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Predictors of Secondary Hyperparathyroidism in Chronic Kidney Disease Stage 3 and 4

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Abstract

Background: The secondary hyperparathyroidism (SHPT) develops early in the course of chronic kidney disease (CKD) and becomes more prominent as kidney function declines. This study aimed at evaluation of the predictors of SHPT in stage 3 and 4 chronic CKD from two Hospitals in Basrah.

Patients and Methods: A cross-sectional observational study in two hospitals in Basrah, from February to September 2016, involving treatment free predialysis 18-69 years patients of stage 3 and 4 CKD, with eGFR of (15- 59 ml/min/1.73 m^2), and not known to have primary hyperparathyroidism. This study involved 84 patients with CKD equal gender distribution. There were 40 patients in stage 3 and 44 patients in stage 4 CKD. Then we measure hemoglobin (Hb), mean corpuscular volume (MCV), 25-hydroxyvitamin D, creatinine, calcium, phosphate, and parathyroid hormone (PTH).

Results : The most powerful predictors for SHPT in our study were the CKD stage and the hypocalcemia. This study showed that serum calcium level is significantly lower in patients with SHPT. There is an inverse relationship between the CKD stage and the development of SHPT. Although estimation of 25-hydroxyvitamin D is critical in predialysis CKD patients, there was no significant association to SHPT. The nondiabetics had higher mean PTH level (pg/ml) compared with diabetic patients (165.36 ± 129.35 vs. 145.64 ± 127.53) but had no statistical significance. There was no significant association between both the gender and anemia to SHPT.

Conclusion: The hypocalcemia and the CKD stage were the most powerful predictors for the SHPT in the predialysis CKD patients.The gender, phosphate level, 25-hydroxyvitamin D level, the degree of anemia, and being diabetics did not show significant relation to future prediction of SHPT.

Keywords: Stages of chronic kidney diseases; Secondary hyperparathyroidism; Hypocalcaemia

Introduction

The secondary hyperparathyroidism (SHPT) develops early in the course of chronic kidney disease (CKD) and becomes more prominent as kidney function declines [1]. Predialysis patients by far outnumber those undergoing maintenance dialysis, but the impact on mortality is unknown [2]. Some epidemiological studies indicate that CKD-related bone loss with associated extra skeletal calcification may cause an increase in the cardiovascular morbidity and mortality [2-5], and adversely influences their quality of life [3]. The SHPT is reported to increase as the CKD progresses from 40% in stage 3 to more than 80% in stage 5 CKD [3].

Predialysis patients do not usually show any changes in their serum calcium and phosphate levels, and their parathyroid hormone (PTH) levels may be slightly higher than reference values [6,7]. These biochemical abnormalities, together with vitamin D dysregulated metabolism and deranged bone turnover, constitute the CKD mineral and bone disorder (CKD-MBD) [3], and being a major uremic toxin; the PTH may be responsible for long-term consequences in CKD [1]. Renal osteodystrophy (ROD) defines the presence of altered bone structure and composition in CKD, and it is one aspect of CKD-MBD, a multi-system disease entity involving abnormalities of mineral metabolism, ROD, and extraskeletal calcification [4,8].

The SHPT manifests as one of two types of ROD: either a high turnover state (osteitis fibrosa) or as mixed uremic osteodystrophy with low bone turnover [9]. The disease burden here includes fibrosis of the bone marrow that can exacerbate the anemia of CKD; abnormal mineralization of bones; bone pain; muscular complaints; spontaneous rupture of the tendons, pruritus, fractures, vascular calcification [9], alterations in cardiovascular structure and function, and immune dysfunction [1].

The increased bone turnover is dominant in CKD stages 3-4 with 90% of the ROD case load as determined by bone biopsy, in contrast to the decreased bone turnover disease which is prevalent in stage 5 CKD [10]. The integration of phosphorus in the pathophysiology of SHPT is related to abnormal mineral metabolism [4,11-16].

The aim of the study is the evaluation of the predictors of secondary hyperparathyroidism in stage 3 and 4 chronic kidney diseases in two hospitals in Basrah.

Patients and Methods

Patients selection

A cross-sectional observational study was implemented in (Basrah and Faiha General Hospitals) in Basrah, Southern of Iraq, from February to September 2016, involving patients attending outpatient and inpatient Medical Departments for clinical evaluation of CKD. The ethical approval included an informed consent from each patient. Primarily, we registered the age, gender, and history of type 2 diabetes mellitus (DM) currently on treatment.

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The enrolment criteria were:

- Aged 18-69 years and met the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) For CKD: Evaluation, Classification, and Stratification, with estimated glomerular filtration rate (eGFR) of (15-59 ml/min/1.73 m^2) i.e. the CKD stage 3 and 4. We use 2009 Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI Creatinine 2009 Equation) for eGFR evaluation which is the recommended by NKF [11,17].
- Not known to have primary hyperparathyroidism.
- Those on no treatment for the last three months (vitamin D supplement, bisphosphonates, calcium or phosphorus binders).

There were 125 patients agreed to participate in this study after they gave written informed consent. We excluded (41 patients); (32 patients) with eGFR less than (15 ml/min /1.73 m^2), and the remaining with an eGFR >60 ml/min /1.73 m^2. The ultimately enrolled patients were 84 patients with (42 males and 42 females). Consequently, the stage of CKD is the basis to divide the patients into two groups with an equal gender distribution: Forty-patients stage 3 CKD (G3) with an eGFR of (30-59 ml/min/1.73 m^2) and forty-four patients stage 4 CKD (G4) with an eGFR of (15–29 ml/min/1.73 m^2).

Blood specimens collection

Blood sampling for measurement of the serum creatinine, hemoglobin (Hb) analysis, mean corpuscular volume (MCV), corrected serum calcium, albumin, phosphorus level, 2,5-hydroxyvitamin D, and PTH were done in the morning.

After sterilization of the cubital area, 10 ml of blood was drawn and put in EDTA tube and clot activator tube. From the blood sample in the EDTA tube, the complete blood count (CBC) was analyzed by (Cell-Dyn Ruby Germany 0001700), with a reference range of 11.5–16.5 g/dl for Hb and 75–100 fL for MCV.

The lab techniques included: Beckman-Coulter Unicell DXC 600Synchron® Clinical System, and Biolyzer 300 Analyticon for the serum creatinine analysis, phosphorus, and calcium. Cobas E411 Analyzer for PTH analysis. Maglumi 1000 Analyzer for 25-hydroxyvitamin D.

Normal values (according to KDIGO) were serum creatinine 0.57–1.25 mg/dL; phosphorus 2.3–4.7 mg/dL; calcium 8.4–11.2 mg/dL; PTH 15- 65 pg/mL; and for 25-hydroxyvitamin D>30 ng/dL and anemia when the Hb concentration is <13.0 g/dL in males and <12.0 g/dl in females [9].

Statistical Analysis

Data were tested using IBM SPSS statistical software version 22.0 for Windows (SPSS Incorporation, Chicago, Illinois, USA), with many continuous and categorical variables, so we used the mean value ± SD for the description of the continuous variables and the frequency and percentage for the categorical variables.

Univariate analysis of variance and nominal regression analysis were used for assessing significance between the possible predictors. Receiver operating characteristic (ROC) curves was used to measure sensitivity and specificity of each predictor, and the cut point at which there were maximal sensitivity and specificity. The study adopts the two-tailed probability values with (p-value) ≤ (0.05) to be statistically significant.

Results

The mean cohort age was 52.8 ± 12.4 years (53.6 ± 10.08 years for the G3, and 52.04 ± 14.3 years for the G4) as seen in Table 1. There were 46 (54.8%) patients with age ≥ 55 years, 20 (23.8%) patients in G3 and 26 (31.0%) patients in G4, while the rest of the cohort were <55 years of age.

The mean PTH levels were 153.80 ± 127.80 pg/mL for the entire groups (in G3 106.9 ± 89.5 pg/mL, and in G4 196 ± 142.7 pg/ mL). There were 48(57.1%) patients with SHPT of the total study groups, 15(17.9%) of whom in G3 and 33 (39.3%) in G4, with mean PTH levels in the males were 116.85 ± 108.22 pg/mL and of the females 190.86 ± 136.34 pg/mL. There were 49 patients with DM (58.3%), 27 patients in G3 (32.1%), and 22 patients in G4 (26.2%).

The gender, age, level of Hb and MCV, being diabetic and even 25-hydroxyvitamin D level failed to show any statistical significance to the development of SHPT using the univariate analysis of variance (Table 2).

The total means serum calcium (mg/dL) was 8.23 ± 0.94, with hypocalcemia in 46 (54.6%) patients (8.44 ± 0.94 for 15 in G3 patients, and 8.01 ± 0.85 for 31 in G4 patients. The hypocalcemia was a powerful predictor for SHPT, with an inverse correlation to SHPT, with excellent sensitivity (92.9%) and specificity (87.1%) for SHPT, (Tables 2 and 4 and Figure 1); at a PTH Cut-off value of 67.25 pg/mL.

The mean serum creatinine (mg/dL) of the whole groups was 2.46

Characteristics		N (%)	eGFR (ml/min/1.73 m^2)	
			G3	G4
N		**84**	**40**	**44**
Age (years)	Mean years (SD)	52.82 (12.43)	53.67 (10.08)	52.04 (14.33)
	≥ 55 N (%)	46 (54.76)	20 (23.80)	26 (30.95)
	<55 N (%)	38 (45.23)	20 (23.80)	18 (21.42)
Gender N (%)	Male	42 (50)	20 (23.80)	22 (26.19)
	Female	42 (50)	20 (23.80)	22 (26.19)
Serum creatinine mg/dl Mean (SD)		2.46 (0.97)	1.62 (0.27)	3.23 (0.70)
Mean eGFR mL/min/1.73 m^2 (SD)		30.26 (13.91)	42.62 (8.93)	19.02 (5.49)
History of Diabetes Mellitus N (%)		49 (58.33)	27 (32.14)	22 (26.19)
Investigations	Mean PTH pg/ml (SD)	153.85 (127.87)	106.94 (89.57)	196 (142.77)
	Serum calcium mg/dL (SD)	8.23 (0.91)	8.44 (0.94)	8.01 (0.85)
	Serum 25-hydroxyvitamin D ng/mL (SD)	26.33 (8.63)	25.86 (8.10)	26.81 (9.10)
	Serum Phosphorus mg/dl (SD)	4.62 (1.24)	4.12 (1.02)	5.06 (1.27)
	Mean Hb g/dL (SD)	9.90 (2.54)	10.33 (2.45)	9.52 (2.52)
	Mean MCV fL (SD)	84.24 (10.71)	85.46 (9.92)	83.13 (11.38)

Table 1: Description of patient's characteristics according to eGFR levels.

± 0.97 (for the G3 group it was 1.6 ± 0.27, and for the G4 group it was 3.2 ± 0.7. The whole groups mean eGFR (ml/min/1.73m^2) was 30.26 ± 13.91, and for the G3 group 42 ± 8.9, while for the G4 19 ± 5.40. There was a robust significant correlation between the G4 CKD and the SHPT, with a moderate sensitivity (67.1%) and acceptable good specificity (75%), (Tables 2-4 and Figure 2), at a PTH Cut-off value of 104.5 pg/mL.

Mean serum phosphorus level (mg/dL) was 4.62 ± 1.24 (4.12 ± 1.02 mg/dL in G3 and 5.06 ± 1.20 mg/dL in G4) with hyperphosphatemia that is evident in 46 patients; 18 (21.4%) of G3 group and 28 (33.4%) of G4. The hyperphosphatemia failed to show significant statistical association to the development of SHPT due to extremely very high odds ratio that is statistically unacceptable using univariate analysis of variance or nominal regression analysis.

The means 25-hydroxyvitamin D level (ng/dL) in both groups is 26.3 ± 8.6, (25.8 ± 8.1 for G3 patients, and 26.8 ± 9.4 for G4 patients) with reduced 25-hydroxyvitamin D in 50(59.5%) patients(23[57.5%] of whom in the G3, and 27[61.3%] patients in the G4). Again, the level of 25-hydroxyvitamin D had shown no statistically significant association to the development of SHPT (Table 2).

Parameter	B	p	95% Confidence Interval	
			Lower Bound	Upper Bound
CKD Stage	-77.757-	0.007	-132.734-	-22.781-
History of DM	23.626	0.436	-36.877-	84.128
Hypocalcemia	80.949	0.033	7.026	154.872
Hyperphosphatemia	109.042	0.003	39.917	178.166
Alkaline Phosphatase	2.127	0.952	-68.959-	73.214
Low MCV	43.880	0.213	-25.976-	113.737
Presence of anemia	-43.173-	0.177	-106.538-	20.191
Low 25-hydroxyvitamin D	3.714	0.898	-54.467-	61.894
Age	-9.374-	0.757	-69.809-	51.062
Male Sex	-40.538-	0.160	-97.636-	16.560

Table 2: Univariate analysis of variance.

Parameter	B	p	Exp(B)	95% Confidence Interval for Exp(B)	
				Lower Bound	Upper Bound
CKD Stage	-21.771-	0.0001	3.507E-10	2.910E-11	4.226E-9
Hypocalcemia	4.270	0.002	71.532	4.845	1056.193
Hyperphosphatemia	24.126	.	30042114376.814	30042114376.814	30042114376.814
*Secondary hyperparathyroidism					

Table 3: Nominal regression analysis of predictors of SHPT.

Predictors	AUC	Asymptomatic Significance	Asymptomatic 95% Confidence Interval		1-Specificity %	Sensitivity %	Cut-off value
			Lower	Upper			
Serum calcium	0.942	3.9798E-12	0.891	0.992	87.1	92.9	67.2
G4 CKD	0.712	0.001	0.601	0.823	75.0	67.1	104.5

Table 4: SHPT predictor's evaluation using ROC curves.

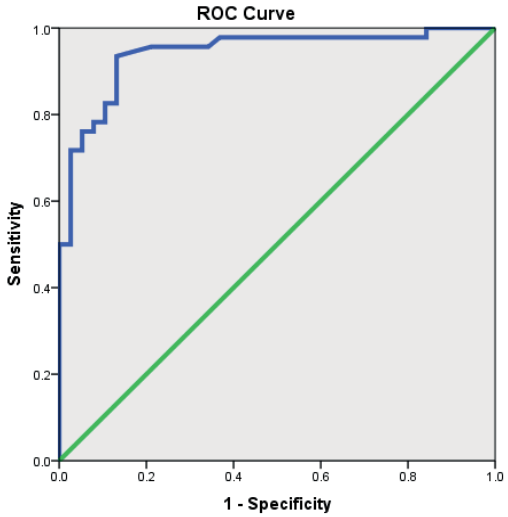

Figure 1: ROC curve (Hypocalcemia vs. SHPT).

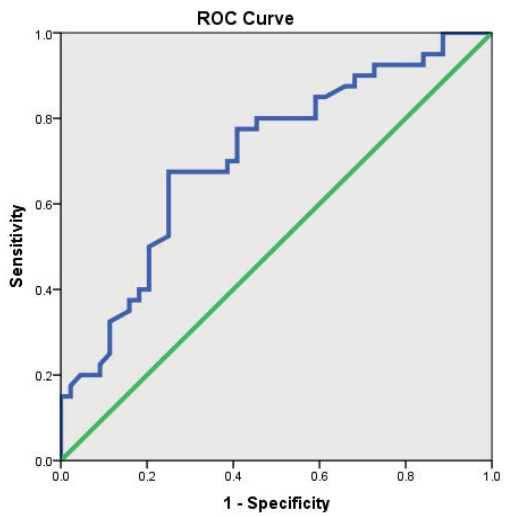

Figure 2: ROC curve (CKD Stage vs. SHPT).

The mean Hb level (g/dL) was 9.9 ± 2.5, with 61 (72.6%) anemic patients (35 [41.7%] of whom in the G3, and 26 (30.9%) patients in the G4. The mean MCV (fL) was 84.2 ± 10.7 for the total study groups (85.4 ± 9.9 for the G3 and 83.1 ± 11.3 for the G4 group). There were 15 (17.8%) patients with microcytosis, six (15.0%) of whom in the G3, and nine (20.45%) patients in the G4 group. The Hb level and the degree of microcytosis had shown no statistically significant association to the development of SHPT (Table 2).

Discussion

The early prediction of SHPT in CKD patients and the detection of the possible predictors can be useful to prevent future bone changes in advanced states [11], and even future early mortality [2]. This study demonstrated the effect of different predictors on the development of SHPT in predialysis patients.

Hypocalcemia is a chief factor affecting PTH secretion in patients with CKD [11,14,17]. This study showed that serum calcium level was significantly lower in SHPT with an odds ratio (71.532), which was similar to many studies worldwide [2,3,15]. The key explanation may be because calcium level (ionized) is directly suppressed PTH by triggering the calcium-sensing receptors in the parathyroid cells [14], and indirectly affect PTH secretion by lowering $1,25(OH)_2D$ production; which inhibits PTH production by an incompletely understood negative feedback mechanism [11,12]. So, when short-term variations in calcium-regulated PTH secretion are insufficient to maintain the ionized calcium concentrations fully, additional compensatory responses are invoked to restore baseline values [14]. However, the serum calcium levels are often, but not steadily, abnormal with GFR reduction [4,11,17].

The second significant predictor for SHPT is the stage of CKD using the nominal regression analysis. There was an inverse relationship between these two variables in this study. Onset, severity, the prevalence of bone disease, bone mineral metabolism, and SHPT are related to the GFR level below (60 mL/ min/1.73 m^2) [18].

Although hyperphosphatemia appears to be principally crucial in the SHPT development, the complication often occurs earlier in stage 3 CKD, even before the hyperphosphatemia occurs [10-13,19-21]; the study could not prove that the hyperphosphatemia is a predictor for the development of SHPT, because of the extremely high OR using the univariate and nominal regression analyses.

There is an inverse non-significant relation between the DM and development of SHPT that the nondiabetic patients have a higher mean PTH compared with diabetic patients (165.36 ± 129.35 vs. 145.64 ± 127.53) pg/ml, with a very high odds ratio of, which was comparable to Ashuntantang et al. [15]. The hyperglycemic state causes low-normal osteocalcin, and a suppressed osteoblasts function in diabetic patients [5,16,17]. As PTH stimulates bone turnover by directly acting on osteoblasts [5], the response of osteoblasts to PTH may be impaired in the hyperglycemic state [15,16]. On the other hand, insulin has an anabolic effect on osteoblasts [8]. DM might have markedly deleterious effects on parathyroid and bone. Poorer vitamin D status might be partly responsible for functional and structural changes in DM [18].

No statistically significant association was seen between anemia and the level of microcytosis and the development of SHPT that was similar to the results of Vhora et al [22]. Again, as with anemia; there was no statistically significant association between gender and the SHPT, and this was similar to Levin et al. [18]. Gender has had no significant effect on SHPT in G3 and G4 CKD patients in our cohort. However, higher PTH was more commonly observed in females compared with males, suggesting that there is a gender difference in the development of SPTH. The raised estrogen and estrogen receptor expression upregulate the mRNA expression levels of PTH in parathyroid cells, which may explain that difference. On the other hand, estrogens have nephroprotective effects which are lost substantially after menopause [3,18].

The KDIGO guidelines suggest that the SHPT due to CKD is age-related [11], which is similar to our study result that 70% of our cohort were elderly with more than half with SHPT. We could not deduce any significant relationship between age and the future SHPT that may be due to our small sample size. Vhora [22] and Kumchev et al. [23-25] had the same results of nonsignificant correlation of age to the SHPT and investigated similar age ranges and means, concluding that it was statistically not significant when compared with the prevalence of SHPT in other study groups.

Study Limitation

The small study sample, study design, and 70% of the sample is ≥ 55 years old were the main study limitations. The results were from single Center, therefore generalization of the results were not feasible.

Conclusions

After adjustment for all variables using the univariate analysis of variance and the nominal regression analysis, the main predictors for the SHPT were hypocalcemia and the stage of CKD. The gender, phosphate level, 25-hydroxyvitamin D level, the degree of anemia, and being diabetics did not show significant relation to future prediction of SHPT.

Author Contribution

Both authors contributed equally to the study.

Discloser

Non.

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