Effect of low dose nicotinic acid on hyperphosphatemia in patients with end stage renal disease

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ABSTRACT

Hyperphosphatemia is a risk factor for ectopic calcification and coronary artery diseases in end stage renal diseases (ESRD). The aim of this study was to assess the effect of low-dose nicotinic acid on hyperphosphatemia in patients with ESRD. This randomized, double-blind clinical trial was done on 70 ESRD patients with serum phosphoure ≥5.5 mg/dl. Patients were randomly divided into two equal groups (n = 35) and the intervention group received niacin 25 mg/day as the initial dose. After 4 weeks, in patients who did not respond to treatment, niacin dose was increased up to 50 mg/dl. At the end of week 8, in case there was no treatment effect, the dose was raised to 100 mg/day. The appropriate response to treatment was defined as serum phosphorous level reductions <5.5 mg/dl. The age was 50.5 ± 14.3 years and duration of dialysis 5.1 ± 5.3 months. In the niacin group, mean phosphorus level decreased from 6.7 ± 0.84 mg/dl at the end of the 1st month to 5.8 ± 1.0 mg/dl at the end of the 2nd month and to 4.4 ± 1.4 mg/dl at the end of the 3rd month (P = 0.004). In the placebo group, mean phosphorus level increased from 6.5 ± 1.2 mg/dl to 7.2 ± 0.91 mg/dl at the end of the 3rd month (P = 0.006). In the niacin group, high density lipoprotein (HDL) increased significantly from 45.00 ± 14.9 to 47.2 ± 11.6 (P = 0.009). We conclude that niacin (100 mg/day) decreased phosphorus serum level and increased HDL serum level in patients on dialysis.

Key words: End stage renal disease, high-density lipoprotein, hyperphosphatemia, nicotinic acid

Introduction

Chronic kidney disease (CKD) is growing worldwide and the incidence of end stage renal diseases (ESRD) is on the rise.[1] Previous studies have reported that hyperphosphatemia results in increased morbidity and mortality rates among patients with CKD. Serum phosphorus levels more than 6.5 mg/dl increase mortality rate about 27% compared to phosphorus levels <6.5 mg/dl.[2,3] Long-term inadequate phosphate control leads to secondary hyperparathyroidism, metabolic bone diseases, calcific uremic arteriolopathy, and cardiovascular calcification. Progressive increases in arterial calcification are associated with higher rates of mortality.[4] Management of hyperphosphatemia in patients with ESRD is not adequate. Calcium containing phosphate binders may sometimes result in adverse effects such as hypercalcemia.[5] Noncalcium phosphate binders, such as sevelamer and lanthanum, are expensive.[6] Several trials have shown that niacinamide and niacin are capable of remarkably reducing serum phosphate levels in patients undergoing dialysis.[7-11]

Other studies have shown that niacin increases high density lipoprotein (HDL) cholesterol and reduces triglyceride levels with potentially favourable cardiovascular effects.[12]

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Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.161020

How to cite this article: Zahed NS, Zamanifar N, Nikbakht H. Effect of low dose nicotinic acid on hyperphosphatemia in patients with end stage renal disease. Indian J Nephrol 2016;26:239-43.

Human and animal experiences in *in vitro* studies have indicated that niacin through inhibiting the cotransporter NaPi2a in the renal proximal tubule and cotransporter NaPi2b in the intestine results in decreased phosphate uptake.[12-16]

Adverse effects of high-dose niacin limit the use of this agent. This study was designed to evaluate the impact of low-dose nicotinic acid on phosphorus levels in chronic dialysate patients with ESRD as the main objective. The effect of niacin on low density lipoprotein (LDL) is investigated as the secondary objective.

Materials and Methods

In this randomized, double-blind clinical trial, 70 dialysis patients referred to the Dialysis Ward of Ashrafi Esfehani Hospital from May 2013 to April 2014 were evaluated. The participants were observed for 12 weeks. Inclusion criteria were age >18 years, ability to give informed consent, ($P \geq 5.5$) mg/dl, dialysis duration for more than 3 months, adequate dialysis (Kt/V >1.2) during the study, and protocol, including calcium carbonate as phosphate binder 2 weeks prior to the study. Exclusion criteria were pregnancy, liver disease, active peptic ulcer disease, taking carbamazepine, history of niacin (or niacin as other drugs' component) sensitivity, and malignancy. Written informed consent was obtained before randomization, as per the institution's protocol. The study was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences. The patients were randomly assigned to either niacinamide or placebo groups. Both participants and the study staff (site investigators and trial coordinating staff) were masked to the treatment.

Niacin and placebo were packaged in identical tablets by Pharmacy Company (Azad Pharmacology University). The patients were prescribed one tablet daily with their meal. Dosages were titrated from 25 mg/day over 12 weeks. Phosphorus level was measured pretreatment and at the end of weeks 4, 8, and 12. When serum phosphorus levels did not reach the normal reference range ($P \leq 5.5$ mg/dl), the dose of nicotinic acid was increased to 50 mg/day at the end of the 1st month and to 100 mg/day at the end of the 3rd month. None of the participants was treated with sevalmer (renagel) because of economic problems. Wash-out period was not permitted by the Ethics Committee of Shahid Behshti University of Medical Sciences; thus, all patients were administered 1500 mg calcium carbonate as phosphate binder during the study. When phosphorus levels exceeded 5.5 mg/dl or decreased to less than 3.5 mg/dl, the dose of phosphate binder was changed in order to continue niacin as the descripted dose. None of the participants used statins or resins.

The patients were followed for 3 months and during this period, serum levels of P, Ca, alanine aminotransferase (ALP), HDL cholesterol, triglycerides (TG), platelet, and parathyroid hormone (PTH) were measured monthly.

Statistical analysis

Descriptive statistics that used means and standard deviations are presented as contentious variables. The Chi-square and Fisher's exact test were used to compare categorical variables. Mann–Whitney's U-test and paired *t*-test were used to compare continuous variables. For all the tests, ($P \leq 0.05$) was considered significant. Data were analyzed using SPSS 20 (SPSS Inc., Chicago, IL, USA).

Results

In this study, 17 patients (35 male and 35 female) with the mean age of 50.5 ± 14.3 (range 16-76) years and mean duration of dialysis 5.1 ± 5.3 months were evaluated. The difference in mean age between niacin and placebo groups was not significant (49.8 ± 14.6 and 51.1 ± 14.1, respectively) ($P = 0.70$). At the end of the first month, the difference between two groups in calcium level was significant [Table 1]; moreover, at the end of the second month, the difference between the two groups in terms of phosphorus and calcium levels was significant [Table 2]. At the end of the third month, mean phosphorus level was significantly different between the two groups [Table 3]. The mean difference in cholesterol, TG, low-density lipoprotein (LDL), AST, ALT, platelet, and bilirubin between the two groups was not significant at the end of the first, second, and third month ($P > 0.05$) [Tables 1 and 3].

In the niacin group, mean phosphorus level significantly decreased from 6.7 ± 0.84 mg/dl at the end of the first month to 5.8 ± 1 mg/dl at the end of the second month and to 4.4 ± 1.4 mg/dl at the end of the third

Table 1: The mean and standard deviation of parameters at the end of first month in two groups (25 mg/day niacin)

Parameters	Niacin	Placebo	*P*
P (mg/dl)	6.7±0.84	6.5±1.2	0.414
Ca (mg/dl)	8.3±1.2	9.1±1.2	0.007
PTH (pg/ml)	316.6±208	280.2±235.6	0.491
Cholesterol (mg/dl)	141.1±44.4	158.5±35.2	0.083
TG (mg/dl)	131.7±39.8	129.5±29.7	0.793
LDL (mg/dl)	67.9±20.5	69.4±35.2	0.451
HDL (mg/dl)	45±14.9	44.1±12.5	0.927
AST (IU/L)	23.1±6.6	22.1±6.1	0.627
ALT (IU/L)	23.5±12.3	22±6.8	0.530
Bilirubin (mg/dl)	1.05±0.23	1±0.38	0.190
Platelet count, $\times 10^3/mm^3$	21,280.0±50,880.2	23,970.0±62,009.2	0.69

P: Phosphate, Ca: Calcium, PTH: Parathyroid hormone, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

month (P = 0.004) [Figure 1]. Moreover, the mean of the secondary outcome (HDL) increased at the end of the third month [Table 4, Figure 2].

In the placebo group, mean phosphorus level significantly increased from 6.5 ± 1.2 mg/dl at the end of the first month to 6.9 ± 1.4 mg/dl at the end of the second month and to 7.2 ± 0.91 mg/dl at end of the third month (P = 0.006) [Table 5].

Flushing (in one patient) and vomiting (in one patient) were detected in the niacin group during the second month.

Table 2: The mean and standard deviation of parameters at the end of second month in two groups (50 mg/day niacin)

Parameters	Niacin	Placebo	*P*
P (mg/dl)	1±5.8	1.4±6.9	0.001
Ca (mg/dl)	1.2±8.2	1.1±8.1	0.024
PTH (pg/ml)	191.3±319.2	213.2±2282	0.451
Cholesterol (mg/dl)	38±144.8	34.6±155.4	0.226
TG (mg/dl)	44.7±137.6	32.9±130.6	0.453
LDL (mg/dl)	18.9±71.4	17.7±69.6	0.649
HDL (mg/dl)	9.4±43.9	10±43.3	0.795
AST (IU/L)	6.3±18.8	7.4±22.8	0.756
ALT (IU/L)	5.6±19.4	6.6±21.1	0.251
Bilirubin (mg/dl)	0.24±0.95	0.32±1	0.244
Platelet count, $\times 10^3/mm^3$	59904.9±233080	54960.5±242860	0.477

P: Phosphate, Ca: Calcium, PTH: Parathyroid hormone, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3: The mean and standard deviation of parameters at the end of third month in two groups (100 mg/day niacin)

Parameters	Niacin	Placebo	*P*
P (mg/dl)	1.4±4.4	0.91±7.2	0.0001
Ca (mg/dl)	0.5±8.3	1.2±8.5	0.317
PTH (pg/ml)	188.8±307.3	201.3±259.7	0.307
Cholesterol (mg/dl)	32.9±147.5	32.5±157.1	0.218
TG (mg/dl)	53.5±139.5	35.1±132.5	0.548
LDL (mg/dl)	23.1±69.9	21.2±72.4	0.643
HDL (mg/dl)	11.6±47.2	10.5±45.7	0.562
AST (IU/L)	6.3±20.4	6.7±22.7	0.148
ALT (IU/L)	6.8±23.05	5.6±21.6	0.247
Bilirubin (mg/dl)	0.19±0.98	0.36±0.99	0.593
Platelet count, $\times 10^3/mm^3$	58862.7±236250	47310.7±243770	0.555

P: Phosphate, Ca: Calcium, PTH: Parathyroid hormone, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Discussion

Recently, niacin and niacinamide derivatives as phosphate-binder agents have been used to manage hyperphosphatemia in patients with CKD. Previous experiences have indicated that nicotinamide inhibits sodium/phosphorous transport in both renal and intestinal brush borders and decreases phosphorus levels in patients undergoing dialysis.[17-20] Although several studies suggest the effectiveness of niacinamide in reducing plasma phosphorus, only one study (2013) investigated low-dose niacin (500 mg/daily).[17]

The present clinical trial evaluated the impact of 100 mg/day nicotinic acid. It was observed that after 8 weeks, mean serum phosphorus level in the niacin group significantly was different from the control group. In line with the results of this study, Vasantha *et al.,* in an open-label study on 30 dialysis patients receiving a dose of NAM 750 mg/day, reported reductions in serum phosphorus level (2.3 mg/dl).[18] Rennick *et al*., in a meta-analysis reviewed seven studies that evaluated the effect of nicotinamide and nicotinic acid on phosphorus serum level in ESRD patients undergoing dialysis and indicated that in the three studies using nicotinic acid as the therapeutic intervention and four studies using nicotinamide, both nicotinic acid and nicotinamide significantly reduced serum phosphorus level.[19] In a randomized, double-blind placebo-controlled crossover trial, Cheng *et al.,* examined the effect of niacinamide (500 mg/day to 1500 mg/day) on 33 patients with

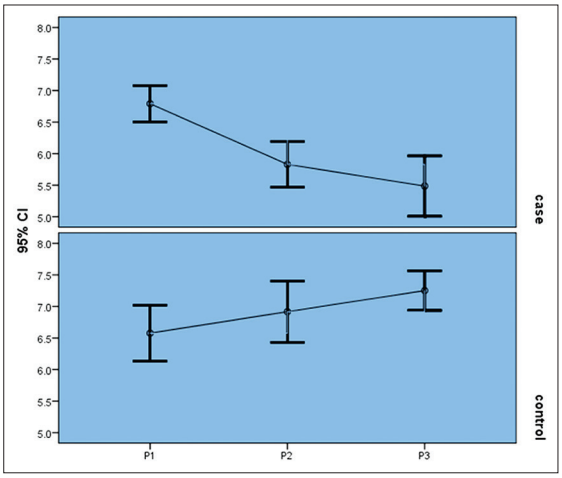

Figure 1: Niacin effect on serum phosphorus levels

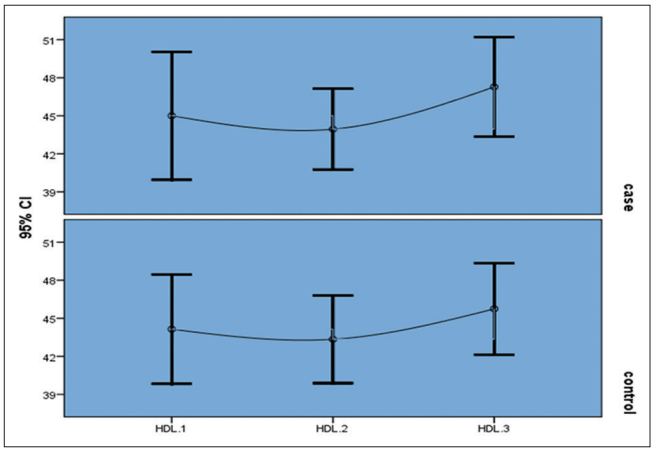

Figure 2: Niacin effect on high density lipoprotein

Table 4: The mean and standard deviation of parameters at the end of first, second and third month in Niacin group

Paramiters	First month	Second month	Third month	*P*
P (mg/dl)	6.7±0.84	5.8±1.0	4.4±1.4	0.004
Ca (mg/dl)	8.3±1.2	8.2±1.2	8.3±0.5	0.09
PTH (pg/ml)	316.6±208.00	319.2±191.3	307.3±188.8	0.10
Cholesterol (mg/dl)	141.1±44.4	144.8±38.00	147.5±32.9	0.23
TG (mg/dl)	131.7±39.8	137.6±44.7	139.5±53.5	0.23
LDL (mg/dl)	67.9±20.5	71.4±18.9	69.9±23.1	0.18
HDL (mg/dl)	45.00±14.9	43.9±9.4	47.2±11.6	0.009
AST (IU/L)	23.1±6.6	18.8±6.3	20.4±6.3	Ns
ALT (IU/L)	23.1±6.6	19.4±5.6	23.05±6.8	Ns
Bilirubin (mg/dl)	1.05±0.23	0.95±0.24	0.98±0.19	Ns
Platelet count, $\times 10^3/mm^3$	212800± 50880.2	233080± 59904.9	236250± 588862.7	Ns

P: Phosphate, Ca: Calcium, PTH: Parathyroid hormone, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 5: The mean and standard deviation of parameters at the end of first, second and third month in placebo group

Parameters	First month	Second month	Third month	*P*
P (mg/dl)	1.2±6.5	1.4±6.9	0.91±7.2	0.006
Ca (mg/dl)	1.2±9.1	1.1±8.1	1.2±8.5	0.001
PTH (pg/ml)	235.6±280.2	213.2±0.8282	201.3±0.7259	0.08
Cholesterol (mg/dl)	35.2±158.5	34.6±155.4	32.5±157.1	0.62
TG (mg/dl)	29.7±129.5	32.9±130.6	35.1±132.5	0.62
LDL (mg/dl)	35.2±69.4	17.7±69.6	21.2±72.4	0.31
HDL (mg/dl)	12.5±44.1	10±43.3	10.5±45.7	0.31
AST (IU/L)	6.1±22.1	7.4±22.8	6.7±22.7	Ns
ALT (IU/L)	6.8±22	6.6±21.1	5.6±21.6	Ns
Bilirubin (mg/dl)	0.38±1	0.32±1	0.36±0.99	Ns
Platelet count, $\times 10^3/mm^3$	62009.2± 239700	54960.5± 242860	47310.7± 243770	Ns

P: Phosphate, Ca: Calcium, PTH: Parathyroid hormone, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

ESRD undergoing hemodialysis. The results indicated significant decreases in serum phosphorus. Moreover, in accord with our study, HDL cholesterol significantly increased in the niacin group.[9]

In the present study, no significant changes in Ca and PTH were detected. Cheng *et al*., observed insignificant changes in serum calcium and PTH levels in the niacin group.[9] In agreement with Kang *et al.,* statically significant increases in HDL were observed in the present study.[17] Similarly, Shahbazian *et al*., in a placebo-controlled clinical study on 48 dialysis patients, showed that the administration of niacinamide 500 mg/day decreased serum phosphate, increased HDL levels and fasting glycaemia, and reduced LDL and triglyceride levels.[20] The important side effects of niacin are vasodilation and flushing;[21] however, in the present study, we detected flashing only in one patient. Although reduction in platelet count occurred in some participants, no cases of thrombocytopenia were reported in the present study.

Use of low-dose niacin is affordable due to low adverse effects and the low cost. Recent studies, suggested that by reducing side effects, nicotinamide can be an inexpensive alternative.[22] However, further studies are recommended to examine if it is an acceptable alternative to sevelamer in patients with economic problems.

The present study is novel in examining the effects of low-dose niacin (100 mg/daily). The obtained results at this low dose may be attributed to differences in nutritional and genetic backgrounds of Iranian patients, though more *in vitro* studies should be conducted to confirm its effects.

The main limitations of our study are small sample size and short duration of follow-up (3 months). Thus, further prospective double-blind clinical trials are recommended with longer follow-up durations and larger populations.

Conclusion

Niacin 100 mg/daily decreased phosphorus serum levels and increased HDL serum levels in patients with ESRD that undergo dialysis.

Acknowledgments

The authors would like to thank the nursing, administrative, and secretarial staff at the Nephrology Department and Clinic of Ashrafi Esfehani Hospital for their kind contribution.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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