Journal of Nephrology & Therapeutics

Hamida et al., J Nephrol Ther 2017, 7:3
DOI: 10.4172/2161-0959.1000295

Research Article Open Access

Mineral and Bone Status in Tunisian Maintenance Hemodialysis Patients: The National Bone and Mineral Metabolism Observatory

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Received Date: May 10, 2017; **Accepted Date:** May 28, 2017; **Published Date:** June 04, 2017

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Abstract

In Tunisia, data assessing the status of mineral and bone disorders (MBD) among dialysis patients is scarce. In order to address this gap in the literature, we sought to conduct this observational study including 4868 patients from 108 hemodialysis facilities nationwide, aiming to: (i) report parameters of MBD during the first quarter 2006, (ii) determine the levels of compliance with the recommendations of the Kidney Disease Outcome Quality Initiative (K/DOQI), and (iii) compare these levels of compliance with those of Dialysis Outcomes and Practice Patterns Study (DOPPS). Mean serum phosphorus, calcium, calcium- phosphorus product and intact parathyroid hormone (iPTH) concentrations were respectively 1.74 mmol/L, 2.28 mmol/L, 3.95 mmol²/l² and 254 pg/ml. MBD's measures were met the K/DOQI's guidelines in 44.1% of cases for serum phosphorus, 42.5% of cases for serum calcium, 68.6% of the cases for calcium phosphorus product, 20.2% of cases for iPTH and 3.3% of cases for these four parameters taken together. These results were comparable to those observed in the DOPPS study. The most phosphate binder prescribed was calcium carbonate (91.2% of cases) with high average daily dose (superior to 1500 mg in 45.8% of cases). Sevelamer and aluminum salt were prescribed respectively in 0.5% and 0.10% of patients. The only active vitamin D available in Tunisia was alfacalcidol; it was prescribed in 49.7% of patients with a mean weekly dose of 4.04 µg. A calcium dialysate bath of 1.75; 1.50 and 1.25 mmol/L were prescribed respectively in 80.2%, 14.7% and 5.1% of cases.

This is the first exhaustive study reporting MBD abnormalities in Tunisia and, to our knowledge, in Africa. A second study was stated in January 2017 which will focus on hemodialysis facilities practices and levels of compliance with new MBD guidelines.

Keywords: Hemodialysis; Mineral metabolism; Calcium; Phosphorus; Calcium-phosphorus product; Parathyroid hormone

Introduction

Incidence of end stage kidney disease (ESKD) patients is progressively increasing in Tunisia from 13 pmp in 1986 to 133 pmp in 2008 [1]. ESKD is usually accompanied by profound changes in mineral metabolism that can lead to clinical complications such as bone disease, musculoskeletal symptoms, and growth retardation [2]. In addition, several recent studies suggested a strong association between abnormal mineral metabolism and mortality [2-4]. Secondary hyperparathyroidism is a physiological response of parathyroid gland to phosphate retention, reduction in synthesis of vitamin D, and hypocalcaemia [5]. It has been shown that secondary hyperparathyroidism is associated with high morbidity and mortality [6]. Several professional bodies issued k/DOQI's guidelines for the management of MBD in dialysis patients, partly in response to growing evidence about the relationship with vascular morbidity and mortality [7,8]. The DOPPS provided useful description of guideline achievement among representative samples of hemodialysis patients in several countries [9-11]. However, many dialysis patients in the world are still not within the target recommended by the K/DOQI for MBD [7], suggesting gaps between global guidelines and local practices. To our knowledge, the status of MBD treatment in Tunisia has not yet been assessed on a national level. In order to address this gap in the literature, we conducted the current study.

Methods

Patients and data collection

This is a national, observational, and multi-centric study including patients of about 80% of dialysis facilities in Tunisia (n=108). MBD parameters were collected during the first quarter of the year 2006. The periodicity of MBD parameters collection was regulated in 1999 by the Tunisian legislator: serum calcium and serum phosphorus, once a month; iPTH and serum aluminum, once a year; calcium in osmoses water, once a semester; and aluminum in osmoses water, once two years [12]. MBD parameters were collected by physicians (hemodialysis physicians or nephrologists) working within the hemodialysis facilities included in this study.

The parameters studied were: sex, age, date of dialysis initiation, dialysate calcium bath concentration, c reactive protein (CRP), serum albumin and serum urea before and after dialysis session, serum phosphorus, serum calcium, iPTH, past history of para-thyroidectomy, and treatment used for the management of MBD marker levels.

Total calcium was corrected according to serum albumin by the following formula: corrected calcemia = total calcemia (mmol/L) +

0.02 × (40 - albuminea g/l). We note that biological measurements were conducted within each center's respective laboratory.

Statistical analysis

All statistical analyses were performed using Photo-Graph TM, scientific software supplied by Genzyme laboratory. After introduction of all parameters, the application generated automatically all results including in particular the percentage of patients having MBD, the percentage of their control according to the K/DOQI recommendations [7] and their comparison to those of DOPPS study [9-11].

Results

A total of 108 hemodialysis facilities had participated in this study, with data collected from 4868 patients. Their mean age ± Standard Deviation (SD) was 53.7 ± 16.8 years. The percentage of male participants was 46%. For all patients we exanimate key aspects of the four commonly used measures of MBD: serum phosphorus, serum total calcium, serum calcium-phosphorus product (Ca×Pho) and serum iPTH. Means ± SD of these parameters were shown in Table 1.

	Mean ± SD
Serum phosphorus (mmol/L)	1.74 ± 0.55
Total calcium (mmol/L)	2.28 ± 0.30
Ca x Pho product ($mmol^2/l^2$)	3.95 ± 1.33
Intact PTH (pg /ml)	413* ± 490
*Median = 254 pg /ml	

Table 1: Characteristics of the commonly used measures.

Serum phosphorus

Mean serum phosphorus concentration ± SD was 1.74 ± 0.55 mmol/L. Serum phosphorus levels were met K/DOQI guidelines (ranged from 1.13 to 1.79 mmol/L) in 44.1% of patients (Figure 1). This rate was comparable to the one observed in 2004 (44%) in the DOPPS study [9-11] as shown in Figure 2. Serum phosphorus was inferior to 1.13 mmol/L in 12.5% of patients and superior to 1.78 mmol/L in 43.4% of them.

Serum calcium

Mean total serum calcium concentration ± SD was 2.28 ± 0.55 mmol/L. Total serum calcium levels were met K/DOQI guidelines (ranged from 2.10 to 2.37 mmol/L) in 42.6% of patients (Figure 1). This rate was comparable to the one observed in 2004 (43%) in the DOPPS study [9-11] as shown in Figure 2. Total serum calcium was inferior to 2.10 mmol/L in 21.8% of patients, between 2.37 and 2.54 mmol/L in 22.2% and superior to 2.54 mmol/L in 13.5% of them.

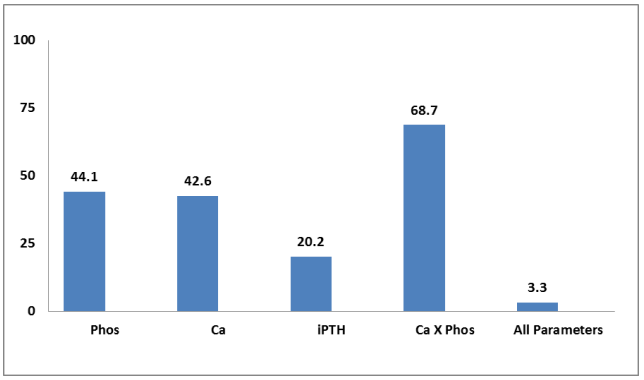

Figure 1: Levels of compliance with the of K/DOQI's Guidelines. Phos: serum phosphorus; Ca: serum calcium; Ca X Phos: serum calcium phosphorus-product.

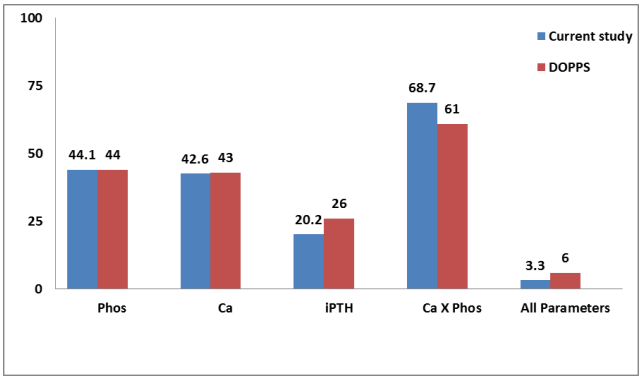

Figure 2: Comparison of levels of compliance with the K/DOKI's guidelines. Phos: serum phosphorus; Ca: serum calcium; Ca X Phos: serum calcium phosphorus-product.

Serum calcium phosphorus- product

Mean serum calcium-phosphorus product concentration ± SD was 3.95 ± 1.33 $mmol^2/l^2$. Serum calcium-phosphorus product was inferior to 4.44$mmol^2/l^2$ - as recommended by the K/DOQI (7) - in 68.7% of patients (Figure 1). This rate was comparable to the one observed in 2004 (61%) in the DOPPS study [9-11] as shown in Figure 2. Serum calcium-phosphorus product was superior to 4.44$mmol^2/l^2$ in 31.3% of patients.

Parathyroid hormone

Median iPTH concentration was 254 pg/ml. Intact PTH levels were met K/DOQI guidelines (ranged from 2.10 to 300 mmol/L) in 20.2% of patients (Figure 1). This rate was comparable to the one observed in 2004 (26%) in the DOPPS study [9-11] as shown in Figure 1. Intact PTH was inferior to 150 pg/ml in 35% of patients (10.5% of them had past history of parathyroidectomy) and superior to 300 mg/ml in 44.7% of them (intact PTH was ranged from 301 to 800 pg/ml in 29.7% of cases and superior to 800 pg/ml in 15% of cases).

In summary, the goals recommended by K/DOQI [7] were met in 44.1% for serum phosphorus, 42.5% for serum calcium, 68.6% for calcium phosphorus product, 20.2% for iPTH and 3.3% for the four parameters taken together (Figure 1). Serum calcium, serum phosphorus and iPTH were met the goals recommended by K/DOQI in 13.5% of patients. These results were comparable to those observed in the DOPPS study [9-11] as shown in Figure 2.

Use of calcium carbonate for the management of MBD marker levels

Phosphate binders were prescribed in 92.1% of patients with calcium carbonate being the most prescribed (91.2% of cases). The mean daily dose of element calcium used was 2260 mg. This dose was superior to 1500 mg in 45.8% of patients. Patients with serum phosphorus inferior to 1.13 mmol/L were treated by calcium carbonate in 11.4% of the cases with a mean daily dose of 2270 mg. Patients with serum phosphorus ranged from 1.13 mmol/L to 1.78 mmol/L were treated by calcium carbonate in 40.6% of cases with a mean daily dose of 2240 mg. Patients with serum phosphorus superior to 1.78 mmol/L were treated by calcium carbonate in 38.9% of cases with a mean daily dose of 2280 mg (Table 2).

Serum phosphorus (mmol/L)	Calcium Carbonate	
	% of patients	Mean daily dose (mg)
< 1.13	11.4	2270
1.13 to 1.78	40.6	2240
> 1.78	38.9	2280

Table 2: Treatment by calcium carbonate according to serum phosphorus levels.

Patients with serum calcium inferior to 2.10 mmol/L were treated by calcium carbonate in 20% of cases with a mean daily dose of 2390 mg. Patients with serum calcium ranged from 2.10 mmol/L to 2.37 mmol/L were treated by calcium carbonate in 38.9% of the cases with a mean daily dose of 2290 mg. Patients with serum calcium ranged from 2.38 mmol/L to 2.54 mmol/L were treated by calcium carbonate in 20.2% of cases with a mean daily dose of 2160 mg. Patients with serum calcium superior to 2.54 mmol/L were treated by calcium carbonate in 11.8% of cases with a mean daily dose of 2090 mg (Table 3).

Serum calcium (mmol/L)	Calcium Carbonate	
	% of patients	Mean daily dose (mg)
< 2.10	20.0	2390
2.10 to 2.37	38.9	2290
2.38 to 2.54	20.2	2160
> 2.54	11.8	2090

Table 3: Treatment by calcium carbonate according to serum calcium levels.

Patients with iPTH inferior to 150 pg/ml were treated by calcium carbonate in 27.6% of the cases with a mean daily dose of 2080 mg. Patients with iPTH ranged from 150 to 300 pg/ml were treated by calcium carbonate in 16.5% of cases with a mean daily dose of 2040 mg. Patients with iPTH ranged from 301 to 800 pg/ml were treated by calcium carbonate in 23.7% of cases with a mean daily dose of 2320 mg. Patients with iPTH superior to 800 pg/ml were treated by calcium carbonate in 11.7% of cases with a mean daily dose of 2460 mg (Table 4).

iPTH (pg/ml)	Calcium Carbonate	
	% of patients	Mean daily dose (mg)
< 150	27.6	2080
150 to 300	16.5	2040
301 to 800	23.7	2320
> 800	11.7	2460

Table 4: Treatment by calcium carbonate according to iPTH levels.

Use of sevelamer for the management of MBD marker levels

Sevelamer was prescribed only in 0.5% of patients with a mean daily dose of 2560 mg. We had no patients treated by sevelamer when serum phosphorus was inferior to 1.13 mmol/L. Patients with serum phosphorus ranged from 1.13 mmol/L to 1.78 mmol/L were treated by sevelamer in 0.20% of cases with a mean daily dose of 2600 mg. Patients with serum phosphorus superior to 1.78 mmol/L were treated by sevelamer in 0.30% of cases with a mean daily dose of 2552 mg.

Patients with serum calcium inferior to 2.10 mmol/L were treated by sevelamer in 0.10% of cases with a mean daily dose of 1600 mg. Patients with serum calcium ranged from 2.10 mmol/L to 2.37 mmol/L were treated by sevelamer in 0.20% of cases with a mean daily dose of 3000 mg. Patients with serum calcium ranged from 2.38 mmol/L to 2.54 mmol/L were treated by sevelamer in 0.10% of cases with a mean daily dose of 2632 mg. Patients with serum calcium superior to 2.54 mmol/L were treated by sevelamer in 0.10% of the cases with a mean daily dose of 1600 mg.

Patients with iPTH inferior to 150 pg/ml were treated by sevelamer in 0.20% of the cases with a mean daily dose of 3600 mg. Patients with iPTH ranged from 150 to 300 pg/ml were treated by sevelamer in 0.10% of cases with a mean daily dose of 1600 mg. Patients with iPTH ranged from 300 to 800 pg/ml were treated by sevelamer in 0.10% of cases with a mean daily dose of 2080 mg. Patients with iPTH superior to 800 pg/ml were treated by sevelamer in 0.10% of cases with a mean daily dose of 2288 mg.

Use of aluminum salt for the management of MBD marker levels

Aluminum salt was prescribed only in 0.10% of patients with a mean daily dose of 3 capsules.

Use of active Vitamin D for the management of MBD marker levels

The only active Vitamin D available in Tunisia is alfacalcidol. It was prescribed in 49.7% of patients with a mean weekly dose of 4.04 µg. Patients with serum phosphorus inferior to 1.13 mmol/L were treated by alfacalcidol in 6.7% of cases with a mean weekly dose of 4.48 µg. Patients with serum phosphorus ranged from 1.13 mmol/L to 1.78 mmol/L were treated by alfacalcidol in 25.7% of cases with a mean

weekly dose of 3.99 µg. Patients with serum phosphorus superior to 1.78 mmol/L were treated by alfacalcidol in 17.2% of cases with a mean weekly dose of 3.99 µg (Table 5).

Serum phosphorus (mmol/L)	Active vitamin D	
	% of patients	Mean weekly dose (µg)
< 1.13	6.7	4.48
1.13 to 1.78	25.7	3.99
> 1.78	17.2	3.99

Table 5: Treatment by active vitamin D according to serum phosphorus levels.

Patients with serum calcium inferior to 2.10 mmol/L were treated by alfacalcidol in 11.3% of cases with a mean weekly dose of 4.69 µg. Patients with serum calcium ranged from 2.10 mmol/L to 2.37 mmol/L were treated by alfacalcidol in 21% of cases with a mean weekly dose of 3.92 µg. Patients with serum calcium ranged from 2.38 mmol/L to 2.54 mmol/L were treated by alfacalcidol in 10.9% of cases with a mean weekly dose of 4.06 µg. Patients with serum calcium superior to 2.54 mmol/L were treated by alfacalcidol in 6.4% of cases with a mean weekly dose of 3.22 µg (Table 6).

Serum calcium (mmol/L)	Active vitamin D	
	% of patients	Mean weekly dose (µg)
< 2.10	11.3	4.69
2.10 to 2.37	21.0	3.92
2.38 to 2.54	10.9	4.06
> 2.54	6.4	3.22

Table 6: Treatment by active vitamin D according to serum calcium levels.

Patients with iPTH inferior to 150 pg/ml were treated by alfacalcidol in 13.1% of cases with a mean weekly dose of 3.75 µg. Patients with iPTH ranged from 150 to 300 pg/ml were treated by alfacalcidol in 8.5% of cases with a mean weekly dose of 3.39 µg. Patients with iPTH ranged from 300 to 800 pg/ml were treated by alfacalcidol in 15.4% of cases with a mean weekly dose of 3.92 µg. Patients with iPTH superior to 800 pg/ml were treated by alfacalcidol in 8.4% of cases with a mean weekly dose of 5.38 µg (Table 7).

iPTH (pg/ml)	Active vitamin D	
	% of patients	Mean weekly dose (µg)
< 150	13.1	3.75
150 to 300	8.5	3.39
301 to 800	15.4	3.92
> 800	8.4	5.38

Table 7: Treatment by active vitamin D according to iPTH levels.

Use of cinacalcet for the management of MBD marker levels

In our study, no patient was treated by cinacalcet because it was not available in Tunisia.

Dialysate calcium bath

Variations among hemodialysis patients and across hemodialysis facilities were reported for the dialysate calcium bath used during hemodialysis. Most patients (80.2%) were prescribed a calcium dialysate bath of 1.75 mmol/L. Only 14.7% and 5.1% of patients were prescribed dialysate calcium bath at respectively 1.5 mmol/L and 1.25 mmol/L.

Patients receiving calcium carbonate as phosphate binder were prescribed a calcium dialysate bath of 1.75 mmol/L in 83% of cases, 1.5 mmol/L in 13% of cases and 1.25 mmol/L in 4% of cases. Patients receiving sevelamer as phosphate binder were prescribed a calcium dialysate bath of 1.75 mmol/L in 80% of cases and 1.5 mmol/L in 20% of cases. Patients receiving aluminum salt as phosphate binder were prescribed a calcium dialysate bath of 1.75 mmol/L in 60% of cases and 1.5 mmol/L in 40% of cases. Patients receiving alfacalcidol were prescribed a calcium dialysate bath of 1.75 mmol/L in 83% of cases, 1.5 mmol/L in 14% of cases, and 1.25 mmol/L in 3% of cases.

Discussion

This observational study reported biological and therapeutic parameters of MBD among about 80% of dialysis facilities in Tunisia. This is the first exhaustive study reporting MBD abnormalities in Tunisia and to our knowledge, in Africa. This study is well suited to analyze guidelines compliance because it involves representative samples of hemodialysis facilities and patients in Tunisia with a large population of hemodialysis.

Dialysis prescription was different between public and private hemodialysis facilities: patients receiving hemodialysis less than 3 times per week were more frequent in public hemodialysis facilities. While the use of high calcium dialysate bath at 1.75 mmol/L was more common in private hemodialysis facilities.

This study shows that patients were met K/DOQI targets for serum phosphorus, serum calcium, serum calcium phosphorus product, iPTH and four parameters together, respectively in 44.1%, 42.6%, 68.7%, 20.2% and 3.3% of cases. Concerning biological parameters, our results were satisfactory and comparable to those observed in DOPPS study realized in 2003 [9-11] and the two French studies realized between 2005 and 2008 [13], and between 2008 and 2012 [14].

Aluminum salts use was limited in 2006 in Tunisia (0.1% of patients) probably due to their potential implication in encephalopathy and adynamic osteopathy [15]. Sevelamer was used only in 0.5% of patients because it was not available in Tunisia and some patient procured it from neighboring countries at their own charge. The most used phosphorus binder in Tunisia was calcium carbonate (91.2% of cases). This study shows that the mean dose used was superior to 1500 mg per day in 45.8% of patients. This dose used was relatively high because of unavailability of non-calcium phosphate binders. Furthermore, patients with serum calcium superior to 2.54 mmol/L were treated by calcium carbonate in 11.8% of cases with a mean daily dose of 2080 mg. This paradoxical prescription was due to inadequate follow-up of biological parameters, inadequate prescription of calcium carbonate dose and unavailability of non-calcium phosphate binders in Tunisia.

Medical treatment of hyperparathyroidism by cinacalcet still difficult to use in Tunisia for unavailability reasons. Consequently, only active vitamin D can be prescribed. Medical treatment failure is common because of occurrence of hypercalcemia and/or hyperphosphatemia, which contraindicates the use of active vitamin D [16]. As observed with calcium salts, some paradoxical prescriptions were revealed in our study: patients were treated by active vitamin D while their serum phosphorus levels were superior to 1.74 mmol/L (17.2% of cases), their serum calcium levels were superior to 2.54 mmol/L (6.4% of cases), or their intact PTH levels were inferior to 150 pg/l (13.1% of cases).

Conclusion

In summary, this observational and exhaustive study is important to determine compliance levels with the K/DOQI's guidelines in Tunisia. Since the realization of this study, sevelamer and cinacalcet were still unavailable in Tunisia, but their use became relatively more frequent because more patients can procure them from neighboring countries. Additionally, during the last five years, we were able to prescribe native vitamin D and to dose it in hemodialysis patients. A second observational study was started in January 2017 aiming to detect changes in the MBD parameters and determine levels of compliance with the new KDIGO's guidelines [17] published in 2009 after the end of the current study.

Acknowledgment

The authors wish to thank Genzyme Laboratory and all hemodialysis physicians and nephrologists of hemodialysis facilities for their precious contribution to the realization of this study.

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