The Influence of Physical Activity on Serum Phosphate Levels in a Group of Hemodialysis Patients

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The prevalence of mineral bone disorders in chronic kidney disease (MBD-CKD) and the cardiovascular risk are increased in hemodialysis (HD) patients. Hyperphosphatemia is one of the complications often associated with increased cardiovascular risk, and in CKD patients, the reduced renal excretion of phosphate is an important cause of elevated serum of this microelement. Physical activity represents another contributing factor in evaluating the risk of cardiovascular disease. The aim of our study was to determine the influence of physical activity on serum phosphate levels in HD patients. The inclusion criteria of this 3-months study were: age > 18 years old, dialysis vintage > 6-months, diuresis > 500 mL/day, PTH values between 100-500 pg/mL, similar dialysis protocol, phosphate daily intake and MBD-CKD therapy. The following parameters were monitored: dry weight, diuresis, associated comorbidities, hemoglobin, serum calcium, phosphate, sodium, potassium, serum albumin, intact parathormon, bicarbonate. The physical activity was assessed during 4 days (3 week-days and 1 during the week-end) for 3 months, and the patients had to complete a questionnaire, too. 49 patients were included and divided in 5 groups, depending on their physical activity. Analyzing the parameters influence on serum phosphate levels, we observed that physical activity, serum calcium and albumin were the only parameters statistically significant ($p = 0.001$, $p = 0.033$, and $p = 0.47$, respectively). The nutritional recommendations of chronic HD patients should be adapted to their individual level of physical activity, in order to avoid an abnormal increase of serum phosphate level, and to improve to over-all outcome.

Keywords: hemodialysis, serum phosphate levels, physical activity, prognosis

The prevalence of mineral bone disorders in chronic kidney disease (MBD-CKD) increases in patients with end-stage renal disease (ESRD), especially in hemodialysis (HD) population [1]. Increased cardiovascular risk secondary to the presence of MBD-CKD represents the aim of numerous studies focused on improving patient prognosis, once an adequate therapy management has been initiated [2,3].

For a better patient outcome, attention should be paid to the correction of serum phosphate levels, as hyperphosphatemia is the most commonly complication associated with increased cardiovascular risk [4]. Immediate treatment measures should be taken both in predialysis and chronic hemodialysis patients, as the decrease of hyperphosphatemia is directly proportional to the decrease of vascular calcification risk. Not only specific medication (phosphates chelators, active vitamin D, calcimimetics) but also diet plays an important role in the management of MBD-CKD [5,6]. In order to achieve better outcomes in reducing hyperphosphatemia, nutritional counseling should be provided for each patient [7,8].

There is common knowledge that serum phosphates absorbed in the intestinal blood results from the daily diet. Only by maintaining an optimal serum level, this microelement contributes to maintaining the integrity of the bone system; the surplus is renal eliminated or by faecal [9]. In regulating the serum concentration of phosphorus interfere: PTH (parathormon), FGF-23 (fibroblast growth factor 23) and vitamin D [10], factors that present abnormal values in CKD patients (as a consequence of the kidney impairment): elevated levels of phosphorus and PTH and low serum calcium and vitamin D.

As already mentioned, the level of serum vitamin D3 depends on the renal function, because in the kidneys the second hydroxylation takes place at position 1 of 25 (OH) D and consequently 1.25 (OH) D is obtained (figs. 1 and 2 [11,12]

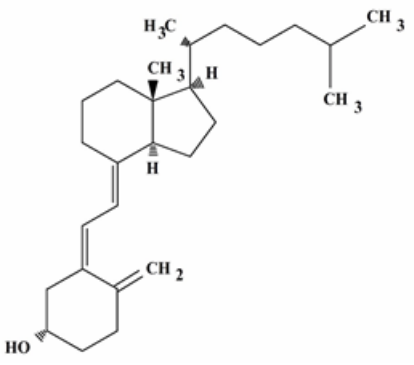

Fig. 1. 25(OH)D – 25-hydroxyvitamin D

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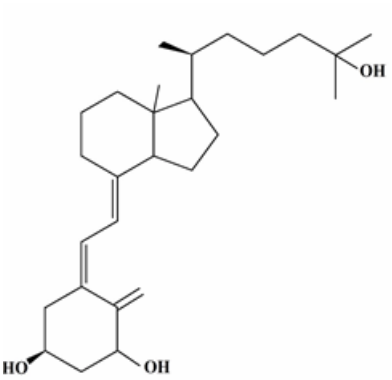

Fig. 2. 1.25(OH)D – 1.25-dihydroxyvitamin D

In CKD patients, the reduced renal excretion of phosphate is an important cause of elevated serum of this microelement [13]. Starting from the fact that the main source of phosphate is represented by the daily food intake and that its excretion is dependent on the renal function [14-17], the hypothesis that an adequate diet is important for the improvement of hyperphosphatemia and consequently the prognosis of MBD-CKD patients is supported [10,18].

Another important role in preventing cardiovascular disease is represented by physical activity [19]. According to the literature, also in chronic HD patients, physically active, even after a mild physical activity, both a decrease in cardiovascular risk and an improvement in the quality of life are noticed [20-23].

Therefore, in HD population, it is important to analyze the influence of physical activity on phosphate metabolism, as different studies concluded hyperphosphatemia has a negative impact long-term prognosis and also there is a clear link between physical activity and the decrease of cardiovascular risk [4,20-23].

There are several data that showed the influence of physical activity on the intestinal absorption of phosphates. Furthermore, in healthy and physically active individuals, the metabolism of calcium and phosphate is linked to the influence of physical exercise on vitamin D3 (1.25(OH)2D3) and PTH levels, and bone metabolism, as well.

One experimental study performed in rats with normal kidney function reported that the sedentary group presented a decrease of the intestinal absorption of calcium and phosphate, but an increase of renal and digestive excretion. Consequently, the decrease in serum levels of calcium and phosphorus contributes to an abnormal phosphate metabolism. In the physical active group, elevated levels of serum calcium and phosphate, and decreased excretion were observed [24], because in normal conditions an increased intestinal absorption and decreased renal excretion is secondary to the elevated serum levels of 1.25(OH)2D3 and lessened serum PTH values. In case of sedentary individuals, a low phosphate intestinal absorption is due to decreased serum levels of 1.25(OH)2D3 [25]. It is important to emphasize that 1.25(OH)2D3 (calcitriol) contributes to the phosphate absorption by influencing the phosphorus-facilitated transcellular transport (coupled with sodium) [26,27].

Additionally, the association of physical activity with serum phosphate increase is supported by studies performed on performance athletes (e.g. boxers, runners). In both groups of subjects, an intense physical activity was correlated with elevated serum phosphate levels [28,29].

Currently, in chronic HD patients, there are no studies presenting the influence of physical activity on MBD-CKD. Therefore, the aim of our study is to determine the influence of physical activity on serum phosphate levels in HD patients with controlled dietary phosphate intake.

Experimental part

Methods

The present study, prospective conducted during a 3-months period, is part of a PhD research which main objective is to determine the nutritional implications on over-all outcome in chronic HD individuals. The inclusion criteria, for this study, consisted in: age > 18 years old, dialysis vintage > 6-months, diuresis > 500 mL/day, PTH values between 100-500 pg/mL, similar dialysis protocol, phosphate daily intake and MBD-CKD therapy. In addition, all included subjects signed the patients' informed consent. The following patients were excluded: those who did not match the above mentioned inclusion criteria, any forms of cancers or active hepatitis, patients with special diets (e.g.: malabsorption syndrome, vegetarian / vegan diet) and those who during the follow-up would be moved to another dialysis center.

After the assessment of the inclusion criteria, 49 patients (57.14% men and 42.86% women) with mean age of 58.86 ± 9.7 years old consent to participate to our physical activity research. Additionally, the following parameters were monitored: dry weight, diuresis, associated comorbidities (diabetes mellitus, hypertension etc), hemoglobin (g/dL), serum calcium (mg/dL), phosphate (mg/dL), sodium (mmol/L), potassium (mmol/L), serum albumin (g/dL), intact parathormon (pg/mL), bicarbonate (mmol/L).

Our patients followed the same dialysis protocol that included: sessions of 4 h, 3 times per week, high flux dialysis with a blood flow of at least 300 mL/min, polysulfone membranes, bolus administration of low molecular weight anticoagulant at the beginning of each dialysis session.

The physical activity was classified according to the classification proposed by Suenaga T in 2002 [30]:

·(1): sedentary – resting 19-21 h, walking < 1 h, muscle exercise < 10 min

·(2): sedentary + walking – resting ≥ 17 h, walking 3-5 hours, muscle exercise < 10 min

·(3): sedentary + brisk walking – resting ≥ 17 h, brisk walking 1-2 h, muscle exercise < 10 min

·(4): sedentary + exercise – resting ≥17 h, brisk walking > 1 hour, muscle exercise > 20 min

·(5): active – resting < 17 h, walking > 6 h, muscle exercise < 10 min

·(6): active + exercise – resting < 17 hours, walking > 4 hours, brisk walking for 1-2 h, muscle exercise > 20 min

This classification was based on 4 stages of activity: resting, walking, brisk walking that corresponds to work and light exercise, and muscle exercise corresponding to heavy work medium and high intensity exercise [30].

These stages of activity were determined by a questionnaire that had to be completed by all the included patients at the beginning of the study. Thus, household (cleaning, gardening, etc), recreational (walking, swimming, running, etc) and the type of work activities were taken into account, each of these activities being included in one of the 4 stages mentioned above. In addition, the patients were asked to estimate the time spent for their different performed activities. The subjects had to quantify their activity during 4 days (3 week-days and 1 during the week-end) for 3 months. After the questionnaire was completed, the subjects were divided only in 5 groups, because no HD individual from our study could be included into the 6th type of physical activity (active

Table 1

THE CHARACTERISTICS OF THE STUDIED PATIENTS DURING THE 3-MONTHS FOLLOW-UP (THE MEAN AND SD VALUES WERE PRESENTED)

Classification of physical activity	Gender	Age (years)	Dry weight (kg)	Diuresis (mL/day)	P (mg/dL)	Ca (mg/dL)	iPTH (pg/mL)	Hb (g/dL)	Na (mmol/L)	K (mmol/L)	Alb (g/dL)	Bicarbonate (mmol/L)
1. sedentary	2 M and 3 W	61 ± 7.38	71.76 ± 17.73	680 ± 204.94	**4.745 ± 0.52**	9.55 ± 1.63	144.3 ± 43.26	10.7 ± 1.03	138.2 ± 1.4	5 ± 0.55	4.2 ± 0.44	19.1 ± 1.47
2. sedentary + walking	12 M and 7 W	61.11 ± 9.56	72.8 ± 12.99	831.58 ± 413.73	**4.668 ± 0.77**	8.91 ± 0.42	214 ± 107.84	10.8 ± 2.32	137.9 ± 2.74	4.9 ± 0.43	4 ± 0.27	19.1 ± 1.57
3. sedentary + brisk walking	10 M and 8 W	55.78 ± 11.18	73.63 ± 10.78	844.44 ± 291.49	**5.513 ± 0.86**	9.22 ± 0.38	233.5 ± 99.77	10.9 ± 1.41	138 ± 1.75	5.1 ± 0.58	4.3 ± 0.25	18.8 ± 1.08
4. sedentary + exercise	1 M and 1 W	60 ± 1.41	69.75 ± 5.3	1300 ± 707.1	**7.095 ± 1.06**	8.0 ± 0.15	316.5 ± 154.83	10.3 ± 0.94	140.1 ± 0.3	5.3 ± 0.25	3.8 ± 0.53	19.5 ± 0.12
5. active	3 M and 2 W	58.8 ± 7.63	75.72 ± 16.9	840 ± 421.9	**7.127 ± 0.7**	9.24 ± 0.08	233.6 ± 123.91	9.9 ± 1.19	135.3 ± 1.71	5.7 ± 0.76	4.1. ± 0.17	19.5 ± 0.96

*Legend: M = man/men; W = woman/women; P = serum phosphate; Ca = serum calcium; iPTH = intact parathormon; Hb = hemoglobin; Na = serum sodium; K = serum potassium; Alb = serum albumin; SD = standard deviation; Bicarbonate = serum bicarbonate.

+ exercise: resting < 17 h, walking > 4 h, brisk walking for 1-2 h, muscle exercise > 20 min) (fig.3).

Each patient received nutritional counseling, because the aim of this study was to determine the influence of physical activity on serum phosphate levels in HD patients with controlled dietary phosphate intake. They received not only a controlled daily amount of phosphate (800-1000 mg/day), but also recommendation regarding to the classification of foods according to the provided level of phosphates. In chronic HD patients, the daily intake of phosphate influences the serum level of this microelement, therefore the adherence of patients to the proposed diet is very important [6,18]. In this study, the adherence of patients to the nutritional counseling was possible based on the analysis of their phosphorus changes during the follow-up. Furthermore, the specific characteristics of patients, including serum phosphate levels, were subsequently evaluated also depending on their physical activity.

Statistical analysis

All data were assessed using SPSS.16 and Excel, and the following tests were performed: descriptive statistics, one-way ANOVA, square R test, categorical regression with optimal scaling using alternating least squares; a p value $p < 0.05$ was considered significant.

Results and discussions

After the evaluation of all parameters, the included subjects (49 patients – 28 men (57.14%) and 21 women (42.86%) – mean age of 58.86 ± 9.7 years old) were divided in 5 groups, depending on their physical activity; their characteristics are presented in table 1.

Analyzing the results, we noticed that the serum phosphate levels were direct proportional with the intensity of the activity, and the highest value was observed in the 5th class (with active patients).

Therefore, we hypothesized that a more intense physical activity could induce a higher value of serum phosphate and we wanted to determine if the serum phosphate levels are influenced exclusively by the degree of physical activity or there are other factors that could explain these results.

A mathematical model was performed using square R test and categorical regression with optimal scaling using alternating least squares, where the serum phosphate value was considered the dependent variable and the rest of the parameters (physical activities, comorbidities, dry weight, diuresis, iPTH, hemoglobin, serum calcium, sodium, potassium, albumin and bicarbonate) represented the predictors. The square R was equal to 0.869 (R value should be close to 1) and we concluded that the estimated model presented statistical significance.

Furthermore, the regression test showed the following results (table 2).

Analyzing the data, we observed that physical activity, serum calcium and albumin were the only parameters statistically significant ($p = 0.001$, $p = 0.033$, and $p = 0.47$, respectively; $p < 0.05$), and, furthermore, the physical activity presented the highest influence on serum phosphate level, finding that supported our initial hypothesis. The coefficient β associated to the physical activity with a value of 0.804 indicated that a 1% increase of the physical activity would elevate serum phosphate

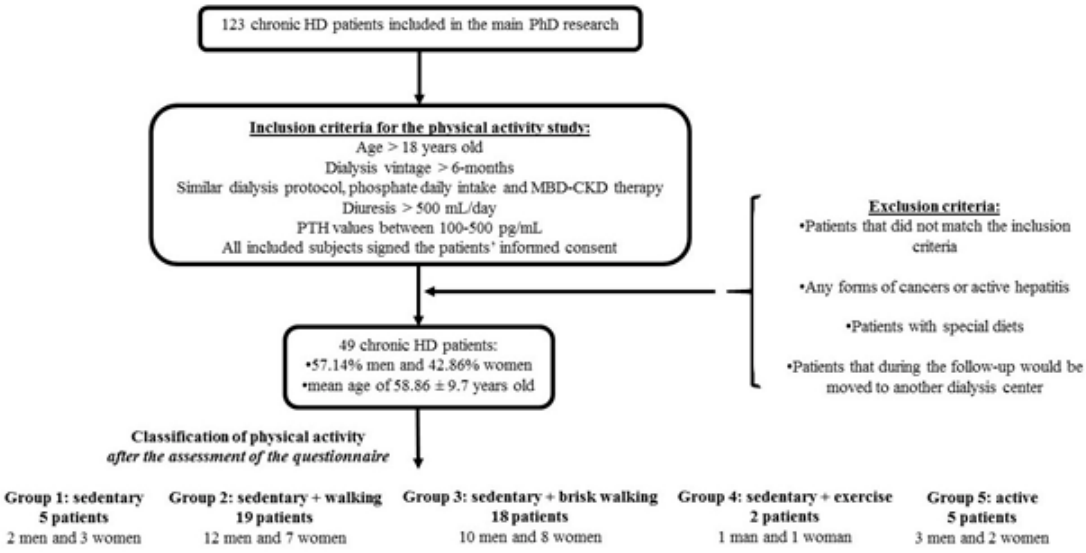

Fig. 3. The study design diagram

Table 2

THE INFLUENCE OF DIFFERENT PARAMETERS ON SERUM PHOSPHATE LEVELS (THE MEAN VALUES WERE COMPARED)

Parameter	Associated coefficient (β)	Standard error	*p-value ($p < 0.05$)*
Physical activity	0.804	0.198	*0.001*
Serum calcium (mg/dL)	0.509	0.212	*0.033*
Serum albumin (g/dL)	-0.434	0.205	*0.047*
Serum potassium (mmol/L)	0.371	0.177	*0.057*
Chronic obliterative arteriopathy of the inferior limbs	-0.450	0.235	*0.081*
Diuresis (mL/day)	0.331	0.186	*0.105*
Serum sodium (mmol/L)	0.344	0.193	*0.105*
Coronary heart disease	-0.281	0.186	*0.171*
Heart failure	0.245	0.164	*0.178*
Serum bicarbonate (mmol/L)	-0.244	0.175	*0.206*
Age (years)	-0.264	0.216	*0.296*
Atherosclerosis	0.206	0.176	*0.314*
Hemoglobin (g/dL)	0.189	0.162	*0.318*
Cardiomyopathy	0.209	0.191	*0.358*
Dry weight (kg)	0.130	0.159	*0.441*
iPTH (pg/mL)	-0.160	0.167	*0.479*
Diabetes mellitus	0.169	0.212	*0.555*
Hypertension	-0.087	0.187	*0.813*
Gender	-0.034	0.181	*0.965*

level with 0.804 mg/dL. Similar was for the serum calcium that determined an increase with 0.509 mg/dL of this microelement. In contrast, any 1% raise of the albumin would determine a decrease with 0.434 mg/dL of serum phosphate.

There are several studies emphasizing the importance of serum phosphate daily intake on the long-term prognosis [31,32]. Furthermore, there are different other parameters that can influence the amount of serum phosphate, such as the level of iPTH, serum calcium, albumin, bicarbonate, residual diuresis, dry weight or even associated comorbidities [33-35].

Our findings are according to these data (e.g. the influence of calcium and albumin – $p = 0.033$, and $p = 0.47$, respectively), but besides these facts, our study, the first from our knowledge, highlights a positive correlation

between serum phosphate levels and the degree of the physical activity. During the follow-up, there was a clear evidence that a more intense physical activity would elevate the values of this microelement and, consequently, the highest mean value of serum phosphate was noticed in the most active group (7.127 mg/dL; $p < 0.05$) – group 5. A similar result was observed in an older experimental study of Yeh et al that noticed an increase of serum phosphate levels in more active rats [24]. The explanation could be that the higher is the degree of physical activity, the more increased is the intestinal absorption of phosphates. In contrast, patients with less intense physical activity presented decreased serum phosphate levels.

Another important result was that any 1% raise of the albumin would determine a decrease with 0.434 mg/dL of serum phosphate. This could be explained by the fact that higher albumin levels where noticed in HD patients with normal physical activity, suggesting the importance of a balanced diet and life-style in this group of population. This finding is in accordance with a new study that emphasized the importance of very-low protein diet associated with ketoacid analogues of essential amino acids that determine a better serum phosphate level control and, consequently, could influence the preservation of vascular wall quality in predialysis chronic kidney disease patients [36].

Summarizing, all these findings indicates that for a balanced diet in HD patients, besides the recommended daily intake protein, phosphate, calcium etc, the nutritional counseling should take into account also the type of physical activity performed by each patient. Therefore, a new algorithm of HD patients' assessment should be implemented, including also the physical activity and MBD-coronary risk score [37], besides the traditional parameters (daily macro- and microelements intake, clinical and bioumoral status, comorbidities).

Conclusions

According to the results of the present study, the nutritional recommendations of chronic hemodialysis patients should be adapted to their individual level of physical activity, in order to avoid an abnormal increase of serum phosphate level.

Our findings represent a new beginning for further research in prescribing the adequate daily intake of macro- and microelements according to patients' life-style, in order to decrease the progression of specific complication of HD individuals (MBD-CKD, acid-base and hydroelectrolytic disorder etc), increasing in this manner the long-term outcome.

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