J Nephropharmacol. 2023; 12(1): e10569.

https://www.jnephropharmacology.com DOI: 10.34172/npj.2022.10569

Journal of Nephropharmacology

Effect of niacin on phosphorus, calcium, parathormone and vitamin D levels in hemodialysis patients; a double-blinded randomized clinical trial

Ali Mohamadi Najafabadi[1], Ali Ahmadi[2], Saeed Mardani[1*]

[1]Department of Nephrology, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]School of Health, Department of Epidemiology and Biostatistics, Shahrekord University of Medical Sciences, Shahrekord, Iran

ARTICLE INFO

Article Type:
Clinical Trial

Article History:
Received: 15 September 2022
Accepted: 12 November 2022
Published online: 22 November 2022

Keywords:
Chronic kidney disease
Hyperphosphatemia
Niacin
Hemodialysis

ABSTRACT

Introduction: Electrolyte abnormalities are one of the most common problems in hemodialysis patients.
Objectives: The present study was conducted to investigate the effect of niacin on the levels of sodium, phosphorus, calcium, intact parathormone (iPTH), alkaline phosphatase (ALP) and vitamin D in hemodialysis patients.
Patients and Methods: In the present double-blinded randomized clinical trial, hemodialysis patients with phosphorus of more than 4.5 mg/dL were included in the study and were treated with niacin. The dose of niacin was increased from 50 mg to 100 mg/d in two stages on a monthly basis. Tests related to the levels of phosphorus, sodium, vitamin D, and calcium were determined before and after the intervention, and the side effects of the treatment were recorded accordingly. Data were analyzed through SPSS version 16.
Results: After the intervention, the serum levels of calcium, vitamin D, and sodium increased significantly ($P<0.05$), while the serum levels of iPTH and phosphate decreased significantly ($P<0.05$). However, the serum level of ALP did not change significantly ($P>0.05$). There was no significant difference in the serum levels of calcium, phosphate, vitamin D, sodium, iPTH, and ALP during the intervention in the both men and women ($P>0.05$). Side effects were not reported in any of the patients.
Conclusion: Niacin can increase vitamin D, sodium and calcium and decreased serum levels of phosphate and iPTH in hemodialysis patients. Therefore, it can be administered as an effective and safe supplement in the hemodialysis patients.
Trial Registration: This trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20190702044076N2; https://en.irct.ir/trial/66567, ethical code #IR.SKUMS.REC.1400.079).

Implication for health policy/practice/research/medical education:
In a double-blinded randomized clinical trial in a group of hemodialysis patients, who treated niacin for the treatment of hyperphosphatemia, we found following two months of this treatment, serum vitamin D and calcium increased significantly, since serum levels of phosphate and intact parathormone were decreased.
Please cite this paper as: Mohamadi Najafabadi A, Ahmadi A, Mardani S. Effect of niacin on phosphorus, calcium, parathormone and vitamin D levels in hemodialysis patients; a double-blinded randomized clinical trial. J Nephropharmacol. 2023;12(1):e10569. DOI: 10.34172/npj.2022.10569.

Clinical Trial

Introduction

The prevalence of chronic kidney disease is increasing in the world, especially in developing countries (1). Hemodialysis and end-stage kidney disease disrupt the quality of life in affected people and their caregivers (2). In addition, factors such as comorbidity high wealth status, old age, more visits, and anemia increase the burden of costs for the patient and the health care system (3). This complication has increased morbidity and mortality. For example, cardiovascular disease affects more than two-thirds of people undergoing hemodialysis and accounts for approximately 50% of deaths (4). As the glomerular filtration rate decreases, the kidney's ability to regulate electrolytes decreases. Therefore, electrolyte disorders such as hyperphosphatemia (subsequently an increase in the serum level of parathyroid hormone), hypocalcemia, and reduction of serum vitamin D in hemodialysis patients can be occurred (5,6). Although some drugs have

***Corresponding author**: Saeed Mardani, Email: Dr.s.mardani72@gmail.com

been administered to control the hyperphosphatemia, they have several side effects and the need to introduce new treatment strategies is felt. For instance, currently, phosphate-binding drugs, despite being effective, are associated with various side effects, including increased blood calcium (such as calcium carbonate) and an increased risk of aluminum poisoning (such as aluminum hydroxide) (7,8), or gastric lanthanosis following administration of lanthanum carbonate (9). Despite advances in dialysis and other available treatments, poor and variable outcomes are still observed among different populations, which is a major concern in hemodialysis (4). Many patients need hemodialysis as the commonest form of kidney replacement, and their access to health services may be limited in some cases; therefore, they may not receive appropriate treatment, in which case their mortality may increase several times (1).

Electrolyte imbalance in hemodialysis patients causes cardiovascular complications and subsequently increases the mortality rate in these patients (10). Hypocalcemia, which is caused by a decrease in the level of 1,25-dihydroxy vitamin D (1,25(OH)2D3), due to stimulation of fibroblast growth factor-23 (FGF23) and a decrease in renal mass and resistance to the calcemic activity of parathyroid hormone (PTH) causes the development of secondary hyperparathyroidism, renal osteodystrophy, vascular calcification and cardiac dysfunction (10,11). In addition, hyponatremia is one of the common electrolyte disturbances in dialysis patients, which is associated with an increased risk of mortality (10). Studies have shown that niacin (nicotinic acid) and its related compounds, including nicotinamide, reduce the absorption of phosphorus in the digestive tract with a different mechanism than the usual phosphate binders. Niacin reduces the digestive absorption of phosphorus due to the inhibition of the phosphorus-sodium co-transporter in the small intestine (12,13).

Objectives

Since, a comprehensive study had not investigated the effect of niacin on electrolyte disturbance and the effect of intact PTH (iPTH), in this study, we aimed to investigate the effect of niacin on sodium, phosphorus, calcium, iPTH and vitamin D levels in a group of hemodialysis patients.

Patients and Methods

Study design

The present study was a before-after double-blinded randomized clinical trial, carried out on 60 hemodialysis patients with hyperphosphatemia referred to the dialysis center of Hajer hospital of Shahrekord in 2020. The inclusion criteria were age over 15 years, phosphorus more than 4.5 mg/dL, at least six months have passed since the start of hemodialysis, no change in treatment and hemodialysis protocols in the last two weeks, and satisfaction with participating in the study. Exclusion criteria were pregnancy, known liver diseases, active peptic ulcer disease, carbamazepine use, drug intolerance, and the need to change the treatment protocol. According to similar studies and considering α=0.01, Power=0.95 and Delta=0.88, the sample size was calculated to be 26 people, however 30 people were included in the study considering the attrition rate (14,15). All patients continued the treatment and the analysis were conducted on 30 patients (Figure 1). The drug is manufactured by Sobhan Daru Company. This drug was purchased directly from the market and patients received it free of charge accordingly.

After obtaining a written consent form, hemodialysis patients who met the inclusion criteria were treated with niacin for two months. The dose of niacin was increased from 50 to 100 mg/d every month and during two stages. Tests related to the levels of calcium, phosphorus, sodium, alkaline phosphatase (ALP), iPTH, and vitamin D were determined and recorded in a checklist. Then, the data were compared before and after the intervention, and the patients were examined for possible side effects.

To perform randomization, the type of drug prescribed is randomized by simple randomization among the participants by the RRApp software. For this purpose, in the order of participation in the research, the participants received niacin (n = 30) or placebo (n = 30) based on the group they were assigned by RRApp software. This study was double-blinded because the patients knowing about the study groups did not informed about the allocation in treatment groups and this allocation conducted randomly. The statistical analyzer received the groups as A and B codes.

Statistical analysis

Data were analyzed using SPSS version 16. The descriptive results were reported as mean ± standard deviation. Paired *t* test was applied to assess the changes before and after intervention for calcium, phosphate, sodium, vitamin D, ALP and iPTH variables. Accordingly, their differences were checked between genders using independent *t* test. *P* value less than 0.05 was considered significant.

Results

Thirty hemodialysis patients with phosphorus more than 4.5 mg/dL, including 15 (50%) women and 15 (0 %) males entered the intervention group as well as 30 patients in the control group. Baseline characteristics of the patients in the both groups were similar and homogenous, without significant differences ($P > 0.05$).

The intervention group was treated with niacin for two months. The mean studied variables before and after the intervention is shown in Table 1. Following the intervention, serum calcium and vitamin D increased significantly ($P < 0.05$), while serum iPTH and phosphate levels decreased considerably ($P < 0.05$). However no

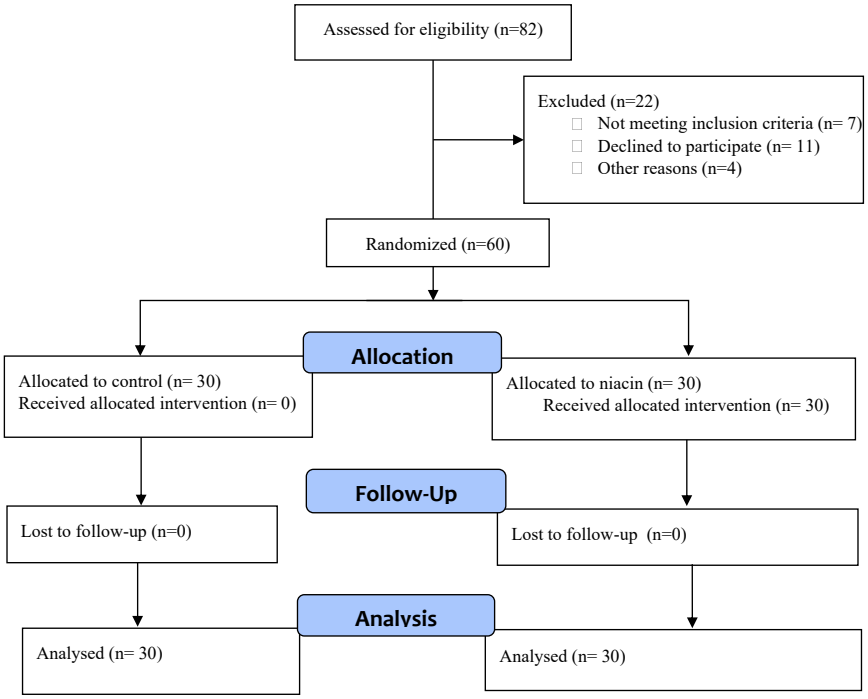

Figure 1. CONSORT flow chart of the study.

significant change was observed in the amount of ALP ($P=0.77$). In this regard, it should be noted that there were no significant changes before and after placebo.

Comparison of the mean change of the studied variables during the intervention according to gender showed that the mean change of calcium, phosphate, vitamin D, sodium, and ALP was not significantly different between the two sexes ($P>0.05$). However, serum levels of vitamin D increased more in men than in women (1.86 versus 0.93 ng/dL). However, the serum level of ALP did not change significantly ($P=0.164$; Table 2). It should be noted that no side effects were reported by the studied patients.

Discussion

The present study was conducted to investigate the effect of niacin on the levels of sodium, phosphorus, calcium, iPTH, and vitamin D in hemodialysis patients. Our findings indicate that after the intervention, the serum levels of calcium, vitamin D, and sodium increased significantly in the intervention group.

In the present study, niacin administration increased serum vitamin D (25-hydroxyvitamin D) too. Studies revealed that niacin increases the precursors of 25-hydroxyvitamin D by improving the blood level of phosphorus and subsequently by reducing the levels of FGF23. FGF23 is the most important inhibitor of 1-alpha hydroxylase enzyme (the enzyme that converts 25-hydroxyvitamin D to 1, 25-hydroxyvitamin D) (16,17). However, a previous study indicated that niacin cannot made changes in plasma calcium, or vitamin D metabolites over three years (18). Another study showed that nicotinic acid can modulates intracellular calcium concentration while, this function depending on its exposure time and initial concentration (19).

We observed that treatment with niacin caused an increase in serum sodium. Although so far no study has investigated the effect of niacin on serum sodium level, probably following the inhibition of the phosphorus-sodium co-transporter in the small intestine, niacin inhibits the reabsorption of phosphorus from inside the intestine into the blood and not transferring sodium into

Table 1. Comparison of the mean of the studied variables before and after the intervention

Serum levels of variables		Mean ± SD	*P* value
Calcium (mg/dL)	Before intervention	7.8 ± 0.31	0.01
	After intervention	7.90 ± 0.22	
Phosphate (mg/dL)	Before intervention	6.02 ± 0.42	<0.001
	After intervention	5.66 ± 0.28	
Sodium (mg/dL)	Before intervention	133.6 ± 3.49	0.001
	After intervention	135.8 ± 2.68	
Vitamin D (ng/dL)	Before intervention	14.36 ± 4.10	0.014
	After intervention	15.76 ± 3.80	
ALP (IU/L)	Before intervention	240.4 ± 36.92	0.778
	After intervention	239.4 ± 37.44	
iPTH (pg/mL)	Before intervention	385.3 ± 257.6	0.001
	After intervention	132.6 ± 350.2	

ALP, Alkaline phosphatase; iPTH, Intact parathyroid hormone.

Table 2. Comparison of the mean change of the investigated variables during the intervention by gender

Serum levels of variables	Male, Mean ± SD	Female, Mean ± SD	Total, Mean ± SD	P value
Calcium (mg/dL)	0.10 ± 0.21	0.14 ± 0.23	0.10 ± 0.21	0.271
Phosphate (mg/dL)	-0.35 ± 0.24	-0.35 ± 0.23	-0.35 ± 0.24	0.942
Sodium (mg/dL)	2.2 ± 3.33	2.8 ± 2.27	2.20 ± 3.33	0.333
Vitamin D (ng/dL)	1.4 ± 2.95	0.93 ± 3.39	1.4 ± 2.95	0.395
ALP (IU/L)	-1.0 ± 19.27	3.93 ± 21.00	-1.0 ± 19.27	0.164
Intact PTH (pg/mL)	22.55 ± 1.35	34.6 ± 23.37	22.55 ± 1.35	0.322

ALP, Alkaline phosphatase; iPTH, Intact parathyroid hormone.

the intestine and preventing the excretion of sodium through digestion and finally improving the hyponatremia of the patients and increasing the plasma sodium (20).

In present study, the serum levels of iPTH and phosphate decreased significantly after intervention. However, Liu et al and Malhotra et al reported that the change of the intact PTH level from baseline to the end of the study did not change in hemodialysis and chronic kidney disease patients (17,18).

In addition, our study indicated that the serum level of phosphorus reduced after niacin intervention. In this regard, Müller et al showed that niacin therapy for 12 weeks reduced serum phosphate levels from 7.2 to 5.0 mg/dL (21). A previous study also indicated that niacin significantly reduced the serum levels of phosphorus and calcium × phosphorus product (Ca×P) in hemodialysis patients (22). Moreover, Ginsberg et al and Khalid et al revealed that nicotinamide reduced the serum level of phosphate concentrations by inhibiting sodium-dependent phosphate transport protein 2B (NaPi2b) by the small intestine in end-stage renal disease (12,23).

The results of our study showed that the treatment of hemodialysis patients with niacin for 2 months in doses of 50 to 100 mg did not change in serum ALP. In the study by Vasantha et al 250 mg nicotinamide capsule for hemodialysis patients with serum phosphorus more than 5 mg/dL, two times a day and for five patients with serum phosphorus more than 8 mg/L, three times a day causes a significant decrease in serum ALP (24). Another study, also reported that the administration of 375 mg niacin capsules for eight weeks caused the serum ALP level to decrease significantly (25). However, the study by Jin Kang et al showed administration of niacin with a fixed dose of 500 mg caused a significant increase in ALP (26). The controversy of our study with other studies can be due to the presence of underlying diseases such as liver, gall bladder, or bones diseases, or it may be affected by the different stages of the disease in the studied population.

In our study, none of the patients receiving niacin had side effects. In the study by Cheng et al, similar results were reported, in such a way that the side effects in the groups receiving placebo and niacin at doses of 500 to 1000 mg were similar, and even at the maximum daily dose of 1500 mg were not associated with side effects. In their study, following the administration of niacin no major adverse events was detected, since only one patient (out of 33) required dose adjustment due to diarrhea, which was resolved by reducing the dose from 1500 to 1000 mg/d (14). Likewise, another study showed that nicotinamide (250 mg capsules which were given twice daily) is safe in hemodialysis patients (24). Meanwhile, another study reported that niacin in patients undergoing dialysis significantly elevated the risk of flushing and thrombocytopenia (22).

Conclusion

After two months of niacin consumption, the serum levels of calcium, vitamin D and sodium increased and serum levels of iPTH, since phosphate decreased in hemodialysis patients. In addition, no side effects were seen in the patients. Therefore, niacin can be an effective and safe drug in the treatment of electrolyte disorders and vitamin D deficiency in hemodialysis patients. A larger sample size is suggested in future studies and it is also recommended to investigate the effectiveness of niacin on the levels of serum electrolytes, vitamin D, iPTH, FGF23, lipid profile and uric acid in hemodialysis patients in longer follow ups. In addition, it is recommended that patients be examined and compared in respect of hematological factors and liver enzyme levels.

Limitations of the study

One of the limitations of this study was not evaluating the effects of niacin in different doses and at longer follow ups. Additionally, it would have been better if the patients were examined regarding the severity of the disease. Correspondingly, lack of investigation of other involved factors such as FGF23, lack of estimation of lipid profile, levels of serum niacin concentration were the other limitation of this study.

Authors' contribution

Conceptualization, investigation, validation: AMN, SM. Methodology, supervision: SM, AA. Formal analysis: AA; Data curation, writing—review and editing: SM, AA and AMN. Resources, writing—original draft preparation, project administration, visualization: SM. Funding acquisition: AMN.

Conflicts of interest

The authors declare that they have no competing interests. The drug was purchased from the market without any relation with the Sobhan Daru Company, which manufactured this drug. As one of the contributing authors to this study, SM acts as the Editor-in-Chief of the journal. It should be noted that his contribution to this journal has not influenced the peer-review process.

Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Shahrekord University of Medical Sciences approved this study protocols (IR.SKUMS.REC.1400.079). Accordingly, written informed consent was taken from all participants before any intervention. The trial protocol was approved by the Iranian Registry of Clinical Trial (#IRCT20190702044076N2; https://en.irct.ir/trial/66567). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was funded by vice chancellor of deputy research of Shahrekord University of Medical Sciences (Grant #5769).

References

1. Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, et al. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy. Am J Nephrol. 2021;52:98-107. doi: 10.1159/000514550.
2. Zazzeroni L, Pasquinelli G, Nanni E, Cremonini V, Rubbi I. Comparison of quality of life in patients undergoing hemodialysis and peritoneal dialysis: a systematic review and meta-analysis. Kidney Blood Press Res. 2017;42:717-727. doi: 10.1159/000484115.
3. Kassa DA, Mekonnen S, Kebede A, Haile TG. Cost of hemodialysis treatment and associated factors among end-stage renal disease patients at the tertiary hospitals of Addis Ababa city and Amhara region, Ethiopia. Clinicoecon Outcomes Res. 2020;12:399-409. doi: 10.2147/CEOR.S256947.
4. Bello AK, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, et al. Epidemiology of haemodialysis outcomes. Nat Rev Nephrol. 2022;18:378-95. doi: 10.1038/s41581-022-00542-7.
5. Patel TV, Singh AK. Role of vitamin D in chronic kidney disease. Semin Nephrol. 2009;29:113-21. doi: 10.1016/j.semnephrol.2009.01.004.
6. Nwosu IF, Ibeson CE, Olawoye A, Kyaw H, Kumar K, Odigwe C, et al. Interpretation of parathyroid hormone levels in renal impairment. Cureus. 2022;14:e25819. doi: 10.7759/cureus.25819.
7. Chan S, Au K, Francis RS, Mudge DW, Johnson DW, Pillans PI. Phosphate binders in patients with chronic kidney disease. Aust Prescr. 2017;40:10-14. doi: 10.18773/austprescr.2017.002.
8. Damment SJ. Pharmacology of the phosphate binder, lanthanum carbonate. Ren Fail. 2011;33:217-24. doi: 10.3109/0886022X.2011.552821.
9. Kampmann J, Hansen NP, Ørsted Schultz AN, Brandt AH, Brandt F. Lanthanum carbonate opacities-a systematic review. Diagnostics (Basel). 2022;12:464. doi: 10.3390/diagnostics12020464.
10. Timofte D, Tanasescu MD, Balcangiu-Stroescu AE, Balan DG, Tulin A, Stiru O, et al. Dyselectrolytemia-management and implications in hemodialysis (Review). Exp Ther Med. 2021;21:102. doi: 10.3892/etm.2020.9534.
11. Zappulo F, Cappuccilli M, Cingolani A, Scrivo A, Chiocchini ALC, Nunzio MD, et al. Vitamin D and the kidney: two players, one console. Int J Mol Sci. 2022;23:9135. doi: 10.3390/ijms23169135.
12. Khalid SA, Inayat F, Tahir MK, Younus A, Ahmad HI, Bokhari SRA, et al. Nicotinic acid as a phosphate-lowering agent in patients with end-stage renal disease on maintenance hemodialysis: a single-center prospective study. Cureus. 2019;11:e4566. doi: 10.7759/cureus.4566.
13. Liu X, Yang R, Dai B, Zhang H, Wang J, Ma N. Nicotinic acid and related compounds: A meta-analysis of their use for hyperphosphatemia in dialysis patients. Medicine (Baltimore). 2018;97:e0117. doi: 10.1097/MD.0000000000010117.
14. Cheng SC, Young DO, Huang Y, Delmez JA, Coyne DW. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3:1131-8. doi: 10.2215/CJN.04211007.
15. Ahmed HM, Yossif E, Abd-Elkader AS, Abdel Aziz EM. The efficacy and safety of niacin on hyperphosphatemia in ESRD patients undergoing hemodialysis: randomized controlled trial. Egypt J Intern Med. 2022;34:33. doi: 10.1186/s43162-021-00080-x
16. Jacquillet G, Unwin RJ. Physiological regulation of phosphate by vitamin D, parathyroid hormone (PTH) and phosphate (Pi). Pflugers Arch. 2019;471:83-98. doi: 10.1007/s00424-018-2231-z.
17. Liu XY, Yao JR, Xu R, Xu LX, Zhang YF, Lu S, et al. Investigation of nicotinamide as more than an anti-phosphorus drug in chronic hemodialysis patients: a single-center, double-blind, randomized, placebo-controlled trial. Ann Transl Med. 2020;8:530. doi: 10.21037/atm.2020.03.228.
18. Malhotra R, Katz R, Hoofnagle A, Bostom A, Rifkin DE, Mcbride R, et al. The Effect of Extended Release Niacin on Markers of Mineral Metabolism in CKD. Clin J Am Soc Nephrol. 2018;13:36-44. doi: 10.2215/CJN.05440517.
19. Li J, Li Y, Zhang P, Niu H, Shi Y. Nicotinic acid modulates intracellular calcium concentration and disassembles the cytoskeleton. Mol Med Rep. 2014;10:2805-10. doi: 10.3892/mmr.2014.2576.
20. Marks J. The role of SLC34A2 in intestinal phosphate absorption and phosphate homeostasis. Pflugers Arch. 2019;471:165-173. doi: 10.1007/s00424-018-2221-1.
21. Müller D, Mehling H, Otto B, Bergmann-Lips R, Luft F, Jordan J, et al. Niacin lowers serum phosphate and increases HDL cholesterol in dialysis patients. Clin J Am Soc Nephrol.

2007;2:1249-54. doi: 10.2215/CJN.01470307.
22. He YM, Feng L, Huo DM, Yang ZH, Liao YH. Benefits and harm of niacin and its analog for renal dialysis patients: a systematic review and meta-analysis. Int Urol Nephrol. 2014;46:433-42. doi: 10.1007/s11255-013-0559-z.
23. Ginsberg C, Ix JH. Nicotinamide and phosphate homeostasis in chronic kidney disease. Curr Opin Nephrol Hypertens. 2016;25:285-91. doi: 10.1097/MNH.0000000000000236.
24. Vasantha J, Soundararajan P, Vanitharani N, Kannan G, Thennarasu P, Neenu G, et al. Safety and efficacy of nicotinamide in the management of hyperphosphatemia in patients on hemodialysis. Indian J Nephrol. 2011;21:245-9. doi: 10.4103/0971-4065.83735.
25. Sampathkumar K, Selvam M, Sooraj YS, Gowthaman S, Ajeshkumar RN. Extended release nicotinic acid - a novel oral agent for phosphate control. Int Urol Nephrol. 2006;38:171-4. doi: 10.1007/s11255-006-0001-x.
26. Jin Kang H, Kim DK, Mi Lee S, Han Kim K, Hee Han S, Hyun Kim K, et al. Effects of low-dose niacin on dyslipidemia and serum phosphorus in patients with chronic kidney disease. Kidney Res Clin Pract. 2013;32:21-6. doi: 10.1016/j.krcp.2012.12.001.