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Biological profile of secondary hyperparathyroidism in chronic renal failure patients

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Abstract

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease, especially in hemodialysis patients. It is characterized by overproduction of parathyroid hormone in response to chronic deterioration of renal function. The aim of this retrospective study was to determine the average time to develop secondary hyperparathyroidism, analyze the initial phosphocalcic profiles, and evaluate the evolution of these profiles in hemodialysis patients, following the recommendations of the KDOQI 2003 and KDIGO 2009 groups.

The study included 134 hemodialysis patients from two private dialysis centers. Data were collected from patients' medical records and analyzed using SPSS software. The results showed that the average time to develop secondary hyperparathyroidism was 3.15 years according to KDOQI recommendations and 4.64 years according to KDIGO recommendations based on parathyroid hormone levels.

The initial assessment revealed an imbalance in phosphocalcic metabolism in approximately 20.1% to 22.5% of patients, a proportion that increased to 27.5% during follow-up, according to both sets of recommendations.

In conclusion, secondary hyperparathyroidism is an inevitable complication of chronic kidney disease, affecting the vital and functional prognosis of hemodialysis patients. Diagnosis primarily relies on parathyroid hormone levels, associated with phosphocalcemia, vitamin D, and PAL analyses. Treatment aims mainly to maintain blood levels of calcium, phosphorus, and vitamin D within recommended limits and to reduce parathyroid response to phosphocalcic disturbances.

Keywords: Secondary hyperparathyroidism; Chronic renal failure; Hemodialysis Phosphocalcic; KDOQI and KDIGO guidelines

1. Introduction

Secondary hyperparathyroidism (SHPT) is one of the most common forms of mineral and bone disorders in chronic kidney disease (CKD), particularly in hemodialysis (HD) patients [1]. It involves the over-secretion of parathyroid hormone, reactive to disturbances in phosphocalcic metabolism (hypocalcemia, hyperphosphatemia, and decreased calcitriol synthesis) in response to chronic renal function deterioration. According to the KDOQI (Kidney Disease Outcomes Quality Initiative) 2003 and KDIGO 2009 (Kidney Disease: Improving Global Outcomes) recommendations, SHPT requires close biological monitoring and early preventive and therapeutic medical management to keep PTH values and phosphocalcic metabolism parameters within recommended ranges, as it increases the risk of morbidity and mortality, mainly related to the development of osteoarticular and cardiovascular complications [2,3].

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The objectives of our study are as follows

- Determine the average time of onset of secondary hyperparathyroidism in hemodialysis patients.
- Specify the initial phosphocalcic profiles of SHPT based on both KDOQI 2003 and KDIGO 2009 recommendations.
- Define recent evolving profiles of SHPT observed during their management and evaluate the compliance rates of biological parameters with K/DOQI and K/DIGO recommendations.

2. Material and methods

Our study is a retrospective descriptive and comparative study involving 134 cases of hemodialysis patients from two private dialysis centers (30 cases at the Marrakech center and 104 cases at the Atlas center), who underwent phosphocalcic assessments and PTH assays at the Avicenna Military Hospital in Marrakech.

Patients were randomly selected from a list of PTH data dated between 2014-2017, and those who had been on hemodialysis for more than 6 months and whose PTH values were above 300 ng/l during their biological follow-up were included. Patients with pre-existing SHPT before starting hemodialysis and deceased patients were excluded from our sample.

Information collection was done using an exploitation form established and filled out from the medical records of dialyzed patients and patient interviews. All data were subsequently entered and analyzed using SPSS software (version 22).

3. Results

In our series, the mean age of our patients was 59.16 ± 12.76 years, with extremes ranging from 21 to 87 years. A maximum frequency was predominant in the age group between 50 and 65 years.

There were 51.5% female and 48.5% male patients, with a sex ratio (female/male) of 1.06.

The mean duration of hemodialysis was 8.6 ± 5.2 years, with 88.1% of cases receiving 3 sessions per week and 11.9% receiving 2 sessions per week.

The mean duration of development of SHPT was 3.15 years according to KDOQI and 4.64 years according to KDIGO based on parathyroid hormone levels.

3.1. Initial Biological Assessment

The average PTH level was 593.11 ± 321.25 ng/l according to K/DOQI. We noted:

- 62.7% of cases had PTH levels in the range [300-585]
- 29.9% of cases had PTH levels between [585 and 1000]
- 7.4% of cases had very high PTH levels above 1000 ng/l

The average PTH was 823±270.9 ng/l according to K/DIGO.

- Among the 111 cases that revealed a PTH above the range recommended by KDIGO, it was noted that 84.7% of patients had a PTH level between [585-1000], and 15.3% of cases had values above 1000 ng/l.

Table 1 Initial Biological Assessment Based on PTH Level (ng/l) According to K/DOQI

PTH (ng/l)		**K/DOQI**			
		[300-585]	**[585-1000]**	**>1000**	**Total**
CALCEMIA	Hypocalcemia	33 (39.3%)	16 (40.0%)	4 (40.0%)	53 (39.6%)
	Normocalcemia	35 (41.7%)	13 (32.5%)	1 (10.0%)	49 (36.6%)
	Hypercalcemia	16 (19.0%)	11 (27.5%)	5 (50.0%)	32 (23.9%)
PHOSPHATEMIA	Hypophosphatemia	12 (14.3%)	8 (20.0%)	1 (10.0%)	21 (15.7%)
	Normophosphatemia	19 (22.6%)	7 (17.5%)	1 (10.0%)	27 (20.1%)
	Hyperphosphatemia	53 (63.1%)	25 (62.5%)	8 (80.0%)	86 (64.8%)
PHOSPHO-CALCIUM PRODUCT	Normal	70 (83.3%)	32 (80.0%)	5 (5.0%)	107 (79.9%)
	High	14 (16.7%)	8 (20.0%)	5 (50.0%)	27 (19.1%)
VITAMIN D	Normal	7 (27.0%)	2 (20.0%)	1 (10.0%)	10 (24.4%)
	Insufficiency	8 (30.7%)	1 (10.0%)	0 (0%)	9 (22.0%)
	deficiency	11 (42.3%)	7 (70.0%)	4 (90.0%)	22 (53.6%)

Table 2 Initial biological assessment according to PTH levels (ng/l) according to K/DIGO

PTH (ng/l)		**K/DIGO**		
		[585-1000]	**>1000**	**Total**
CALCEMIA	Hypocalcemia	32 (34.0%)	7 (41.2%)	39 (35.1%)
	Normocalcemia	54 (57.5%)	7 (41.2%)	61 (55.0%)
	Hypercalcemia	8 (8.5%)	3 (17.6%)	11 (9.9%)
PHOSPHATEMIA	Hypophosphatemia	6 (6.4%)	1 (5.9%)	7 (6.3%)
	Normophosphatemia	48 (51.1%)	6 (35.3%)	54 (48.6%)
	Hyperphosphatemia	40 (42.5%)	10 (58.8%)	50 (45.1%)
PHOSPHO-CALCIUM PRODUCT	Normal	74 (92.5%)	12 (70.6%)	86 (77.5%)
	High	20 (7.5%)	5 (29.4%)	25 (22.5%)
VITAMIN D	Normal	7 (21.2%)	2 (25.0%)	9 (22.0%)
	Insufficiency	7 (21.2%)	0 (0%)	7 (17.1%)
	deficiency	19 (57.6%)	6 (75.0%)	41 (61.0%)

3.2. Final biological assessment

The mean PTH level was 697.2±686.26 ng/l.

- According to KDOQI
  - 14.2% of cases met the PTH target.

However, the following observations were made:

- 27.6% of cases showed elevated PTH levels between]300-585].
- 28.4% of cases had elevated PTH levels between]585-1000].
- 17.9% of cases had very high PTH values above 1000 ng/l.
- 11.9% of cases had low PTH levels between [0-150].
- According to KDIGO:

- 41.8% of cases had PTH levels in line with KDIGO recommendations.

The following observations were made:

- 11.9% of cases had low PTH levels between [0-130].
- 28.4% of cases had elevated PTH levels between]585-1000].
- 17.9% of cases had very high PTH values above 1000.

Table 3 Final biological assessment based on PTH levels (ng/l) according to K/DOQI

PTH (ng/l)		K/DOQI					
		[0-150]	**[150-300]**	**[300-585]**	**[585-1000]**	**>1000**	**Total**
CALCEMIA	Hypocalcemia	3(18.7%)	1 (5.2%)	6 (16.2%)	6 (15.8%)	0 (0.0%)	16 (12.0%)
	Normocalcemia	6(37.5%)	9 (47.4%)	19(51.4%)	16 (42.1%)	11(45.8%)	61 (45.5%)
	Hypercalcemia	7(43.8%)	9 (47.4%)	12(32.4%)	16 (42.1%)	13(54.2%)	57 (42.5%)
PHOSPHATEMIA	Hypophosphatemia	4(25.0%)	4 (21.1%)	7 (18.9%)	4 (10.5%)	3(12.5%)	22 (16.4%)
	Normophosphatemia	8(50.0%)	13(68.4%)	21(56.7%)	18 (47.4%)	9 (37.5%)	69 (51.5%)
	Hyperphosphatemia	4(25.0%)	2 (10.5%)	9 (24.4%)	16 (42.1%)	12(50.0%)	43 (32.1%)
PHOSPHO-CALCIUM PRODUCT	Normal	12(75.0%)	18(94.7%)	29(78.4%)	27 (71.1%)	11(45.8%)	97 (72.4%)
	High	4 (25.0%)	1 (5.3%)	8 (21.6%)	11 (28.9%)	13(54.2%)	37 (27.6%)
VITAMIN D	Normal	9 (56.3%)	7 (36.8%)	15(40.5%)	22 (57.9%)	9 (37.5%)	6 (46.3%)
	Insufficiency	1 (6.3%)	9 (47.4%)	12(32.4%)	11 (28.9%)	8 (33.5%)	41(30 .6%)
	Deficiency	6 (37.5%)	3 (15.8%)	10(27.0%)	5 (13.2%)	7 (29.2%)	31 (23.1%)

Table 4 Final biological assessment based on PTH levels (ng/l) according to K/DIGO

PTH (ng/l)		**K/DIGO**				
		[0-130]	**[130-585]**	**[585-1000]**	**>1000**	**Total**
CALCEMIA	Hypocalcemia	3 (18.8%)	10(17.9%)	6 (15.8%)	1 (4.2%)	20 (14.9%)
	Normocalcemia	9 (56.3%)	38(67.9%)	25 (65.8%)	18 (75.0%)	90 (67.2%)
	Hypercalcemia	4 (25.0%)	8 (14.3%)	7 (18.4%)	5 (20.8%)	24 (17.9%)
PHOSPHATEMIA	Hypophosphatemia	3 (18.8%)	5 (8.9%)	2 (5.3%)	2 (8.7%)	12 (9.0%)
	Normophosphatemia	7 (43.8%)	35(62.5%)	17 (44.7%)	7 (26.1%)	66 (49.3%)
	Hyperphosphatemia	6 (37.5%)	16(28.6%)	19 (50.0%)	15 (62.5%)	56 (41.8%)
PHOSPHO-CALCIUM PRODUCT	Normal	12(75.0%))	47(83.9%)	27 (71.1%%)	11 (45.8%)	97 (72.4%)
	High	4 (25.0%)	9 (16.1%)	11 (28.9%)	13 (54.2%)	37 (27.6%)
VITAMIN D	Normal	8 (50.0%)	23(41.1%)	22 (57.9%)	9 (37.5%)	62 (46.3%)
	Insufficiency	2 (12.5%)	20(35.7%)	11 (28.9%)	8 (33.3%)	41 (30.6%)
	Deficiency	6 (37.5%)	13(23.2%)	5 (13.2%)	7 (29.2%)	31 (23.1%)

4. Discussion

The development of secondary hyperparathyroidism is the most striking biological manifestation of CKD. It results from multiple intertwined factors, the earliest of which is phosphate retention due to reduced nephron mass [4].

Given that PTH is the primary hypercalcemic and hypophosphatemic hormone, the diagnosis of SHPT currently relies on measuring parathyroid hormone (PTH). While monitoring requires biological follow-up of serum calcium, phosphate, 25-hydroxyvitamin D, and sometimes bone biopsy.

4.1. Reference values in normal subjects

Normal values reported in package inserts range from 6.2 to 29 pg/mL for the lower range to 16 to 97 pg/mL for the higher range, confirming a possible dispersion of results depending on the assays used [5].

4.1.1. Target values in CKD

The K/DOQI guidelines from 2003 recommend fixed concentration ranges for PTH in dialysis patients, with target values between 150 and 300 pg/mL, regardless of the type of assay or kits used. In contrast, the 2009 KDIGO recommendations adopted a more flexible approach, acknowledging possible variations in reference values depending on the measuring device [1,6,7].

The PTH goal in dialysis patients was between two and nine times higher than normal, associated with normal serum phosphate and calcium levels in a normal subject.

Our patients developed SHPT after a mean dialysis duration of 3.15±4.02 years according to KDOQI recommendations and 4.6±4.3 years according to KDIGO.

All studies reported in Table (V) followed the KDIGO 2009 recommendations and noted a development duration of hyperparathyroidism around 4 to 5 years after the start of dialysis.

Table 5 The average duration of development of HTPS in the literature according to KDIGO

Isouani et al (rabat) [8]	4,9 ±2 ans
Cherkaoui et al (rabat) [9]	5±2 ans
Hanae et al (dakar) [10]	3,68±2,3 ans
Notres série	4,6±4,3 ans

The management of secondary hyperparathyroidism (HPTS) aims to normalize calcium levels, vitamin D concentration, phosphorus levels, parathyroid hormone (PTH), and maintain bone mass while limiting the risks of fractures, cardiovascular calcifications, and mortality.

4.2. Combatting Phosphate Retention

4.2.1. Dietary Management

Hemodialysis patients should avoid industrially processed products rich in preservatives, phosphate-rich sodas, and limit animal protein intake. It is also recommended to vary protein sources. [11,12]

4.2.2. Phosphate Binders

Phosphate binders decrease phosphate absorption, converting it into an insoluble form excreted in feces. To maximize effectiveness, they should be taken with phosphate-containing meals. The 2017 KDIGO guidelines highlighted the use of calcium-based binders in patients without hypercalcemia due to their affordability but recommended limiting their use in the presence of vascular calcifications, adynamic bone disease, or continuously low PTH levels. [10,13]

4.3. Maintaining Calcium, Vitamin D, and PTH within Recommended Levels

4.3.1. Adequate Calcium Intake

Calcium intake should be maintained as in the normal population, between 800 and 1000 mg/day, with a total daily elemental calcium intake not exceeding 1.5 to 2.0 g to avoid the risk of hypercalcemia and calcifications. [12,14].

4.3.2. Dialysate Calcium Concentration

KDIGO recommends dialysate calcium concentrations between 1.25 and 1.50 mmol/L, evaluating trends in calcium and PTH levels. [15,16].

4.3.3. Vitamin D and Analogues

Vitamin D reduces serum PTH levels by increasing calcium levels. It is essential to address vitamin D deficiency or insufficiency in hemodialysis patients, with treatment initiated as early as possible. [17,18,19]

4.3.4. Calcimimetics

Calcimimetics are a preferred treatment for hyperparathyroidism, as they help to counteract the control of calcium and vitamin D on PTH secretion, and to achieve a favorable effect on PTH, calcium, and phosphorus levels with a single treatment.

In our series, the most prescribed medications for hyperparathyroidism during the total dialysis duration were calcium salts in 99% of cases and the vitamin D derivative alfacalcidol (UN-ALFA*) in 96.3% of cases.

4.4. Parathyroidectomy: :

Despite medical treatment, parathyroidectomy (PTX) may be necessary for refractory secondary hyperparathyroidism. Indications include :[20,21]

- Uncontrollable hyperparathyroidism,
- PTH levels reaching or exceeding 800 or 1000 ng/L, and
- Treatment-resistant symptoms

According to the study by Foley et al. [22], approximately 5 to 10% of patients undergoing RRT undergo PTX treatment in cases of severe HPTS, and this percentage increases significantly with the duration of dialysis. [23].

In our study, 10.4% of cases underwent parathyroidectomy after a mean duration of dialysis of 8.6±4.2 years, showing consistency with the literature regarding the average duration before surgical intervention, as shown in the table below.

4.5. Biological Evolution

4.5.1. Calcium Levels

Interpret each calcium value based on PTH and vitamin D levels measured simultaneously, calcium intake, and therapeutic modalities. Targets for calcium levels vary between KDOQI (2.10-2.37 mmol/L) and KDIGO, comparable to those of a normal subject (2.12-2.55 mmol/L).

In our series, the results of serum calcium obtained in 45.5% and 67.5% of cases respectively met the recommended ranges for KDOQI and KDIGO, showing a 10% improvement compared to the initial assessment.

4.5.2. Phosphorus Levels

The KDOQI targets for phosphatemia range from 1.13 to 1.78 mmol/L, while the KDIGO targets tend towards the normal laboratory ranges (0.8-1.60 mmol/L), with a negative difference of 0.33 mmol/L for the minimum value and a positive difference of 0.18 mmol/L for the maximum value between the KDOQI and KDIGO standards.

The results of phosphatemia in our series showed an improvement in phosphatemia control compared to the initial assessment of 20.15% vs. 51.5% and 48.6% vs. 49.3%, respectively, according to KDOQI and KDIGO.

4.5.3. PTH levels

In our series, PTH control is low in 14.2% according to KDOQI standards, according to the study by El Mazani et al [24], while according to KDIGO, the percentage is close to half (41.8%).

Furthermore, the prevalence of HPTS decreased from 100% to 73.9% for KDOQI and from 82.8% to 46.3% for KDIGO in our patients.

4.5.4. 25-OH-Vitamin D

The KDIGO recommendations proposed the same targets and therapeutic schemes as those for the general population (> 75 nmol/l or 30 ng/l).

During the biological evolution of our patients, we noticed an improvement with a decrease in the percentage of vitamin D deficiency trending towards 23.1% and a slight increase in vitamin D insufficiency trending towards 30.6%.

4.5.5. Phosphocalcic Product

Analysis of the phosphocalcic product in KDOQI is among the independent predictors of overall and cardiovascular mortality. KDIGO, however, considers separately analyzing calcium and phosphorus levels to be more judicious, allowing therapeutic evaluation parameter by parameter.[25]

In our series, the evaluation of the phosphocalcic product showed that the majority of cases (72.4%) had a phosphocalcic product within the normal range, which is consistent with the results of the multicenter study in Tunisia (68.7%) [26] and the Iranian studies by Muzavi et al. and Hayati et al. (82%)[27].

5. Conclusion

Secondary hyperparathyroidism is an inevitable complication of chronic kidney disease that results from a cascade of phosphocalcic metabolic alterations, which jeopardizes the vital and functional prognosis of hemodialysis patients. The diagnosis of SHPT is essentially biological, based on the measurement of PTH, which is associated with phosphocalcic assessment, vitamin D measurement, and ALP.

Treatment is primarily preventive, aiming to maintain calcium, phosphorus, and 25-OH Vitamin D levels within recommended ranges and to reduce parathyroid response to phosphocalcic disorders.

Our work has allowed us to highlight the following characteristics:

- The average time for SHPT development within the first four years of dialysis.
- The initial predominance of vitamin D deficiencies is concurrent with the increase in PTH beyond recommended levels.
- A significant decrease in SHPT prevalence following therapeutic intervention.
- Therapeutic control is more effective for calcium and phosphorus levels compared to PTH in the absence of calcimimetic therapy in Morocco.
- A high percentage of our patients responded better to KDIGO criteria than to KDOQI criteria because they are more comprehensive

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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