, 5).

A. Statistical Analysis

Analysis was done using SPSS version 21. Mean ± SD/Median (IQR) were calculated for all the quantitative variables (age, height, weight, BMI, serum albumin, serum calcium, serum phosphate, alkaline phosphate and IPTH) as appropriate. Chi-square tests were applied as appropriate to find a significant association of various categorical variables (Gender, CKD categories, BMI, etc.) with parathyroid status and further stratified with early and late CKD with vitamin D status to see its influence on hyper parathyroid.

III. Results

There was a total of 265 patients in our study in which 145 (54.7%) were male and 120 (45.3%) were female. The mean age of patients was 53.94 ± 15.08 with a minimum of 15 and a maximum of 104 years. Out of 265 patients, 146 were found in late CKD while 119 were in early CKD. Mean values of all quantitative variables were analyzed with parathyroid status and found nothing significant in both normal and hyper parathyroid (Table I). When bone mineral profile and hyper parathyroid were compared after categorization, we found a statistically significant relationship between them (Table II).

The most prevalent comorbid was diabetes 151 (75.7%) followed by hypertension 74(24.3%) and only 5 (1.1%) had no comorbid. Hyper parathyroid (iPTH> 68 pg/ml) was seen in the majority of the patients 190 (71.2%). Out of these 190 patients, vitamin D deficiency was seen significantly in 142 (79.1%) patients with a p-value <0.001. The majority of hyperthyroid patients were found to be in late CKD 128 (87.7%) with a significant p-value <0.001 (Table III). There is no significance found when hyperparathyroidism was analyzed with gender, age group (old and less old) (Table III). In hyperthyroid patients, mean calcium, phosphorus, vitamin D were 8.98 ±0.86, 2.42 ± 1.09, and 9.11± 5.28.

TABLE I: BASELINE CHARACTERISTICS OF STUDIED POPULATION IN RELATION WITH PARATHYROID STATUS

	PARATHYROID STATUS						
	Normal n=75			Hyper n=190			
	Mean ± SD	Min-Max	Median (IQR)	Mean ± SD	Min-Max	Median (IQR)	p-Value
Age (year)	54.21 ± 12.26	16 – 80	55 (13)	52.29 ± 14.54	15-85	53 (17)	0.94
Height (m)	5.17 ± 0.587	4.11-6.80	5.2 (0.55)	5.27±0.492	4-6	5.2 (0.50)	0.33
Weight (kg)	60.33± 14.39	32-100	56 (23.15)	64.38 ± 14.63	29-112	64 (15.70)	0.74
BMI (kg/m^2)	23. 64± 5.85	14.95-39.81	23.50 (6.98)	26.24 ± 7.51	3-49.31	25.32 (8.25)	0.54
Serum Calcium (mg/dl)	9.46± 0.63	8.2-10.6	9.5 (0.85)	8.98 ±0.86	5.7-11	9.2 (0.90)	0.50
Serum Creatinine (mg/dl)	2.03 ± 0.64	1.2- 4.1	18 (0.80)	3.2 ± 2.05	1.2-13	2.5 (1.9)	0.19
Phosphate (mg/dl)	3.75 ± 0.68	2.2-5.5	3.7 (0.95)	2.42 ± 1.09	2.1-7.3	4.2 (1.3)	0.69
Alkaline phosphate	105.44 ± 72.33	47-402	90 (61.50)	138.47± 95.98	34-802	110 (71)	0.18
Albumin (mg/dl)	3.87 ± 0.64	2.4-4.8	4.1 (0.8)	3.75 ± 0.58	1.2-4.9	3.9 (0.7)	0.07
Vit.D (ng. /ml)	12.5 ± 5.86	3-23	12 (9.4)	9.11± 5.28	3-26	8.2 (7)	0.07

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TABLE II: RELATIONSHIP OF BONE MINERAL PROFILE WITH HYPERPARATHYROIDISM

	PARATHYROID STATUS			Total	P-Value
	iPTH<150	iPTH<150-300>	iPTH>300		
Calcium (mg/dl)					
Normal(<8.4-10.2>	137 (69.2%)	43 (21.7%)	18 (9.1%)	198 (100%)	
Low (<8.4)	15 (32.6%)	17 (37%)	14 (30.4%)	46 (100%)	0.001
High (>10.2)	17 (81%)	3 (14.3%)	1 (4.8%)	21 (100%)	
Total	169 (63.8%)	63 (23.8%)	33 (12.5%)	265	
Phosphorus (mg/dl)					
Normal <2.3-4.7>	132 (69.5%)	39 (20.5%)	19 (10%)	190 (100%)	
Low (<2.3)	3 (75%)	0 (0%)	1 (25%)	4 (100%)	0.017
High (>4.7)	34 (47.9%)	24 (33.8%)	13 (18.3%%)	71 (100%)	
Total	169 (63.8%)	63 (23.8%)	33 (12.5%)	265	
Alkaline Phosphase (mg/dl)					
Normal	149 (70.3%)	51 (24.1%)	12 (5.7%)	212 (100%)	
Low	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0.001
High	19 (36.5%)	12 (23.1%)	21 (40.4%)	52 (100%)	
Total	169 (63.8%)	63 (23.8%)	33 (12.5%)	265	
Albumin (mg/dl)					
Lower(<3.5mg/dl)	36 (51.4%)	24 (34.3%)	10 (14.3%)	70 (100%)	
Normal(>3.5 mg/dl)	133 (68.2%)	39 (20%)	23 (1.8%)	195 (100%)	0.031
Total	169 (63.8%)	63 (23.8%)	33 (12.5%)	265 (100%)	
Vitamin D Status (ng/ml)					
Normal	65 (83.3%)	9 (11.5%)	4 (5.1%)	78 (100%)	
Moderae Deficiency	52 (73.2%)	10 (14.1%)	9 (12.7%)	71 (100%)	0.001
Severe Deficiency	51 (44.3%)	44 (38.3%)	20 (17.4%)	115 (100%)	
Total	169 (63.8%)	63 (23.8%)	33 (12.5%)	265 (100%)	

TABLE III: BASELINE CHARACTERISTICS OF CATEGORICAL VARIABLE IN RELATION WITH PARATHYROID STATUS

	PARATHYROID STATUS		Total	P-Value
	Normal	Hyper		
Gender				
Male	48 (33.1%)	97 (66.9%)	145(100%)	0.075
Female	27 (22.5%)	93 (77.5%)	120(100%)	
Total	75 (28.3%)	190 (71.7%)	265	
Age Status				
Less Old (<55 Years)	38 (27.7%)	99 (72.3%)	137 (100%)	0.89
Old (>55 Years)	37 (28.9%)	91 (71.1%)	128(100%)	
Total	75 (28.3%)	190 (71.7%)	265	
CKD Status				
Early CKD	57 (47.9%)	62 (52.1%)	119 (100%)	
Late CKD	18 (12.3%)	128 (87.7%)	146 (100%)	0.001
Total	75 (28.3%)	190 (71.7%)	265	

TABLE IV: ASSOCIATION OF VITAMIN D WITH PARATHYROID STATUS STRATIFIED BY CKD STATUS

CKD Status	Vitamin D Status	Parathyroid Status		Total	P-Value
		Normal	Hyper		
Early	Normal	28 (66.7%)	14 (33.3%)	42	0.004
	Deficient	29 (37.7%)	48 (62.3%)	77	
Late	Normal	8 (22.2%)	28 (77.8%)	36	0.075
	Deficient	10 (9.1%)	100 (90.9%)	110	
Total	Normal	36 (46.2%)	42 (53.8%)	78	0.001
	Deficient	39 (20.9%)	148 (79.1%)	187	
	Total	75 (28.3%)	190 (71.7%)	265 (100%)	

When vitamin D status was compared with parathyroid status after stratification with CKD status, it was found that vitamin D deficiency was significantly associated with hyperparathyroidism in the case of early CKD (p-value 0.004) while no significance was seen in late CKD (Table IV).

IV. Discussion

Bone disease (osteodystrophy) is one of the complications of late CKD which is caused by multiple factors and associated with increased concentration of intact parathyroid hormone (iPTH). Decreased renal mass leading to decreased activation of vitamin D and subsequently decreased calcium absorption from the intestine coupled with retention of phosphorus are the main culprits behind developing secondary hyperparathyroidism [14]. This is the traditionally understood cascade of bone mineral derangement which usually starts when glomerular filtration rate (GFR) declines below 30 ml/min/1.73^2 (CKD 4) [15]. This results in a wide spectrum of bone diseases with commonly encountered one is osteitis fibrosa cystica (high bone turnover) where iPTH levels are raised. Other bone diseases are osteoporosis, osteomalacia (low bone turnover), and mixed bone disease [16]. We have found 190 (71.2 %) out of a total of 265 patients with hyperparathyroidism who were suffering from a variable degree of CKD. The majority of them were found

in late CKD. Diabetes mellitus was the most common comorbidity seen followed by hypertension.

The mean age of our studied population is about 54 years. Elias RM et al studied secondary hyperparathyroidism and found elderly (age>65 years) were at more risk of this complication than the young [17]. When we divided our studied population into age groups (old >55 years and less old <55 years) we did not find any difference regarding the risk of developing secondary hyperparathyroidism in both groups (Table III). However, [17] explained further regarding the possible contribution of other factors i.e. use of furosemide, baseline calcium, and vitamin D status which might be confounding or contributing factors beyond his finding. He recommended those factors should be studied more. Reference [18] also got our attention regarding the potentiality of loop diuretic causing raised parathyroid. In [18], low GFR is the most important predictor of causing secondary hyperparathyroidism. In our study, we have also found a significantly increased ratio of hyper parathyroid to normal parathyroid with the progression of CKD (Hyperparathyroidism increased with worsening of CKD). Mean iPTH remains above normal in all CKD stages with more increase in CKD 5. This signifies the development of secondary hyperparathyroidism when nephron mass declines substantially. Phosphorus levels also increased with the severity of chronic kidney disease. Reference [19] studied the CKD population with a bit lower mean age of 44 years and found hyperparathyroidism in 55.2%. The majority of them were found to be in the advanced CKD stage similar to ours. Reference [20] found 40% hyperparathyroidism in CKD stage 3 and 80% in CKD 4.

Vitamin D deficiency is another cause of secondary hyperparathyroidism other than CKD [21]. Comparing the results with a study done by SM Kim, diabetes came as not only the most common causative agent of chronic kidney disease, but vitamin D deficiency was also seen in a higher proportion in diabetic than in non-diabetic [22]. We have found vitamin D deficiency in a significant proportion (70.4%) in our population as per cut-off level < 25 ng/ml. In the early stages of CKD, the influence of vitamin D deficiency has been found for the development of hyperparathyroidism but was not in late CKD (Table IV). This suggests that the development of secondary hyperparathyroidism is independent of vitamin D status when CKD has progressed beyond stage 3 (GFR<30 ml/kg/173^2. This fact helps us in understanding that when nephron mass decreases to a certain degree where replenishment of nutritional vitamin D deficiency does not help in controlling raised iPTH (secondary hyperparathyroidism). But at the same time, this inference should not be taken against the vitamin D replenishment as per its established beneficial role in the body's immune system and cardiovascular health [23].

The biggest fear in secondary hyperparathyroidism is not only limited to bone disease (osteodystrophy), but with time, the risk of cardiovascular disease becomes multifold due to vascular calcification [24], [25]. Most CKD patients die from heart disease more than renal disease because of accelerated atherosclerosis due to this calcification [26], [27]. To overcome this devastating complication in the wake of progressing CKD, timely corrective measures are necessary.

V. Conclusion

Secondary hyperparathyroidism is significantly present among CKD patients and its prevalence increases with the progression of CKD. Vitamin D deficiency contributes to its prevalence in early stages of CKD but not late. A significant morbidity and mortality are associated with secondary hyperparathyroidism. A judicious approach is needed to overcome this complication. In the early stages of CKD, correction of vitamin D deficiency, low phosphorus diet with the addition of phosphate binder if serum phosphorus is raised and in later stages, addition of active vitamin D (calcitriol) with or without the use of calcimimetics may help to overcome complications.

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