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Biological profile of secondary hyperparathyroidism in chronic renal failure

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Abstract

Introduction: Secondary hyperparathyroidism (SHPT) is a frequent complication of chronic renal failure and is associated with high morbidity and mortality. Our goal is to study the average time of development of SHPT, and the biological profile in accordance with recommended standards.

Patients and methods: Retrospective descriptive study, including 134 chronically hemo-dialysed patients. Demographic, clinical, phosphocalcic and therapeutic data were analyzed. The phosphocalcic parameters were defined by KDOQI 2003 and KDIGO 2009 recommendations.

Results: The average time to onset of SHPT is 3.15 ± 4.02 years according to KDOQI standards and 4.6 ± 4.3 years according to KDIGO standards. The most commonly administered SHPT treatments are calcium salt and Vitamin D active. At the end of the study, 73.9% for KDOQI and 46.3% for KDIGO had hyperparathyroidism. The rates of compliance of the phosphocalcic indicators were higher with the KDIGO than with KDOQI recommendations for serum calcium, phosphate and parathyroid hormone (PTH).

Discussion: We noted a significant improvement between the two initial and recent periods concerning phosphocalcic parameters in general and hyperparathyroidism in particular. We found that the delay in the diagnosis of CKD, the duration of dialysis, the cost and availability of treatments, and the minimal frequency of kidney transplant in our country make it difficult to get the biological parameters to the recommended targets,

Conclusion: It is necessary to underline the interest of a good biological monitoring to ensure a good evaluation of the therapeutic conduct, and a better prevention against the serious complications of SHPT.

Keywords: Secondary hyperparathyroidism; KDOQI/ KDIGO recommendations; Parathyroid hormone; Chronic renal failure

1. Introduction

Secondary hyperparathyroidism (SHPT) represents one of the most frequent forms of mineral and bone disorders in chronic kidney disease (BMD-CKD) particularly in haemodialysis (HD) patients [1]. It corresponds to the hypersecretion of parathyroid hormone (SHPT) in response to disturbances in phosphocalcic metabolism in response to chronic renal function impairment. According to the recommendations of KDOQI (Kidney Disease Outcomes Quality Initiative 2003) and KDIGO 2009 (Kidney Disease: Improving Global Outcomes), SHPT requires close biological monitoring and early preventive and therapeutic medical management to keep PTH values and phosphocalcium metabolism parameters within the recommended ranges, as it increases the risk of morbidity and mortality, mainly related to the development

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of osteoarticular and cardiovascular complications [2, 3]. In this respect, the management of SHPT constitutes a therapeutic challenge between clinician and patient in view of the constraints of costs, availability of drugs, and monitoring. The objective of the work was to: - Determine the average time of onset of secondary hyperparathyroidism in haemodialysis patients and specify their initial phosphocalcic profile - Define the evolutionary profiles of the recent SHPT observed during their management and evaluate the compliance rates of biological parameters to the K/DOQI and K/DIGO recommendations.

2. Material and methods

This is a retrospective descriptive and comparative study, involving 134 cases of haemodialysis patients, carried out at the biochemistry department of the military hospital of Marrakech in collaboration with two private dialysis centres in Marrakech (The Marrakech and Atlas centres), spread over 3 years between 2014 and 2017.

Patients with a PTH value higher than 300 ng/l, and who had been on haemodialysis for at least 6 months before the start of the study were included in this study. Patients with secondary hyperparathyroidism before the start of haemodialysis were excluded from the study.

We studied the socio-demographic characteristics of the patients (age, sex, comorbidities, duration, frequency of haemodialysis and the causal nephropathy), clinical signs, biological report (calcium and phosphate levels, alkaline phosphatase (ALP), PTH, 25-OH-vitamin D, complete blood count (CBC), albumin, blood electrolytes, thyroid stimulating hormone (TSH), c-reactive protein (CRP)), imaging results (cervical ultrasound, parathyroid scintigraphy), type of treatment and anatomopathological results.

In our HMA laboratory, the technique used for the determination of PTH is electrochemiluminescence (ECLIA assays) which is used on the Elecsys® and Cobas® immune-analysis systems.

Statistically, the data were entered and analysed using SPSS 22.0 software.

3. Results

The mean age of our patients was 59.16 ± 12.76 years with extremes ranging from 21 to 87 years. A slight female predominance was noted (51.5%) with a F/H sex ratio of 1.06.

The etiologies at the origin of chronic renal failure were undetermined (NID) in 28.4% of cases. On the other hand, the other nephropathies were of diabetic origin (DN) in 20.9% of cases, vascular in 19.4%, polycystic kidney disease (PKD) in 11.2% of cases, glomerulonephritis (GN) in 6.7% of cases, and the other causes represent 5.2%.

Forty-eight percent of our patients were followed up before haemodialysis for a mean duration of 29.54± 41.43 months. The average duration of haemodialysis was 8.6±5.2 years. The patients received haemodialysis at a rate of 3 sessions per week in 88.1% of cases and 2 sessions per week in 11.9% of cases.

The most frequent clinical signs were joint pain in 57.5% of cases, diffuse bone pain in 50.6% of cases. The mean time to onset of Secondary Hyperparathyroidism (SHP) was 3.15±4.02 years according to KDOQI standards in all patients and 4.6±4.3 years according to KDIGO standards in 111 patients (Table 1).

Table 1 Time to onset of hyperparathyroidism according to the KDOQI and KDIGO standards

Duration (in years)	Minimum	Maximum	Average	Standard deviation
According to KDOQI	0,60	19,33	3,1549	4,02122
According to KDIGO	0,60	18,06	4,6360	4,36935

The initial plasma mean values of the SHPT diagnosis were according to KDOQI and KDIGO, respectively: PTH at 593.11±321.25 and 823±270.9 ng/L, Calcium at 2.5±0.3 and 2.19±0.3 mmol/L, Phosphorus at 1.67±0.6 and 1.7±0.68 mmol/L, Calcium phosphate product at 3, 58±1.64 $mmol^2/l^2$ and 3.74±1.7 $mmol^2/l^2$, APL at 149.7±154.06 and 203±230.12 U/L, and 25-OH vitamin D 51.19±40 and 46.1±34 nmol/l.

The percentages of hyperphosphatemia, hypocalcaemia, and vitamin D deficiency were 64.18%, 39.55%, and 53.7% respectively according to KDOQI vs 45%, 35.1%, and 61% according to KDIGO.

There was a predominance of Vitamin D deficiency ranging from 42.3% to 90% in relation to all the PTH ranges listed in Table 2. 70% of the patients had normocytic normochromic anemia and 14% of the cases had normal hemoglobin levels.

The rest of the biological report parameters are reported in Table 2.

Table 2 different non-phosphocalcic biological parameters

	Minimum	**Maximum**	**Average**	**Standard deviation**
Albumin g/l	29.00	49.00	40.2	3.5
Natremia mmol/l	126.00	151.00	136.8	4.1
Potassium mmol/l	2.80	13.00	5.6	1.78
Blood glucose mmol/l	3.02	14.92	5.4	2.2
TSH IU/l	0.01	5.89	1.6	0.96
CRP mg/l	0.22	142.00	11.8	19.7

Cervical ultrasound revealed a single parathyroid nodule in 32.1% of cases and multiple nodules in 10.2% of patients. It was normal in 50%, while in 7.2% of cases the parathyroid gland was not visible because of its association with a nodular goiter. The scintigraphy was in favour of parathyroid hyperplasia in 56.7% of the cases, and nodular hyperplasia in 12.5%. While it was normal in 31.3% of cases.

The most common treatments for HTPS were calcium salts in 99% of cases and active Vitamin D in 98.6% of cases. Parathyroidectomy (PTX) was required in 10% of patients. At the end of 2017, 73.9% of patients for KDOQI and 46.3% for KDIGO had hyperparathyroidism. Of the 14 cases that underwent parathyroidectomy, 50% of the cases (7cas) had PTH less than 130 ng/l (6 cases of subtotal PTX and 1 case of partial PTX) and 21.4% of the cases had PTH above 1000 ng/l (2 cases of partial PTX and 1 case of subtotal PTX). Among the 120 patients put on medical treatments, 45% of the cases (54 cases) had a normal PTH level according to KDIGO.

After treatment, the compliance of the phosphocalcic indicators with the targets recommended by KDOQI was 45.5%, 51.1%, 14.2%, respectively for the calcium, the phosphate and the PTH (table 3); whereas for the KDIGO it was about 67.5%, 49.3% and 41.8% respectively for the three parameters mentioned above.

Table 3 Distribution of PTH versus treatments according to K/DOQI

Treatments		**PTH**				**Total**
		[0-130]	**[130-585]**	**]585-1000]**	**+1000**	
Parathyroidectomy	Total of patients	7	2	2	3	14
	%	50.0%	14.3%	14.3%	21.4%	100.0%
Medical treatment	Total of patients	9	54	36	21	120
	%	7.5%	45.0%	30.0%	17.5%	100.0%
Total	Total of patients	16	56	38	24	134
	% of parathyroidectomy	11.9%	41.8%	28.4%	17.9%	100.0%

Evolution: The mean PTH was 697.2± 686.26 ng/l. 14.2% of the cases met the PTH target recommended by the KDOQI. 41.8% of cases had PTH within the KDIGO recommended standards.

4. Discussion

Our patients had developed SHPT after a mean time to dialysis of 3.15±4.02 years according to KDOQI recommendations and 4.6±4.3 years according to KDIGO. Studies have reported a delay in the onset of hyperparathyroidism around 4 to 5 years after the start of dialysis according to KDIGO 2009 recommendations [4, 5]. These results can be explained by the phosphocalcic disturbance that appears at an early stage of chronic kidney disease, and which requires early management as well as regular follow-up before the haemodialysis stage.

Calcimimetic is a treatment of choice for hyperparathyroidism, since it allows the control of blood calcium and vitamin D on the secretion of PTH [6]. However, its lack of availability as well as its cost, limits its prescription in Morocco. In our series, the most prescribed drugs for hyperparathyroidism during the total duration of dialysis were calcium salts in 99% of cases and the vitamin D derivative: alfacalcidol (UN-ALFA*) (96.3%).

In our study, 10.4% of patients had parathyroidectomy after a mean duration of dialysis of 8.6±4.2 years, this shows agreement with the literature for the mean duration before surgical management [7, 8].

The impact of renal mineral and bone disease on the haemodialysis patient has been studied and analysed in several international multicenter clinical studies based on representative samples of patients and dialysis centres: DOPPS [9] "Dialysis Outcomes and Practice Patterns Study" in its 5 phases, the COSMOS study [10], the faro study of Italy [11], and others including Tunisia [12], China [13], Argentina [14] and Serbia [15]. These studies evaluate the degree of compliance with the normal margin after therapeutic management and the risk of mortality. On the other hand, in Morocco, there are only monocentric studies, not representative of the reality of the minerobone profile in Moroccan haemodialysis patients and of the therapeutic management.

In our series, the results of the blood calcium levels obtained in 45.5% and 67.5% of the cases met the recommended ranges for KDOQI and KDIGO respectively, with an improvement of 10% compared to the initial assessment, and the mean blood calcium level was 2.35±0.27 mmol/l. In comparison with the percentage of control of blood glucose in all the series in the literature, which varies between 40%-60% for KDOQI and 53-77% for KDIGO, the mean blood glucose level varies between 2.13-2.35 mmol/l.

Phosphate blood levels in our series showed an improvement in the control of phosphate levels from baseline of 20.15% vs 51.5% and 48.6% vs 49.3% according to KDOQI and KDIGO, respectively, and with a decrease in mean phosphate blood levels ≈0.15mmol/l. The percentages of phosphate levels control in the literature series vary between 37.6-60% according to KDOQI and between 26.7% -61% according to KDIGO, and with a mean phosphate blood level between 1.16-2.4mmol/l.

In our series, PTH control is low in 14.2% according to KDOQI standards according to the study of El Mazani et al [16], while according to KDIGO, the percentage is close to half (41.8%). This can be explained by the narrow use of calcimimetics, and by the fact that the diagnosis of HTPS was not pre-established in the other studies. The other studies had a percentage of control that varied between 10-36% according to KDOQI, and 14-57% according to KDIGO. On the other hand, the results of the FARO study [11] had the best percentages. On the other hand, the prevalence of HTPS decreased from 100% to 73.9% for KDOQI and from 82.8% to 46.3% for KDIGO in our patients, which represents a significant improvement following the treatments.

In our study and in all series, there is a higher percentage of patients who meet the criteria for KDIGO compared to KDOQI. This may be explained by the fact that the targets for serum calcium and PTH have a wider range and are easier to achieve.

During the biological evolution of our patients, we noticed an improvement by decreasing the percentage of vitamin D deficiency tending to 23.1% and a slight increase of vitamin D insufficiency tending to 30.6%.

In our series, the evaluation of the phosphocalcic product showed that the majority of cases (72.4%) had a phosphocalcic product within the norms, which is in agreement with the results of the multicenter study of Tunisia [12] (68.7%) and the Iranian studies of Muzavi et al [17] and Hayati et al [18] (82%).

5. Conclusion

Secondary hyperparathyroidism is an unavoidable complication of chronic kidney disease. It results from a cascade of phosphocalcic metabolic alterations that jeopardize the vital and functional prognosis of uremic patients, especially in haemodialysis patients.

The diagnosis of HTPS is based on the immunological determination of PTH, associated with the phosphocalcic balance, the determination of vitamin D and the bone marker ALP, in spite of the non-homogeneity of the kits available on the market and of the ranges of PTH recommended for haemodialysis patients.

The treatment is primarily preventive in order to maintain the levels of blood calcium, phosphate and 25. OH Vitamin D within the recommended norms, and to reduce the parathyroid response to phosphocalcic disorders. This treatment consists of dietary rules, medical treatment (phosphorus binder, vitamin D and its derivatives, calcimimetic), and finally surgical treatment.

Our work, has allowed us to raise some of the following characteristics:

- The average time of development of HTPS in the first four years of dialysis
- The initial predominance of vitamin D deficiency is concomitant with the increase of PTH beyond the recommended standards
- The decrease in the prevalence of SHPT is significant following therapeutic management,
- Therapeutic control is more effective for serum calcium and phosphorus levels than for PTH in the absence of calcimimetics in Morocco
- The high percentage of our patients who met the criteria of KDIGO better than those of KDOQI since they are more extensive

Thus, it is necessary to underline the interest of a good biological monitoring to ensure a good evaluation of the therapeutic conduct, and a better prevention against the serious complications of HTPS. This justifies a closer collaboration between the biologist, the clinician, the dietician and the surgeon.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare that no conflict of interest exist.

Statement of informed consent

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

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