Epidemiology of calcium phosphate metabolism disturbances among dialysed patients in Poland in 2003-2009

Tomasz GÓRSKI[1]
Bogdan BIEDUNKIEWICZ[1]
Ewa KRÓL[1]
Przemysław RUTKOWSKI[1]
Marcin RENKE[1,2]
Bolesław RUTKOWSKI[1]

[1]Katedra i Klinika Nefrologii, Transplantologii i Chorób Wewnętrznych, GUM
Kierownik:
Prof. dr hab. med. *Boleslaw Rutkowski*

[2]Klinika Chorób Zawodowych, Metabolicznych i Wewnętrznych, GUM
Kierownik: Dr hab. med. *Marcin Renke*

Purpose: The aim of the present study was to analyse changes in identification and treatment of calcium phosphate metabolism disturbances in Poland in 2003-2009.

Material and methods: The study was an observational trial, and the data were collected based on annual surveys from dialysis units in Poland.

Results: As a result of the examinations it was found that during the study period significant improvements in calcium and phosphate indicators occurred. Due to the dissemination of knowledge on metastatic calcifications and related mortality and morbidity issues among patients with Chronic Kidney Disease, the number of patients dialysed with fluids containing recommended concentrations of calcium (1.25 mmol/l) has increased, and the amount of the highest dosage of calcium-based phosphate binders significantly decreased.

Conclusions:

Thanks to the annual updated recommendations of the Board of the Polish Nephrology Consultant's Working Group which were based on the worldwide recommendations it was found that the data obtained in our studies showed a comparable, and in some cases better, percentage of dialyzed patients in Poland who achieved the recommended values of laboratory parameters of calcium and phosphate, in relation to other developed countries.

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Key words:
• calcium-phosphate metabolism
• epidemiology
• chronic kidney disease

Epidemiologia zaburzeń gospodarki wapniowo-fosforanowej wśród pacjentów dializowanych w Polsce w latach 2003-2009

Cel: Analiza zmian w diagnostyce i leczeniu zaburzeń gospodarki wapniowo-fosforanowej w Polsce w latach 2003-2009.

Materiał i metodyka: Badanie obserwacyjne, podczas którego zbierano corocznie dane ze stacji dializ w Polsce.

Wyniki: Stwierdzono w badanym okresie znaczącą poprawę ocenianych wskaźników gospodarki wapniowo-fosforanowej. W związku z popularyzacją wiedzy o przerzutowych zwapnieniach i związanych z nimi zwiększoną śmiertelnością i zachorowalnością wśród pacjentów z przewlekłą chorobą nerek, liczba pacjentów dializowanych z płynami o niskim stężeniu wapnia (1,25 mmol/l) wzrosła, ponadto zmniejszyła się istotnie ilość chorych używająca najwyższe dawki wapniowych preparatów wiążących fosforany

Wnioski: Wprowadzenie zaktualizowanych zaleceń Grupy Roboczej powołanej przez Krajowego Konsultanta ds. Nefrologii, które zostały oparte na zaleceniach światowych spowodowało, że dane uzyskane w badaniach wykazały porównywalny, a w niektórych przypadkach nawet większy odsetek pacjentów dializowanych w Polsce, którzy osiągnęli zalecane wartości ocenianych parametrów laboratoryjnych gospodarki wapniowo-fosforanowej, w stosunku do pacjentów leczonych w innych krajach rozwiniętych.

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Słowa kluczowe:
• gospodarka wapniowo-fosforanowa
• epidemiologia
• przewlekła choroba nerek

Introduction

In recent years, interest in epidemiology has increased. This may be proven by the fact that there is an increasing need for epidemiological data among those responsible for the creation of state budgets, as well as insurance and pharmaceutical companies. Such data may be used in planning decisions that are important for consultants in the field of medicine, heads of wards, managers of hospitals and payers. Epidemiological studies can also be used to determine the effectiveness and quality of treatment, compare drug action or therapeutic methods, and to see the impact of treatment on the prevalence of diseases and the mortality of patients.

This paper presents the epidemiology of calcium and phosphate metabolism disorders in Poland in 2003-2009, its analysis, and the changes that were observed in this field during a seven-year observation.

The aim of this paper is to investigate the changes in the basic indicators of calcium and phosphate during the investigated period, with regard to the recommendations of Polish experts [1,2] as well as to international guidelines [3-5] and worldwide data [6].

To this end, a survey was carried out concerning the parameters of calcium and phosphate, and the procedures and drugs used to treat the above-mentioned disorders.

Adres do korespondencji:
Prof. dr hab. med. Bolesław Rutkowski
Kierownik Katedry i Kliniki Nefrologii, Transplantologii i Chorób Wewnętrznych GUMed
ul. Dębinki 7, 80-211 Gdańsk
tel.048 58 349 25 05
fax 048 58 346 11 86
e-mail: bolo@gumed.edu.pl

Material and Methods

The data were elaborated based on annual surveys from individual dialysis units in Poland performed from 2003 until 2009. The study was led as an observational trial collecting data after the end of each studied year, which correlated with a long period of data collecting and interpretation. Each questionnaire was based on the cumulated data of patients treated in centres participating in this study. Calcium and phosphate serum concentrations were estimated using methods available in each individual laboratory. Generally, the majority of them used standard photometric methods, but ionized calcium was measured by ion-selective electrode potentiometry.

For the quantitative determination of intact parathyroid hormone (PTH) in human serum and plasma an *in vitro* chemiluminescent microparticle immunoassay (CMIA) or immuno-radio-metric assay (IRMA) was used.

Unfortunately, calcium values have not been standardized to albumin-corrected calcium, although these analyses tried to control significant conditions of data comparability.

All of this data was validated using publications and information from the Polish National Registry [7-9].

Results

The data were initially collected in accordance with the recommendations of K/DOQI and the Polish Nephrology Working Group, but the final part took place when KDIGO came into force. The presented results are based on surveys sent to all Polish dialysis units every single year and were possible thanks to the Polish physicians who supported our activities.

The data presented in table I, collected from 2003 until 2009, show that the percentages of dialysis units and patients that participated in the study fluctuated in the ranges 86%-42% and 76%-41%, respectively.

Laboratory parameters

In the course of a seven-year observation, a minority of patients fell within the recommendations range for phosphorus, the values of which maintained on a similar level. Nevertheless, more than 50% of patients had hyperphosphatemia. A total of 10% of analysed patients had hypophosphatemia, among whom each fifth patient (data from 2009) had unacceptable death risk lab values (Tab. II).

Table III illustrates the positive trend of calcium concentration declining, between 2003 and 2008, when the percentage of patients with the highest calcium concentration (>9.5 mg/dl) decreased significantly from 33% to 18%. The number of patients falling within the guidelines range increased insignificantly, but the numbers of hypocalcemic patients significantly increased to 38.5%.

PTH recommended values (KDIGO 100-600 pg/ml) were achieved by almost 60% of patients; however, 15% had lower, and 27% had more severe PTH concentration than recommended (Tab. IV).

Treatment methods

Figure 1 shows an increased number of dialysis sessions with recommended dialysate calcium concentration in comparison to the initial years of the study. The percentage of patients receiving dialysate with calcium values of 1.75 mmol/l significantly decreased from 9% in 2003 (even 12% in 2004) to 2.5% in 2009.

There were observed different fluctuations of usage of phosphate binders: a decreased number of patients receiving high dosage of calcium-based phosphate binder (down to 18%) and an increased percentage of patients who did not receive the above-mentioned drugs (15%) (Tab. V); initially increasing number of patients receiving non-calcium phosphate binder – sevelamer, which was indicated for more

Table I

Percentage of dialysis units and patients participating in the calcium-phosphate metabolism disturbances trial in Poland.

Procent stacji dializ i pacjentów uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

Year	No of dialysis units	No of patients
2003	176/204 (86%)	8676/11440 (76%)
2004	163/206 (79%)	8744/12443 (70%)
2005	149/209 (71%)	8621/13094 (66%)
2006	181/214 (85%)	10204/13780 (74%)
2007	133/225 (59%)	7976/14645 (55%)
2008	166/234 (71%)	9858/15980 (62%)
2009	103/245 (42%)	6746/16520 (41%)

Table II

Serum phosphate categorical analysis in patients who participated in the calcium-phosphate metabolism disturbances trial in Poland.

Analiza stężenia fosforanów u pacjentów uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

Year	Serum phosphate (mg/dl)					
2003	<5.0		5.1-6,0	6.1-7.5	7.6-9.0	>9.0
Patients (%)	37		22	23	12	6
2004	<3.5	3.6-5.5	5.6-6.0	6.1-7.5	7.6-9.0	>9.0
Patients (%)	10	39	13	22	11	5
2005	<5.5		5.6-6.0	6.1-7.5	7.6-9.0	>9.0
Patients (%)	49		14	22	10	5
2006	<5.5		5.6-6.0	6.1-7.5	7.6-9.0	>9.0
Patients (%)	50.5		12.5	22.5	10	4.5
2007	<3.5	3.6-5.5	5.6-6.0	6.1-7.5	7.6-9.0	>9.0
Patients (%)	10	43	12	21	9	5
2008	<3.5	3.6-5.5	5.6-6.0	6.1-7.5	7.6-9.0	>9.0
Patients (%)	11	43	13	21	8	4
2009	<2.1	2.1-3.4	3.5-5.0	5.1-9.5	>9.5	
Patients (%)	2	8	39	48.5	2.5	

Table III

Serum calcium categorical analysis in patients who participated in the calcium-phosphate metabolism disturbances trial in Poland.

Stężenia wapnia u pacjentów uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

Year	Serum calcium (mg/dl)			
2003	<8.0	8.1-9.6	9.6-10.5	>10.5
Patients (%)	16	51	25	8
2004	<8.4	8.4-9.5	9.6-10.5	>10.5
Patients (%)	25.5	48	21.5	5
2005	<8.4	8.4-9.5	9.6-10.5	>10.5
Patients (%)	29	50	17	4
2006	<8.4	8.4-9.5	9.6-10.5	>10.5
Patients (%)	32.5	49.5	15	3
2007	<8.4	8.4-9.5	9.6-10.5	>10.5
Patients (%)	34	50	13	3
2008	<8.4	8.4-9.5	9.6-10.5	>10.5
Patients (%)	30	52	15	3
2009	<8.5	8.6-10	>10	
Patients (%)	38.5	54.5	7	

Table IV

Serum PTH categorical analysis in patients who participated in the calcium-phosphate metabolism disturbances trial in Poland.

Stężenia PTH u pacjentów uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

Year	Serum PTH (pg/ml)				
2003	<100	101-300	301-500	>500	
Patients (%)	26	35	17	22	
2004	<150	151-300	301-500	501-800	>800
Patients (%)	30	25.5	20	16	8.5
2005	<150	151-300	301-500	501-800	>800
Patients (%)	31	26	17.5	12	13.5
2006	<150	151-300	301-500	501-800	>800
Patients (%)	30	25.5	18.5	13	13
2007	<150	151-300	301-500	501-800	>800
Patients (%)	24,5	25	21,5	13	16
2008	<150	151-300	301-500	501-800	>800
Patients (%)	24	25.5	21	15	14.5
2009	<100	100-601		>601	
Patients (%)	15	60		27	

Table V

Calcium carbonate dosage in patients who participated in the calcium-phosphate metabolism disturbances trial in Poland.

Dawka węglanu wapnia u pacjentów uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

Year	Calcium carbonate dosage (g/day)					
2003	0	<1	1-3	4-6	7-9	>9
Patients (%)	10	3	46	29	7	5
2004	0	<1	1-3	4-7	>7	
Patients (%)	9	3	50	27	11	
2005	0	<1	1-4	5-7	>7	
Patients (%)	11	3	57	21	8	
2006	0	<1	1-4	5-7	>7	
Patients (%)	11	3.5	58	20	7.5	
2007	0	<1	1-4	5-7	>7	
Patients (%)	14	2.5	58.5	18	6.5	
2008	0	<1	1-4	5-7	>7	
Patients (%)	13	2	64	16	5	
2009	0	<1	1-4	>4		
Patients (%)	15	3	64	18		

patients between 2003-2008 (2-10%) and went down in 2009 (4%), and a decreasing percentage of patients had taken aluminium-based phosphate binder (9%) (Fig. 2). It should be stressed that in 2009 lanthanum-based phosphate binder was indicated for 0.5% of patients. Figure 2 shows also that 4% of patients were treated by calcimimetics available in Poland from 2005, 45% of patients received vitamin D analogues, and a decreasing numbers of patients had parathyroidectomy performed (PTX) as well.

Discussion

The current study is the largest observational trial regarding bone and mineral disorders in Poland playing an informative role in mineral metabolism in the recent past. The number of dialysis units and patient percentages in this observation fluctuated in the ranges 86%-42% and 76%-41%, respectively. Nevertheless taking into account number of patients participating in this survey one how to mention that results of this study are representative for whole cohort of Polish dialysed patients. Measured parameters of the above-mentioned metabolism were indicated based on expert recommendations [1-5].

Despite calcium-phosphate disturbances, treatment progression, based on dietary restriction, adequate dialysis therapy, phosphate binders, calcimimetics and new generation vitamin D usage, still more than 50% of patients have hyperphosphatemia - one of the most common disturbances among ESRD patients (Tab. II). That is why, despite the fact that there is not a single treatment goal, attention should be paid to its confirmed role in cardiovascular disease progression [10-14].

The same and even more important roles are played by hypercalcemia and hypocalcemia as risk factors which have been associated with increased morbidity and mortality as well as abnormalities in serum phosphorus, or parathyroid hormone (PTH) concentrations [11-13]. The lowest mortality risk for calcium concentration lies between 8.6 to 10.0 mg/dl and albumin corrected calcium concentration Ca(Alb) (7.6 to 9.5 mg/dl), which represents 54.5% of the studied population. The highest risk of mortality, greater than 10.0 mg/dl, represents 7% of patients in Poland [15]. In addition, the high percentage of hypocalcemic patients with high risk of adynamic bone disease, which represents more than 38% of the observed population, is worrying because it is an important predictor of CV (cardiovascular) diseases (Tab. III).

As we mentioned earlier, calcium values have not been standardized to albumin-corrected calcium, however values achieved thanks to repetitive methodology let us show trends changes.

It should be noted that between 2003 and 2008 the percentage of patients with the highest calcium concentrations (>9.5 mg/dl) decreased significantly from 33% to 18%. Observed phenomenon could be caused by several factors, such as decreasing dosage of calcium-based phosphate binders and calcium concentration in dialysate, non-calcium phosphate binder and calcimimetics usage.

The above indicators are inseparably related with another important parameter of bone and mineral disorders – PTH. This well-controlled indicator as an independent risk factor is not associated with relative risk of death caused by hyperphosphatemia, but increased hyperparathyroidism and adynamic bone disease have been associated with serum calcium and serum phosphorus increases leading to CV calcification [11].

The PTH recommendations range [4,5] shown in table IV was not achieved in 15% of patients with adynamic bone disease (<100 pg/mg) or in 27% of patients with secondary hyperparathyroidism (>600 pg/ml), probably caused by hyperphosphatemia co-existing with hypocalcemia. The reasons for low PTH could be associated with diabetes, aging population, usage of high doses of vitamin D and calcium-based phosphate binder as well as aluminium-based phosphate binder.

Dialysis therapy development is still ongoing, from the first dialysis, via evolution of dialysis machines, dialysers and lines [16], to trials based on molecular biology or genetics [17]. Technology is not the only are of development; medicines and treatment options are also progressing. Our observations confirm and extend the state of knowledge about identification and treatment options of mineral disorders.

It should be stressed that we observed a slow but significant and advantageous change in the direction of calcium dosage and high calcium concentration in dialysate (Figure 1 and Tab. V). A high indication of calcium-based phosphate binder as well as dialysate calcium value is associated with calcium active balance and even higher

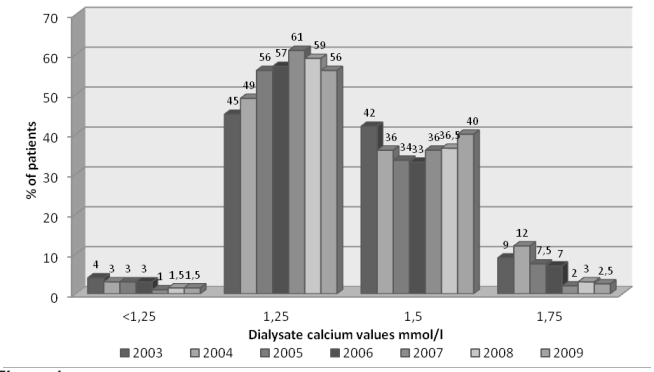

Figure 1

Dialysate calcium values in patients who participated in the calcium-phosphate metabolism disturbances trial in Poland.

Stężenia wapnia w dializacie u pacjentów uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

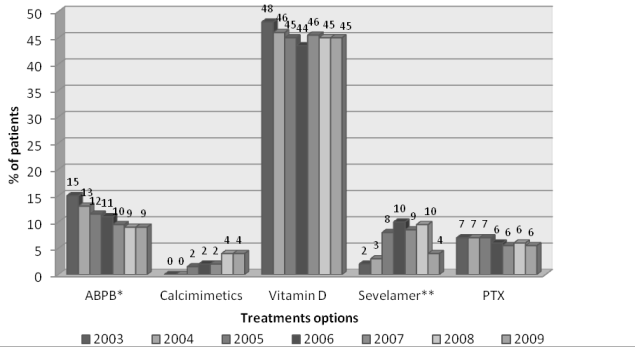

Figure 2

Procedures used in patients participating in the calcium-phosphate metabolism disturbances trial in Poland.

Zastosowane procedury u uczestniczących w ocenie zaburzeń gospodarki wapniowo-fosforanowej w Polsce.

**Aluminium-based phosphate binder*

***Data includes average 30% of patients receiving calcium-based phosphate binders and sevelamer simultaneously*

risk of death. Correct maintenance of the above-mentioned parameter has a huge impact on correct parathyroid gland function and calcification prevention [18-22]. Unfortunately, the percentage of patients given non-recommended dosages of calcium based phosphate binder (18%) and calcium concentration (42.5%), which could cause metastatic calcification and calciphylaxis, is still too high.

Unfortunately, 9% of patients are still treated with aluminium-based phosphate binder, causing the threat of adynamic bone disease [23,24]. Non-calcium, non-aluminium phosphate binders (4.5%) [25-30] were used in a limited capacity as well as calcimimetics (4%) [29-32] because of a lack of extra funding from the national budget (currently calcimimetics are reimbursed).

Only 45% of patients use vitamin D analogues stopped PTH synthesis in order to prevent renal osteodystrophy, bone fracture and pain (Fig. 2). Above treatment reduces parathyroid hormone levels but may results in increasing the risk of vascular calcification in dialysis patients. On the other side new generation vitamin D - paricalcitol which treats high serum PTH levels, with a reduced risk of hypercalcemia and hyperphosphatemia is used in Poland very rare [33-36].

Summary

This national study of a large group of dialysed patients shows that in seven years of observation an increased number of patients achieved the recommended indicators of mineral and bone disorders. Simultaneously, the number of PTX, the number of patients dialysed with fluids containing recommended concentrations of calcium, as well as the amount of the highest dosage of calcium given in compounds that bind phosphates, decreased. This was caused by the introduction of dietary restriction, new generation phosphate binders, calcimimetics and, even more, the following of expert recommendations.

The epidemiological data obtained in our studies showed a comparable percentage of dialysed patients in Poland who achieved the recommended values of laboratory parameters of calcium and phosphate, in relation to other developed countries, confirmed by results from DOPPS IV (The Dialysis Outcomes and Practice Patterns Study) [6]. It should be stressed that the outcomes above are achieved with limited availability of the above-mentioned new generation medicines.

Nowadays a key task is to identify and monitor the calcium-phosphate metabolism disturbances among CKD patients (stage 5). These however appear is earlier stages of CKD and that's we should challenge this problem watchfully, adequately to the course of the disease [37].

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