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ORIGINAL ARTICLE

COSMOS: the dialysis scenario of CKD–MBD in Europe

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ABSTRACT

Background. Chronic kidney disease–mineral and bone disorders (CKD–MBD) are important complications of CKD5D patients that are associated with mortality.

Methods. COSMOS is a multicentre, open cohort, prospective, observational 3-year study carried out in haemodialysis patients from 20 European countries during 2005–07. The present article describes the main characteristics of the European dialysis population, the current practice for the prevention, diagnosis and treatment of secondary hyperparathyroidism and the differences across different European regions.

Results. The haemodialysis population in Europe is an aged population (mean age 64.8 ± 14.2 years) with a high prevalence of diabetes (29.5%) and cardiovascular disease (76.0%), and 28.7% of patients have been on haemodialysis more than 5 years. Patients from the former Eastern countries are younger (59.3 ± 14.3 versus 66.0 ± 13.9), having a lower proportion of diabetics (24.1 versus 30.7%). There were relevant differences in the frequency of measurement of the main CKD–MBD biochemical parameters [Ca, P and parathyroid hormone (PTH)] and the Eastern countries showed a poorer control of these biochemical parameters (K/DOQI and K/DIGO targets). Overall, 48.0% of the haemodialysis patients received active vitamin D treatment. Calcitriol use doubled that of alfacalcidiol in the Mediterranean countries, whereas the opposite was found in the non-Mediterranean countries. The criteria followed to perform parathyroidectomy were different across Europe. In the Mediterranean countries, the level of serum PTH considered to perform parathyroidectomy was higher than in non-Mediterranean countries; as a result, in the latter, more parathyroidectomies were performed in the year previous to inclusion to COSMOS.

Conclusions. The COSMOS baseline results show important differences across Europe in the management of CKD–MBD.

INTRODUCTION

Chronic kidney disease–mineral and bone disorders (CKD-MBD) are current complications of CKD patients with end-stage renal disease (CKD5D). Despite the great advances in the knowledge of the pathogenesis of these disorders and the availability of new drugs, the control of CKD–MBD is still inadequate and it has been associated with increased morbidity and mortality [1–5].

In order to improve CKD–MBD outcomes, in 2003, the National Kidney Foundation launched the Kidney Dialysis Outcome Initiative (K/DOQI) [6], some years later, in 2009, the Kidney Disease: Improving Global Outcomes (K/DIGO) initiative launched new CKD–MBD guidelines [7].

Since the publication of the K/DOQI guidelines, several retrospective and prospective epidemiological studies have been carried out in order to better identify the main factors implicated in CKD–MBD outcomes [8–14]. COSMOS (Current Management of Secondary hyperparathyroidism—a Multicenter Observational Study) is a Pan-European prospective study which aims to survey MBD and clinical practice patterns in CKD5D patients [15, 16]. The main objective of COSMOS is to survey bone mineral disturbances in the haemodialysis population in Europe and current practice for the prevention, diagnosis and treatment of secondary hyperparathyroidism. In the present report, the most relevant baseline clinical, biochemical and practice patterns in Europe are presented.

MATERIALS AND METHODS

COSMOS is a 3-year, multicentre, open-cohort, prospective observational study surveying bone and mineral disturbances in 20 European countries including 4500 prevalent CKD5 patients older than 18 years from 227 dialysis centres. Facilities were identified using a stratified, random selection methodology and 20 patients from each haemodialysis facility were randomly recruited. The number of patients per country was proportional to the haemodialysis population of each country. The larger countries were divided into three to five geographic areas, and haemodialysis sites were randomly selected within those predefined areas. Germany was divided into four regions (north, south, west and east), Italy and France into three regions (north, centre and south), Spain into three regions (north, south and east) and Poland into five regions (north, south, east, west and centre). The detailed study protocol design has been published elsewhere [15]. Only haemodialysis centres with more than 40 patients were included.

Centre and patient data were entered by site investigators into a web-based data entry system. Recruitment of sites and patients began in February 2005 and finished in July 2007. Data were collected in two web-based-specific forms (Table 1). Each centre completed a centre-specific form with 15 questions and 119 items including site characteristics and practice patterns and a patient form with 27 questions and 185 items [15] (Supplementary material, Table S1A and B). The patient data included laboratory parameters from the previous 6 months before inclusion. The mean values for these 6 months were calculated for each patient. The serum parathyroid hormone (PTH) assay used was recorded in the majority of

Table 1. Variables collected from each site (centre-specific form) and from each patient (patient form)

Centre-specific form	Patient form
1. Site characteristics (type and funding)	1. Year of birth
2. Centre size (number of patients)	2. Gender
3. Frequency of bone x-ray profile	3. Prescribed dry weight
4. Type of x-ray	4. Height
5. Timing of laboratory data collection	5. Aetiology of CKD
6. Frequency of PTH measurement	6. Year of initiation dialysis
7. Frequency of Ca and P measurement	7. Type of haemodialysis treatment
8. Use of a standard dialysate calcium	8. Haemodialysis hours per week
9. Type of PTH assay used	9. Comorbidity of diabetes
10. Level of PTH considered to initiate treatment	10. Bone biopsy (diagnosis)
11. Route and frequency of vitamin D analogues/metabolites administration	11. Presence of symptomatic bone fractures in previous 1 year
12. Level of PTH considered for parathyroidectomy	12. Presence and year of parathyroidectomy
13. Type of parathyroidectomy	13. Cardiovascular disease events
14. Number of parathyroidectomies performed in the last year	14. Cigarette smoking
15. Clinical guidelines followed	15. Presence of calcifications, technique used for detection and location
	16. Calcium concentration in dialysate
	17. Phosphate binder usage
	18. Nutritional vitamin D usage
	19. Vitamin D metabolites/analogues usage
	20. Calcimimetics usage
	21. Erythropoietic-stimulating agents usage
	22. Serum parathyroid hormone (previous 6 months)
	23. Serum phosphate (previous 6 months)
	24. Serum calcium (previous 6 months)
	25. Serum albumin (previous 6 months)
	26. Haemoglobin level (previous 6 months)
	27. Serum aluminium (previous 6 months)

Ca, calcium; P, phosphorous; PTH, parathyroid hormone; CKD, chronic kidney disease.

centres (79.3%). In the corrections of PTH values, the Elecsys PTH (Roche Diagnostics) was used as a comparator due to its better performance [17] and also because it was the assay more often used in COSMOS (42% of the reported assays). PTH levels from sites measuring bio-intact assay (3.5%, 8 centres) were corrected multiplying by 1.95, as it has been previously described [18, 19]. Each investigator received a username and password and data could only be introduced or modified by the investigator. In order to prevent typographical mistakes, the values introduced in quantitative variables were contrasted with predetermined ranges; otherwise, the investigator was required to correct the introduced value.

The analysis of data (centre and patient forms) was done for the whole COSMOS population. In addition, a further analysis was performed grouping European regions according to economic, historical and sociocultural similarities. The countries were divided into Eastern (Croatia, Czech Republic, Hungary, Poland, Romania and Slovenia) and Western European countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain,

Sweden, Switzerland and UK). Additionally, a second geographical analysis divided Europe into Mediterranean (Croatia, France, Greece, Italy, Portugal, Slovenia and Spain) and non-Mediterranean countries (Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, the Netherlands, Poland, Romania, Sweden, Switzerland and UK).

Categorical variables were described as the percentage of patients and quantitative variables as the mean and standard deviation. One-way analysis of variance (ANOVA) test for continuous variables and the χ^2 test for categorical variables were used to analyse differences between European regions using the Statistical Analysis Software SAS® (version 9.2). The Cochran–Mantel–Haenszel test was also used for categorical variables to adjust by age and gender when comparing the different European regions.

RESULTS

Seventeen out of the 20 included countries recruited more than 80% of the targeted population—14 of them reached 93.9% or higher, two others more than 50% (Germany and Italy) and one country recruited 24% (UK). Overall, 76.8% of the targeted population was recruited (Table 2).

Most of the dialysis centres participating in COSMOS were hospital-based (67.8%), non-academic (73.3%) and publicly funded (64.6%). (For a full list of centres participating in the COSMOS study, please see the supplementary material online). In Eastern Europe and Mediterranean countries, the percentage of hospital-based dialysis centres was significantly higher than in Western Europe and non-Mediterranean countries, respectively. No statistically significant differences between public or private funding were observed across regions (Table 3).

Almost 60% of the dialysis patients included were men and were older than 65 years (overall mean age 64.8 ± 14.2 years) (Table 3). In Western countries, the percentage of patients older than 65 years was higher (mean age 66.0 ± 13.9 years), almost 7 years older on average than in the Eastern countries. The Mediterranean patients were also older (3 years) than the non-Mediterranean patients. Small, but significant, differences in body mass index and smoking habits were observed

Table 2. Facilities and patients targeted and achieved for recruitment in number (*n*) and percentages (%)

Country	Targeted		Achieved		Achieved/targeted	
	Facilities (*n*)	Patients (*n*)	Facilities (*n*)	Patients (*n*)	Facilities (%)	Patients (%)
Austria	5	100	5	98	100.0	98.0
Belgium	7	140	6	120	85.7	85.7
Croatia	3	60	3	62	100.0	103.3
Czech Republic	7	140	7	140	100.0	100.0
Denmark	3	60	3	58	100.0	96.7
Finland	2	40	2	39	100.0	97.5
France	38	760	32	633	84.2	83.3
Germany	73	1460	51	1018	69.9	69.7
Greece	10	200	10	199	100.0	99.5
Hungary	6	120	6	120	100.0	100.0
Italy	50	1000	28	554	56.0	55.4
The Netherlands	6	120	6	119	100.0	99.2
Poland	15	300	15	302	100.0	100.7
Portugal	10	200	11	203	110.0	101.5
Romania	7	140	7	140	100.0	100.0
Slovenia	2	40	2	46	100.0	115.0
Spain	22	440	21	413	95.5	93.9
Sweden	4	80	4	80	100.0	100.0
Switzerland	3	60	3	60	100.0	100.0
UK	20	400	5	96	25.0	24.0
Total	293	5860	227	4500	77.5	76.8

Table 3. Characteristics of sites and patients

Facilities	All (n = 227)	East (n = 40)	West (n = 187)	P-value	Medit. (n = 107)	Non-Medit. (n = 120)	P-value
Type of centre							
Hospital-based (%)	67.8	92.5	62.6	<0.001	74.8	61.7	0.035
Non-academic (%)	73.3	79.5	72.0	0.3	71.7	74.8	0.6
Public (%)	64.6	75.0	62.4	0.1	64.2	65.0	0.9
Patients	n = 4500	n = 810	n = 3690		n = 2110	n = 2390	
Age (years) (Mean ± SD)	64.8 ± 14.2	59.3 ± 14.3	66.0 ± 13.9	<0.001	66.4 ± 13.8	63.4 ± 14.4	<0.001
≥65 (%)	58.1	40.0	62.1	<0.001	63.5	53.4	<0.001
Gender (males) (%)	59.7	55.7	60.5	0.011	60.2	59.2	0.3
Body mass index (kg/m^2) (mean ± SD)	25.5 ± 10.3	25.2 ± 5.2	25.3 ± 5.0	0.6	24.9 ± 4.8	25.6 ± 5.2	<0.001
<20.0 (%)	11.2	12.7	10.8	0.2	12.5	10.0	<0.001
20.0–<25.0 (%)	43.0	41.5	43.4		44.6	41.6	
25.0–<30 (%)	30.4	31.7	30.2		29.5	31.3	
≥30.0 (%)	15.4	14.1	15.7		13.4	17.1	
Smokers (%)	14.2	14.8	14.0	0.1	12.7	15.4	0.5
Years on haemodialysis	4.2 ± 4.4	3.8 ± 4.0	4.2 ± 4.5	0.014	4.7 ± 5.0	3.7 ± 3.8	<0.001
<1 (%)	18.7	19.6	18.5	0.1	17.1	20.1	<0.001
1–5 (%)	52.7	54.6	52.2		50.4	54.7	
>5 (%)	28.7	25.8	29.3		32.6	25.2	
Primary aetiology of CKD							
Diabetic nephropathy (%)	20.4	16.5	21.3	<0.001	17.7	22.8	<0.001
Hypertension[a] (%)	19.3	14.8	20.3		20.8	18.0	
Glomerulonephritis (%)	17.8	21.5	17.0		17.3	18.3	
Inters/obs nephropathy[b] (%)	12.8	20.9	11.1		12.7	12.9	
Unknown (%)	11.3	7.7	12.1		15.0	8.0	
PKD (%)	8.7	10.0	8.5		8.7	8.7	
Tumours (%)	1.6	1.1	1.7		1.7	1.5	
Others (%)	8.0	7.5	8.1		6.1	9.6	
Diabetes (%)	29.5	24.1	30.7	0.016	26.2	32.5	<0.001
Registered CV events (%)	76.0	76.4	75.9	0.6	76.2	75.8	0.8
Calcification (%)	41.8	26.7	45.1	<0.001	48.2	36.2	<0.001

Continued

Table 3. Continued

Facilities	All ($n = 227$)	East ($n = 40$)	West ($n = 187$)	P-value	Medit. ($n = 107$)	Non-Medit. ($n = 120$)	P-value
Type of haemodialysis technique							
Conventional low flux (%)	52.8	66.5	49.7	<0.001	51.1	54.2	0.001
Conventional high flux (%)	37.6	26.0	40.2		37.5	37.7	
Haemodiafiltration and other (%)	9.6	7.4	10.1		11.3	8.1	
Ca conc. in the dialysate (mEq/L)							
2.5 (%)	29.8	42.7	26.8	<0.001	19.9	37.2	<0.001
3.0 (%)	49.5	30.1	54.0		57.3	43.6	
3.5 (%)	20.7	27.2	19.3		22.8	19.2	

Statistical differences between patients from the European regions were adjusted by age and gender. CKD, chronic kidney disease; CV, cardiovascular; Ca conc., calcium concentration.
[a]Includes nephroangiosclerosis.
[b]Interstitial and obstructive nephropathy.

between non-Mediterranean and Mediterranean countries (Table 3). Slightly less than 20% and 30% of the whole COSMOS population has been on haemodialysis for <1 and more than 5 years, respectively (Table 3). The Mediterranean countries had significantly more long-term (>5 years) and fewer short-term (<1 year) patients on dialysis (Table 3).

The primary aetiology of CKD showed significant variations among the different European regions. This was particularly evident in Western Europe. Diabetic nephropathy, hypertension and glomerulonephritis accounted for almost 60% of the causes of CKD (Table 3). Diabetic nephropathy as aetiology of CKD, and diabetes as a diagnosis in the haemodialysis population were significantly more frequent in the Western and non-Mediterranean countries ($P < 0.02$). In the whole COSMOS population, the percentage of CKD diabetic patients on dialysis at the time of recruitment was close to 30% (Table 3). The lowest percentage of diabetics (24.1%) was observed in the Eastern countries.

Conventional low- and high-flux dialysis were the most frequently used dialysis techniques (90.4% of patients). Haemodiafiltration and other techniques were used in 9.6% of patients; this figure was slightly higher (11.3%) in the Mediterranean countries (Table 3). The calcium concentration in the dialysate used in the different facilities ranged from 2.5 to 3.5 mEq/L; the most frequently used concentration was 3.0 mEq/L (49.5%, Table 3). This figure was mainly driven by the Western countries. In the Eastern countries, the percentage of facilities using 3.5 mEq/L was ~9% higher than in the Western countries (Table 3).

The percentage of patients with any kind of cardiovascular event was uniformly high (76.0%) and the percentage of patients in whom calcification was reported was 41.8% (Table 3). Vascular and valvular calcifications were the most frequent (34.1 and 14.9%, respectively). Reported calcifications were higher in Western, and Mediterranean countries.

In 57.7% of the centres, PTH was frequently measured (every 3 months or more frequently); this was particularly evident in the Western countries. In the remaining centres, PTH was investigated either less frequently or not routinely (Table 4). Serum calcium and phosphorous were measured monthly or even more frequently in more than 90% of the centres. This strategy was quite homogeneous across the four European regions analysed.

Figure 1 shows overall the percentage of patients achieving the K/DIGO and the K/DOQI targets. Western and Mediterranean countries showed a better control of biochemical parameters (Table 4). Most patients (70.5%) showed serum phosphorous levels above the normal range (K/DIGO recommendation).

In those centres reporting the PTH assay used (79.3%), Elecsys PTH (Roche Diagnostics), Immulite 2000-intact PTH (DPC) and ELISA-PTH (Schering-Cis Bio) were the most used (33.3, 18.9 and 13.9%, of the reported assays, respectively) representing 66.1% of the reported assays. The remaining 33.9% correspond to other 11 assays used scattered in 61 centres that they were not included in the corrections or comparisons. Serum PTH was higher in patients from centres using Immulite 2000-intact PTH than in patients from centres using Elecsys PTH (329.1 ± 358.2 versus 284.0 ± 324.5, $P = 0.006$), but no significant differences were found between the ELISA-PTH and Elecsys PTH (316.5 ± 342.2 versus 284.0 ± 324.5, $P = 0.08$).

In COSMOS, the majority of centres (94.5%) initiated active vitamin D treatment (calcitriol, alfacalcidol and paricalcitol) with PTH levels between 150 and 499 pg/mL, half of them between 155 and 299 pg/mL and the other half between

Table 4. Facilities: frequency of measurement of biochemical parameters

Facilities	All (n = 227)	East (n = 40)	West (n = 187)	P-value	Medit. (n = 107)	Non-Medit. (n = 120)	P-value
Frequency of PTH measurement							
Every 3 months or less (%)	57.7	40.0	61.5	<0.001	63.6	52.5	0.1
More than every 3 months (%)	39.2	47.5	37.4		35.5	42.5	
Non-routinely (%)	3.1	12.5	1.1		0.9	5.0	
Frequency of Ca and P measurement							
Every 1 month or less (%)	92.1	97.5	90.9	0.2	90.7	93.3	0.5
More than every 1 month (%)	7.9	2.5	9.1		9.3	6.7	
Patients	n = 4500	n = 810	n = 3690		n = 2110	n = 2390	
K/DOQI initiative							
Ca (mg/dL)							
<8.4 (%)	12.7	15.4	12.1	<0.001	12.9	12.5	0.011
8.4–9.5 (%)	57.8	49.5	59.7		59.7	56.0	
>9.5 (%)	29.5	35.0	28.3		27.3	31.5	
P (mg/dL)							
<3.5 (%)	7.2	6.7	7.2	<0.001	9.7	4.9	<0.001
3.5–5.5 (%)	51.5	40.8	53.8		58.3	45.4	
>5.5 (%)	41.4	52.5	39.0		32.0	49.7	
PTH (pg/mL)							
<150 (%)	36.5	42.1	35.4	<0.001	31.6	41.1	<0.001
150–≤300 (%)	29.1	24.9	29.9		30.8	27.5	
>300–≤800 (%)	27.0	23.4	27.7		29.4	24.8	
>800 (%)	7.4	9.6	7.0		8.2	6.7	
K/DIGO initiative							
Ca (mg/dL)							
Below normal range (%)	16.5	18.5	16.1	0.001	16.9	16.1	0.8
Within normal range[a] (%)	77.0	72.3	78.0		76.6	77.3	
Above normal range (%)	6.5	9.1	5.9		6.5	6.6	
P (mg/dL)							
Below normal range (%)	2.8	2.4	2.9	0.001	4.2	1.5	<0.001
Within normal range[a] (%)	26.7	21.7	27.8		32.5	21.5	

Continued

Table 4. Continued

Facilities	All ($n = 227$)	East ($n = 40$)	West ($n = 187$)	P-value	Medit. ($n = 107$)	Non-Medit. ($n = 120$)	P-value
Above normal range (%)	70.5	75.9	69.4		63.3	77.0	
PTH (pg/mL)							
<2 times the upper limit[a] (%)	31.2	37.0	30.1	<0.001	26.2	35.9	<0.001
2–9 times the upper limit[a] (%)	56.1	47.8	57.7		60.8	51.7	
>9 times the upper limit[a] (%)	12.7	15.2	12.2		13.0	12.3	

Patients: percentage of patients distributed according to different ranges of calcium (Ca), phosphorous (P) and PTH. Statistical differences in patients were adjusted by age and gender.
[a]Normal range for serum P 3.0–4.5 mg/dL, serum Ca 8.5–10.2 mg/dL and serum PTH 10–65 pg/mL.

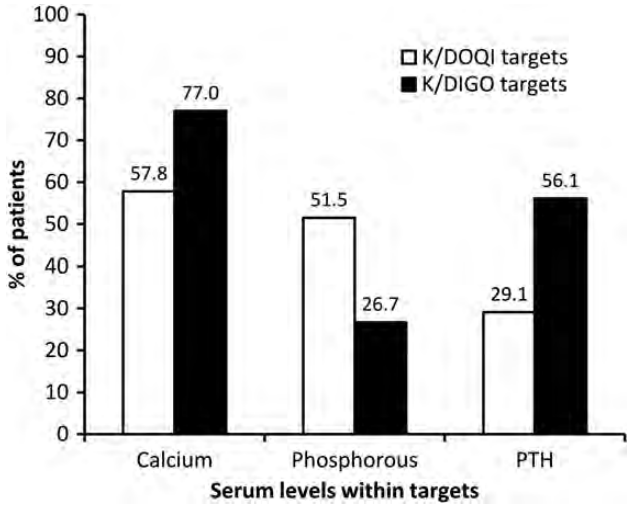

FIGURE 1: Percentage of patients within K/DOQI and K/DIGO targets for serum calcium, phosphorous and PTH.

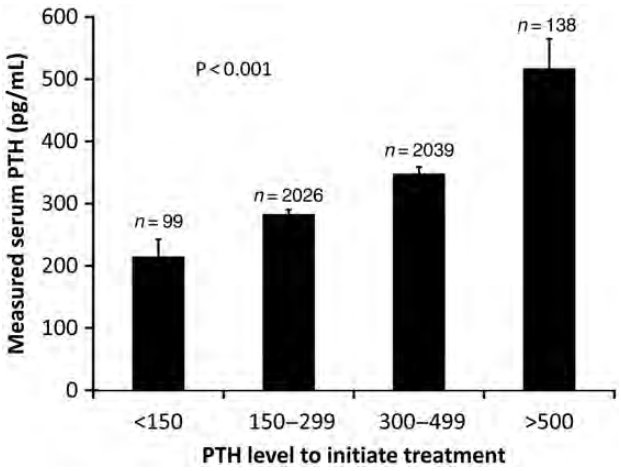

FIGURE 2: Measured serum PTH in patients (patient form) and serum PTH levels a patient is considered to require active treatment to lower PTH (centre-specific form) (mean ± standard error of the mean). ANOVA test was used to analyse statistical differences.

300 and 499 pg/mL (Table 4). There were differences in the levels of PTH required to initiate treatment across the different European regions (Table 4). The higher the level of PTH considered by each centre to initiate active treatment, the higher the measured levels of serum PTH found in patients (Figure 2).

Active vitamin D was used in 48% of patients (Table 5), calcitriol and alfacalcidol, in similar percentages, accounted for 93.3% of the active vitamin D use and paricalcitol for 6.7%. The most frequent route of administration was oral (daily + intermittent). These two combinations represented 77.9% of the active vitamin D use, but the oral daily (46.7%) was the most common form. The intravenous route was much more commonly used in the Western and Mediterranean countries. There were differences in the use of calcitriol or alfacalcidol in the Mediterranean and non-Mediterranean countries. Calcitriol use was double that of alfacalcidol in Mediterranean countries and the opposite was seen in non-Mediterranean countries. Vitamin D as nutritional replacement was used in 30.6% of patients. A total of 6.3% of patients were receiving calcimimetics.

The majority of COSMOS patients (86.4%) were receiving phosphate binders, 63.4% received calcium-containing phosphate binders, the latter increasing to 83.1% in the Eastern countries. Despite the high percentage of phosphate binder prescription, 70.5% of patients showed serum phosphorous levels above the K/DIGO recommended target (Table 4).

Table 5. Facilities: serum PTH levels required to initiate treatment of secondary hyperparathyroidism and preferred route and frequency of vitamin D (vit. D) administration

Facilities	All (n = 227)	East (n = 40)	West (n = 187)	P-value	Medit. (n = 107)	Non-Medit. (n = 120)	P-value
Level of PTH to initiate treatment							
<150 pg/mL (%)	2.3	5.1	1.7	0.1	2.9	1.7	0.3
150–299 pg/mL (%)	47.5	51.3	46.7		40.8	53.4	
300–499 pg/mL (%)	47.0	35.9	49.4		53.4	41.4	
>500 pg/mL (%)	3.2	7.7	2.2		2.9	3.4	
Frequency/route of active vit. D administration							
Intravenous and intermittent (%)	16.7	5.0	19.3		29.9	5.0	<0.001
Oral and intermittent (%)	43.6	52.5	41.7		41.1	45.8	
Oral and daily (%)	39.6	42.5	39.0	0.1	29.0	49.2	
Patients	n = 4500	n = 810	n = 3690		n = 2110	n = 2390	
Active vit. D	48.0	48.7	47.8	0.7	45.3	50.4	<0.001
Calcitriol (%)	21.2	22.6	20.9	0.4	25.7	17.2	<0.001
Alfacalcidol (%)	23.6	25.6	23.2	0.2	13.9	32.2	<0.001
Paricalcitol	3.2	0.5	3.8	<0.001	5.8	1.0	<0.001
Active vit. D route							
Intravenous (%)	22.1	5.8	25.8	<0.001	39.4	8.5	<0.001
Oral intermitent (%)	31.2	23.1	33.0		30.9	31.4	
Oral daily (%)	46.7	71.1	41.2		29.7	60.1	
Vit. D nutritional replacement (native vitamin D and/or calcidiol)							
25 (OH) D (%)	14.2	22.0	12.5	<0.001	13.7	14.7	<0.001
Vit D (%)	14.6	1.2	17.5		13.0	16.0	
Both (%)	1.8	2.1	1.8		0.5	3.1	
None (%)	69.4	74.7	68.2		72.8	66.3	
Phosphate binders (%)	86.4	91.5	85.3	<0.001	86.4	86.4	1.0

Patients: types of vit. D derivatives, route of administration and phosphate binders. Data from the centre-specific form (facilities) and patient-specific form (patients). Statistical differences were adjusted by age and gender.

Most dialysis facilities considered parathyroidectomy when PTH was above 750 pg/mL (87.2%). There were differences between Mediterranean and non-Mediterranean countries, the latter indicating earlier the surgical procedure (Figure 3A). The proportion of Mediterranean facilities not performing parathyroidectomies in the previous year was higher than in the non-Mediterranean countries (Figure 3B); however, overall, the percentage of parathyroidectomised patients was 6.6% with no differences across all European regions. Subtotal and total parathyroidectomy with implants was the preferred surgical approach (88.5%). Only 17.2% of facilities preferred the total parathyroidectomy.

DISCUSSION

COSMOS is a prospective study in which haemodialysis centres and patients were randomly selected from 20 European countries. The only study with comparable characteristics is the Dialysis Outcomes and Practice Patterns Study (DOPPS). However, there are relevant differences between both study designs; for instance, a sampling proportional to the haemodialysis population of each country was performed in COSMOS, meanwhile in DOPPS, each European country aimed to recruit the same sample size with similar number of centres and patients [20]. Thus, while DOPPS design facilitates

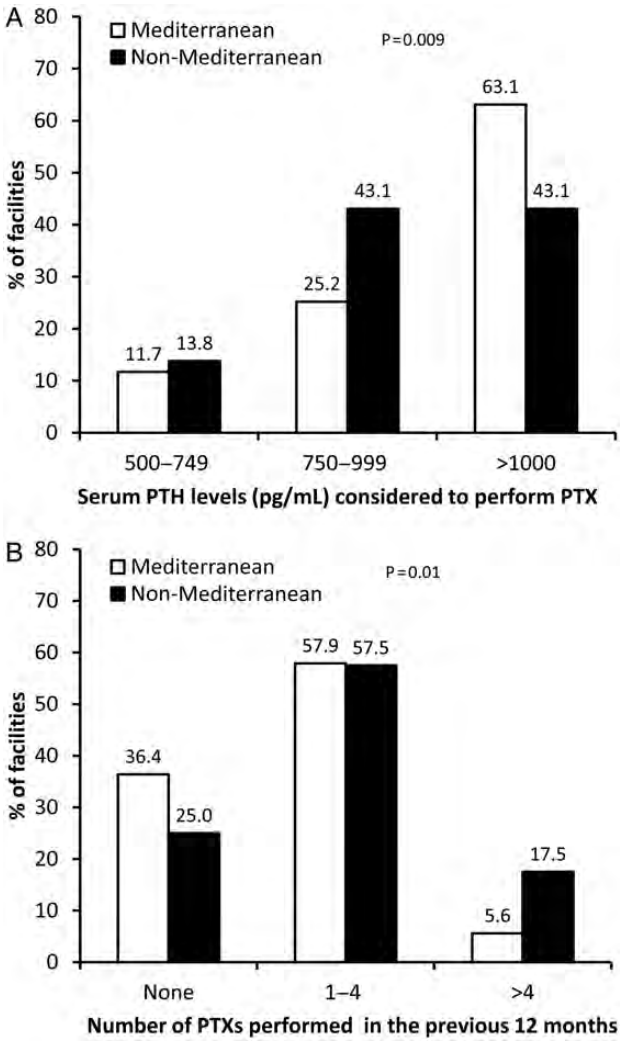

FIGURE 3: Serum PTH levels considered to perform parathyroidectomy (PTX) (**A**) and number of PTX performed during the previous 12 months (**B**) (centre-specific form). Statistical differences were assessed by the χ^2 test.

making country comparisons, the COSMOS design has a proportional representation of Europe as a whole. Initially, in order to obtain a representative sample of the European haemodialysis population, COSMOS aimed to recruit 5860 patients from 293 dialysis centres. Upon study completion, 77.5 and 76.8% of targeted centres and patients, respectively, were recruited. Only the UK was underrepresented with regard to the initial targets; therefore, COSMOS baseline data can be considered representative of the European haemodialysis population during 2005–07.

Some results observed in COSMOS are consistent with previous reports. Despite the NECOSAD, from the Netherlands, a cohort of incident patients (not prevalent as COSMOS), they reported a similar mean age of the haemodialysis patients to COSMOS (63 ± 14). The mean age of haemodialysis patients from non-Mediterranean countries and Western countries (the groups of countries including the Netherlands) were also similar in COSMOS (63.4 ± 14.4 and 66.0 ± 13.9, respectively) (Table 3). The percentages of men were 58.0 and 59.7% in NECOSAD and COSMOS, respectively [21]. The results from COSMOS are also comparable with those obtained in the European countries participating in DOPPS [22]; however, the COSMOS patients were slightly older (60.4 ± 15.2 versus 64.8 ± 14.2). This small difference might be due to the different period of data collection; data from Euro-DOPPS dialysis units were collected from May 1998 through November 2000, whereas in COSMOS, the data were collected from February 2005 through July 2007, indicating that the European haemodialysis population is getting older. The mean age found in COSMOS is also consistent with another recent epidemiological study (ARO) carried out in Europe between January 2005 and December 2006, almost the same period in which a great part of the baseline COSMOS data were collected (63.4 years in COSMOS and 63.1 years in ARO) [12]. The demographic characteristics of the COSMOS population are also consistent with the recent Italian studies FARO and RISCAVID [13–14, 23] and the French Phosphorus and Calcium Observatory (FPCO) [24, 25] study.

Diabetes is becoming highly prevalent in Europe and elsewhere. From 1995 to 1999, the prevalence of type 2 diabetes increased considerably, particularly in the UK, Germany and France [26]. The COSMOS data revealed that the most important primary cause of CKD in Europe is diabetic nephropathy (20.4%), higher than that observed in the NECOSAD study [8] and Euro-DOPPS [22], supporting the remarkable increase in the prevalence of this disease. The percentage of diabetes as a diagnosis in the haemodialysis population was also very high (29.5%) (almost one-third suffering from this disease) being similar to that found in the FPCO [24] but higher than the figures reported in NECOSAD (incident patients older than 50 years) [27] and Euro-DOPPS [28]. The percentage of diabetics is slightly different in COSMOS and ARO (29.5% in COSMOS and 25.9 in ARO) studies [12]. However, the countries included in ARO are mainly from Eastern Europe and from the Mediterranean area. The percentage of diabetics in these European regions in COSMOS was more similar to the ARO (24.1 and 26.2 in Eastern and Mediterranean countries, respectively). The differences in the percentage of diabetics among the different European regions might reflect a widespread group of factors such as genetic, cultural and economic resources.

The proportion of patients with history of cardiovascular disease was very high in COSMOS (76.0%) and similar to that found in ARO [12], FARO [23] and other studies [29], but much higher than that found in NECOSAD [30], in the FPCO [24] and in a recently published Spanish report [31]. In contrast, the reported prevalence of calcifications found in COSMOS was lower than previous non-observational studies designed to detect vascular calcifications [32, 33]. As COSMOS was not specifically designed to detect or follow vascular calcifications, it is likely that the latter has been underestimated in COSMOS.

DOPPS reported in the late 1990s that European haemodialysis patients were treated mainly by low-flux (63.1%) and high-flux haemodialysis (25.2%) [34]. COSMOS baseline data, which represent a wide European dialysis scenario, reveal, almost 6–7 years later, a trend towards an increased use of

high-flux techniques, especially in Western Europe (40.2% of patients). KDIGO clinical practice guidelines recommend the use of a dialysate calcium concentration between 2.5 and 3.0 mEq/L [7]; other authors even recommend lower values [35]. In COSMOS, it was found that a high percentage of patients (20.7%) was dialysed with a high calcium dialysate concentration (3.5 mEq/L), mainly driven by the Eastern countries (27.2% of patients).

A great variability among the PTH available assays has already been described [17, 36]. In some cases, the differences are so important that a correction is needed; in our study that was the case of the bio-intact PTH in which the measured serum values were multiplied by a correcting factor of 1.95 [18, 19]. There were no significant differences between the Elecsys PTH (Roche Diagnostic) and the ELISA-PTH (Schering-Cis Bio), but significant differences were observed between Elecsys PTH and Immulite 2000-intact PTH (DPC), suggesting the convenience to correct the latter. Unfortunately, the correction was not possible due to the fact that COSMOS did not collect information regarding whether the PTH analysis was measured in serum or plasma, data needed to make the PTH correction [36].

K/DOQI targets achievement was assessed for comparative purposes. A slightly better control of all bone laboratory parameters was found in COSMOS compared with the NECOSAD [37], but the results were similar to most of other contemporary studies such as RISCAVID [14], FARO [13], FPCO [25] and ARO [12]. The results were not the same across the different European regions considered in the analysis. Eastern countries showed a poorer control of the main laboratory parameters, particularly serum phosphorous levels, compared with Western countries. In addition, patients from Eastern and non-Mediterranean countries showed a higher percentage of patients with low serum PTH levels (<150 pg/mL) (Table 4), despite the fact that there were no important differences in the percentage of patients treated with active vitamin D metabolites (Table 5). This result is particularly striking in the Eastern countries, because these patients tended to be younger and with a lower proportion of diabetics. Differences in the modality of treatment, such as a higher percentage of patients treated with phosphate binders (particularly calcium containing phosphate binders) in the Eastern countries, may account for some of these differences.

The distribution of patients within K/DIGO targets was also investigated. The K/DIGO initiative recommend to maintain the CKD5 patients within the normal range for serum calcium and phosphorous and within two to nine times the upper limit of the normal range for serum PTH [7]. As the K/DIGO guidelines referred only to 'normal ranges or times fold from normal ranges', but no specific serum values are mentioned, we decided to use cut-off values for comparison (Table 4) based on the data of several publications and documents [17, 38–43] and also based on the more current decision-making values used in clinical practice. The cut-off values selected as normal ranges were 3.0–4.5 mg/dL for serum phosphorous, 8.5–10.2 mg/dL for serum Ca and 10–65 pg/mL for serum PTH.

Using the K/DIGO criteria, we found results that merit some comments. One striking observation was the high percentage of patients that we found above the recommended serum phosphorous targets (70.5%). The Eastern and non-Mediterranean countries showed the highest percentages (75.9 and 77%, respectively), but also a poorer control of serum PTH.

These high figures stress the difficulties in achieving some guidelines targets, which in some cases, like in serum phosphorus, despite the fact that 86.4% of patients were receiving phosphate binders, only 26.7% achieved the recommended K/DIGO serum phosphorus values. The knowledge of these results involve some potential benefits and risks. On the one hand, they can stimulate a more careful and systematic control of the phosphate including a more tailored use of phosphate binders [44, 45], but on the other hand, there is a potential risk to think that these kind of 'normal targets' will never be achieved, becoming more an 'academic and ideal but not a practical, feasible and achievable goal', a fact which may relax the willingness and effort to achieve them.

Another interesting finding is the results observed in serum PTH. Despite the wider range of 'normality' in PTH of the K/DIGO compared with the K/DOQI targets, only 56.1% of patients showed PTH levels within the recommended two to nine times the upper limit of the normal range, despite 48% of them receiving calcitriol, alfacalcidol or paricalcitol, 30.6% native vitamin D or calcidiol, 6.3% calcimimetics and 86.4% phosphate binders. The analysis of the PTH levels out of target (43.9%) revealed that 71.1% of them showed serum PTH levels in the 'low-bone turnover' range.

The different availability and the cost of the drugs used to treat secondary hyperparathyroidism and other abnormalities of the CKD–MBD constellation may have contributed to the different control in some of the biochemical parameters observed in COSMOS. However, the different strategies and policies followed by each centre or country may have also played a role. For example, the centres which planned to initiate treatment with active vitamin D at lower serum PTH levels achieved in their patients lower serum PTH levels (Figure 2).

In COSMOS, the minority of haemodialysis patients (30.6%) were receiving some form of native vitamin D, similar to the FPCO (32.3%) [24]. In contrast, 48% of the patients received active vitamin D metabolites, a figure higher than that observed in the FPCO [24], but lower than that found in the FARO [13] and RISCAVID [14]. In agreement with data from the FPCO [24] and FARO [13], oral administration of active vitamin D was the predominant route of administration in COSMOS. The oral use of active vitamin D metabolites was more frequent in Eastern and non-Mediterranean countries.

A larger proportion of COSMOS patients received phosphate binders (86.4%) as it has been described in previous studies [13, 21, 46]. Given the fact that the use of high doses of calcium-containing phosphate binders has been associated with increased coronary artery and aortic calcification [47–50], it is important to note that calcium-containing phosphate binders were the most common phosphate binders prescribed (63.4%) in the COSMOS population, higher than that found in the FPCO (57.0%) [25] and in FARO (47%) [13], reaching

the highest proportions in Eastern and non-Mediterranean countries (Table 5).

Despite the existing effective therapies for the treatment of secondary hyperparathyroidism, the proportion of haemodialysis patients parathyroidectomized was still high (6.6%), similar to the FPCO (7.1%) [24]. However, it is important to stress that COSMOS and FPCO baseline data reflect just the beginning of the use of new drugs, like calcimimetics and new vitamin D receptor activators such as paricalcitol, so that the possible benefits of these new compounds in the management of secondary hyperparathyroidism cannot be evaluated in this baseline COSMOS analysis.

There were important differences within the European regions in the serum cut-off PTH levels used for deciding when to perform a parathyroidectomy. In the Mediterranean countries, 63.1% of dialysis centres considered performing a parathyroidectomy when PTH was higher than 1000 pg/mL, in contrast to lower cut-off levels found in the non-Mediterranean countries (Figure 3A). As a consequence, the percentage of dialysis centres performing parathyroidectomies in the previous 12 months of the inclusion in COSMOS was lower in the Mediterranean countries (63.6 versus 75.0%, Figure 3B). Despite the differences observed in the general criteria in deciding when to perform a parathyroidectomy, the percentage of parathyroidectomized patients was homogeneous across all regions compared (6.6%).

One important limitation of COSMOS and other observational studies in which the prescription of drugs is recorded is that the real intake of them is unknown as it is a matter of adherence and compliance. In CKD 5D, almost all patients are receiving multiple treatments. Some of the drugs can be perceived to be more important for the patient than others due to multiple reasons such as better knowledge of the complications of this specific problem, mobility advantages, pain relief, positive effect on well-known heart risk factors, and several others. All these circumstances may impact the adherence and compliance of drugs used in the control of the CKD–MBD, which are not prescribed to solve either acute symptoms or obvious problems for the patient, thus they can be easily considered less important, reducing or discontinuing their intake and consequently impacting negatively on the achievement of CKD–MBD targets. The implementation of educational programmes designed to explain and clarify the importance and advantages of keeping the serum biochemical markers of CKD–MBD under control may help to improve results in this area [51].

In summary, the COSMOS baseline results show a real scenario of the European haemodialysis population characterized by an elevated age and a high prevalence of diabetes and cardiovascular disease. The management of secondary hyperparathyroidism shows differences across Europe. Patient demographics, medical history, comorbidities, treatment options and laboratory parameters are still heterogeneous in the different European regions analysed. Some of the observed differences can be attributed to differences in financial resources and health-care models, but others cannot be related to them.

Using the K/DIGO targets for CKD–MBD serum parameters, a great percentage of CKD 5 patients are quite outside the recommended ranges in the three main serum biochemical parameters analysed, mainly in serum phosphorus. Recent advances in the pathogenesis of CKD–MBD together with the progressive use of new safe and active drugs may contribute to a better control of these disorders in renal patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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