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Original Research Article

Phosphocalcic Status of Morocco Chronic Hemodialysis Patients and Adherence to Kidney Disease Improving Global Outcomes (KDIGO) Recommendations

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Abstract

Introduction: Phospho-calcium balance disorders are very common in chronic hemodialysis. They are accompanied by a high risk of mortality, mainly due to cardiovascular complications. In this context, the KDIGO finalized recommendations updated to improve the quality of life of chronic hemodialysis and warn the complications which can engage the prognosis for survival. The objective of our study was to analyze the phosphocalcic status in Morocco chronic hemodialysis patients and to estimate the conformity of the results with the recommendations KDIGO. ***Materials and methods:*** This is a retrospective study over a period of 8 months from January to August 2018 which includes chronic hemodialysis patients followed at the laboratory of Biochemistry-Toxicology of the Moulay Ismail military hospital and the nephrology-hemodialysis clinic from Meknes. The biochemical parameters evaluated were determined on Cobas®6000 from Roche Diagnostics and then compared to the targets of the KDIGO recommendations. ***Results:*** A total of 86 patients were enrolled in the study. The average age of our patients was 44.86 ±12.65 years, with a sex ratio of 1.38. The percentages of patients with phosphocalcic data consistent with the KDIGO recommended targets for calcemia, phosphoremia and PTH1-84 were 75.5%, 50% and 43% respectively. Finally, 17.4% of patients met the KDIGO 2009 recommendations by combining all three criteria. ***Conclusion:*** The results obtained during this study should encourage clinicians to improve management of chronic hemodialysis patients.

Keywords: Calcium, chronic hemodialysis, KDIGO2009/2016, phosphorus, Parathyroid hormone, vitamin D, alkaline phosphatase.

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem that affected more than 353 million people worldwide in 2015 with increasing incidence. The occurrence of CKD is often the cause of severe complications that are life-threatening to patients.

Bone and mineral disorders (BMD) are among the most common complications during CKD and more particularly in hemodialysis patients. These disorders are characterized by biochemical disturbances of phosphocalcic metabolism, bone remodeling, bone demineralization and the development of vascular calcifications. The phosphate retention observed in secondary hyperparathyroidism to CKD plays an essential pathophysiological role in the occurrence of BMD. Numerous studies show that BMD is strongly associated with high cardiovascular mortality and morbidity in chronic hemodialysis (CHD) patients.

BMD remain a major concern of learned societies, in particular KDOQI (kidney disease outcomes quality initiative) which developed clinical, biological and therapeutic strategies recommendations in 2003. These recommendations were then updated in 2009 and in 2017 by the KDIGOs (Kidney Diseas Improving Global Outcomes) while improving them to help nephrologists for better management of HDC patients and to have better adherence to recommended targets.

Several studies carried out in Morocco and elsewhere have shown that the concentrations of calcium, phosphorus and PTH are not systematically controlled in all hemodialysis patients. The objective of

our retrospective study is to analyze the phosphocalcic status of hemodialysis patients at the Meknes Moulay Ismail military hospital (MIMH), to determine the prevalence of secondary hyperparathyroidism and to evaluate the degree of adherence of the biological parameters to the target values proposed by the various KDIGO recommendations.

PATIENTS AND METHODS

This is a retrospective study carried out in the biochemistry laboratory of the MIMH in Meknes over a period of 8 months from January to August 2018 in collaboration with the nephrology-hemodialysis clinic of Meknes. In this study we enrolled adult patients with end-stage chronic renal failure (CRF) treated by hemodialysis on conventional hemodialyzer's at a rate of 3 sessions per week. CRF patients on periodic dialysis and acute renal failure were excluded from the study. All patients were clinically stable and signed informed consent. For each patient, we collected information from the records concerning: age, sex, duration of dialysis, personal history, presence of diabetes and high blood pressure.

The patients recruited were collected on an empty stomach and before the hemodialysis session on a heparinized tube for the determination of the following parameters: calcium, phosphorus, glucose, iPTH, creatinine, urea, total alkaline phosphatase and 25 hydroxy vitamin D. The parameters studied were evaluated after centrifugation on the Cobas ®6000 automatic device from Roche Diagnostic. Plasma urea and creatinine were determined respectively by the enzymatic urease method and by the Jaffé colorimetric method. The calcium level was determined by colorimetry with ortho-cresolphthalein-complexon, the usual values are between 85 and 100 mg / l. The phosphoremia was evaluated by colorimetric method using ammonium molybdate with usual values between 27 and 45 mg / l. total alkaline phosphatase was determined by colorimetry using para-nitrophenylphosphate with usual values of 40-129 IU / l in men and 35-104 IU / l in women.

The iPTH assay was performed by electrochemiluminescence (ECLIA), with usual values below 65 mg / l. Hyperparathyroidism is defined as an increase in PTH with a level greater than 9 times the upper limit of normal. The 25 hydroxyvitamin D was assayed by an ECLIA type immunological method.

Our results were then compared to the targets of the kidney disease 2009 recommendations. The target biological values proposed by the KDIGO are: calcium level between 84 and 104 mg / l (2.1 -2.6 mmol / l), phosphoremia between 32 and 60 mg / l (0.8-1.5mmol / l), iPTH between 134 and 603 pg / ml (14.7-66 mmol / l) and total alkaline phosphatases between 12.9 and 20 µg / l. For statistical analysis, quantitative variables were expressed as mean ± standard deviation. Qualitative variables were expressed as a percentage.

RESULTS

A total of 86 patients were included in the study. The mean age of our patients was 44.86 ± 12.65 years with extremes ranging from 24 to 80 years. A male predominance was recorded with a percentage of 58% and a sex ratio M / F of 1.38. The mean duration of hemodialysis was 80 months at the time of the study, with a standard deviation of 43 months and a range of [6 - 220] months. Among the cardiovascular risk factors found, also considered as risk factors for chronic renal failure, we mainly noted age, dyslipidemia and diabetes. In fact, 46% of patients were 50 years old or over, 65% of patients presented with dyslipidemia and 12% with diabetes.

Biologically, the mean serum calcium was 94.7 ± 9.22 mg / l. 15.1% of the patients had a low serum calcium level, 65.1% a normal serum calcium level and 19.8% a high serum calcium level. The mean phosphoremia was 44.12 ± 20.29 mg / l. low phosphoremia was found among 21% of patients, 33.7% presented normal phosphoremia and 45.3% had high phosphoremia. The mean PTH level was 310.5 ± 389.3pg / ml. Patients with normal PTH level represented 26.8%, and 73.2% had higher-than-normal rate of which 14.28% had hyperparathyroidism. The mean level of 25OH-vitamin D was 32.6 ± 43.5 ng / ml and 61.6% of patients had vitamin D deficiency. Mean Alkaline Phosphatase level (ALP) was 152.3 ± 184.02IU / L and 53.4% of patients had increased bone turnover (PAL> 100 IU / l).

The percentage of conformity of the results of the phosphocalcic balance compared to the KDIGO recommendations was 75.5% for serum calcium, 50% for phosphoremia and 43% for intact PTH. Finally, 17.4% of patients met the KDIGO 2009 recommendations by combining the three criteria (Table 1).

Table-1: Biological data and percentage of compliance in our patients with KDIGO recommendations.

Variable	Moyenne	Cible KDIGO (% de patients dans la cible)
Calcium (mg/l)	94.7 ± 9.22 mg/l	75.5%
Phosphore (mg/l)	44.12±20.29 mg/l	50%
PTH (pg/l)	310.5 ± 389.3 pg/l	43%
Ensemble des paramètres		17,4%

DISCUSSION

The determination of the phosphocalcic status of hemodialysis patients in our series made it possible to measure the rate of adequacy of the "phosphocalcic balance" indicator with the KDIGO recommendations. This rate was 17.4% by the combination of the three parameters (calcium, phosphate and PTH). It is similar to that reported in the study of Mahamat et al. in Senegal (17.78%) and Benabdellah et al. in Morocco (22.5%) [11.5]. But this result exceeds the rate found in the study by Mnif et al. (10.4%) [12] while remaining significantly lower than the rate reported by El Hebil et al. in 2017 (52.3%) and by Arenas et al. in Spain (31.5%) [13].

Several studies have clearly underlined the great difficulty in reaching the targets of the recommendations for chronic hemodialysis patients [5, 14, 15] The low adherence rate of our series may be due to the lack of means and the low socio-economic level of the patients, making it difficult to access treatments, especially for non-calcium phosphorus chelators and calcimimetics which remain relatively expensive as reported by Benabdellah et al [5]. On the other hand, the difficulty in reaching the recommendation targets can be explained by the insufficient number of hemodialysis sessions as reported by Larabou et al [15] where they recommend at least three hemodialysis sessions per week. In contrast, in the El Hebil et al [13] study, an improvement was noted between 2010 and 2017 in terms of the overall degree of adherence to KDIGO recommendations in the same patients. They explain their result by better management including good availability of treatment and more rigorous medical monitoring, as well as better patient compliance with treatments and dietary measures [13]

The mean age of our patients was 44.86 ± 12.65 years and the age group over 50 was the most represented. This is consistent with the results found in Europe and particularly in France where CKD increases considerably with age [18]. However, in many countries of sub-Saharan Africa, CRI primarily reaches economically active young adults [19]. The male predominance of CKD terminal found in our series was highlighted in most studies [6, 7, 8]. This could be explained by the harmful effects of male hormones and smoking on the course of chronic kidney disease [7, 8].

Hyperphosphatemia is a common complication in advanced stages of chronic kidney disease and especially in people on dialysis [4, 5]. It was found in 45.3% of our HDC patients. This rate is moderately lower compared to the values reported in Algeria (60%) and France (55.1%) [20, 21]. The DOPPS study (Dialysis Outcomes and Practice Patterns Study) conducted in 7 countries (France, Spain, Italy, Germany, England, Japan, United States), confirms the presence of hyperphosphatemia in more than 50% of chronic hemodialysis patients, and qualifies phosphorus as a biological parameter difficult to correct despite treatment with chelators [22]. The phosphoremia adherence rate to the KDIGO recommendations was 50%. This rate is higher than that reported in the Mnif et al study in Tunisia (38.1%) [12] but it is close to that of African countries with 61% in northern Morocco [5], 60.9% in Senegal [10] and 57.3% in Martinique [11]. The latest quarterly report from the United States Renal Data System (USRDS) confirmed that phosphoremia in dialysis patients was high (greater than 1.45mM) in one-third (34%), normal in 50 to 60% and low in 10 to 15% of patients. This distribution has remained substantially unchanged for the last two decades despite the enormous development of the therapeutic arsenal in this field, in particular with the advent of intestinal phosphate binders without calcium, based on lanthanum or iron, calcimimetics and activators of the less hyperphosphatemic vitamin D receptor [23] This suggests that the physiopathological mechanisms involved in the genesis and persistence of hyperphosphatemia in this third of patients is not fully understood, without also eliminating the non-negligible part non-adherence to treatment [24].

The control of phosphatemia, or even its normalization, is therefore a major element in the early management of disorders of mineral and bone metabolism in chronic renal disease. Since 2009, the new international recommendations KDIGO no longer cites a target for phosphatemia but a “tending towards the normality of the phosphatemia, nor of the measurement of the circulating concentration of the phosphocalcic product (CaxP)” [25]. They suggest that the correction of phosphatemia either by dietary measures, or by intestinal phosphate binders or by inhibitors of intestinal phosphate absorption could potentially improve the survival of patients on dialysis, but no randomized or controlled studies has so far demonstrated this. The KDIGO recommendations, in their last version of 2016, also insists that it is necessary to take into account the other elements of the mineral and bone metabolism disorders of CKD such as the presence or absence of cardiovascular calcifications and / or disorders of bone remodeling, in deciding which type of intestinal phosphate sequestrant should be prescribed for each patient [25]. Along with hyperphosphatemia appears a decrease in vitamin D responsible for hypocalcemia. Renal synthesis of calcitriol decreases as glomerular filtration decreases. This decrease is due to the reduction in the renal mass capable of synthetizing calcitriol, but also to hyperphosphatemia. Phosphate retention acts directly by suppressing renal synthesis of calcitriol and complexing circulating calcium. In our series, 61.6% of patients present a vitamin D deficiency and among 15.1% of them it was associated hypocalcemia. The reported cases of normal or elevated serum calcium may be due to the use of replacement therapy or the presence of severe secondary hyperparathyroidism. serum calcium levels of 75.5% of HDC patients was in

line with KDIGO recommendations. This rate is comparable to that reported in the Benabdellah et al. study in the Moroccan eastern region [5]. It is superior to that of Gbaguidi et al. from Martinique [10] with 62.7%, Laradi et al. from France [9] with 63.6%.

The hyperphosphatemia and hypocalcemia thus developed induce an increase in the secretion of PTH by the parathyroids, which tends to bring phosphorus and calcium back to values close to normal, which develops secondary hyperparathyroidism of renal origin. In our series, 14.28% of our patients presented with secondary hyperparathyroidism. The adherence rate of PTH to the KDIGO recommendations (43%) is similar to that found in the study by Benabdellah et al. [5], and less good compared to the results of Gbaguidi et al. in Martinique (60.8%) [10] and Mnif et al. in Tunisia (54.9%) [12]. Finally, PAL, markers of bone remodeling, are stimulated by secondary hyperparathyroidism, the aim of which is to bring serum calcium values closer to normal limits. In our study, 53.4% of patients had increased PAL and high bone turnover. Elevated serum parathyroid hormone levels and the resulting secondary hyperparathyroidism are associated with high bone turnover, release of phosphate and increased phosphatemia. Thus 100% of hyperparathyroid patients had high bone turnover, and 80% had hyperphosphatemia. However, parathyroid hormone may also increase phosphatemia through non-yet elucidated extraosseous mechanisms, as suggested by the fact that parathyroid hormone infusion in dialysis patients increases phosphatemia regardless of the type of normal / low bone turnover or high [26]. In addition, there has long been fairly strong clinical data demonstrating that control of secondary hyperparathyroidism by parathyroidectomy significantly reduces phosphatemia [27]. Likewise, analyzes grouping studies with the calcimimetic cinacalcet HCl in the treatment of secondary hyperparathyroidism in dialysis patients show that the proportion of patients with hyperphosphatemia is higher in the highest quartiles of parathyroid hormone. Also, that phosphatemia is better controlled when parathyroid hormone is effectively lowered by calcimimetic [28,29]. Control of parathyroid hormone is therefore an integral part of the management of hyperphosphatemia in patients on dialysis.

The KDIGO recommendations with regard to the prevention of phophocalcic metabolism abnormalities offer personalized therapeutic management for each patient by considering the rate and variation of each parameter separately, while taking into account the patient's nutritional status and quality of hemodialysis. The objective is to keep serum calcium within normal values, phosphoremia close to the lower normal limits and PALs between 2 and 9 times the normal value [9].

CONCLUSION

CKD is constantly increasing in our country. BMD is very common in chronic hemodialysis patients. Their seriousness strongly justifies a personalized therapeutic strategy aimed at reaching the targets of the KDIGO recommendations or at least approaching normal limits. The results obtained during this study, as well as those reported by various authors, show that there is a low rate of adherence to these international recommendations. These results should further encourage clinicians to improve monitoring of chronic hemodialysis patients, with the aim of improving their quality of life and preventing dramatic complications that can be life-threatening.

Declaration of Interest

The authors declare that they have no conflict of interest in connection with this article.

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