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The efficacy and safety of niacin on hyperphosphatemia in ESRD patients undergoing hemodialysis: randomized controlled trial

Hanan Mahmoud Ahmed¹, Esraa Yossif^{2*} , Alaa S. Abd-Elkader³ and Essam M. Abdel Aziz¹

Abstract

Background: Hyperphosphatemia is a common complication of end-stage renal disease (ESRD) and particularly affects hemodialysis (HD) patients. Elevated serum phosphorus contributes to the development of secondary hyperparathyroidism, chronic kidney disease–mineral bone disorder (CKD-MBD), metastatic calcifications and calcific uremic arteriolopathy. There is a significant association between hyperphosphatemia and increased morbidity and mortality in ESRD patients including cardiovascular morbidity and mortality, and it is also associated with prolonged hospitalization of HD patients. This study aim to evaluate the serum phosphorus lowering effect of niacin in HD patients.

Results: There was a decrease in phosphate values during the first 3 months of the study in the niacin group, with a significant change in phosphate level at the third month (5.90 ± 0.52 vs. 6.42 ± 0.65 (mEq/l); $P < 0.001$) and at the sixth month (5.12 ± 0.41 vs. 5.76 ± 0.47 (mEq/l); $P < 0.001$) compared to the control group. It was noted that both groups had an insignificant difference regarding baseline parathormone (PTH), though the PTH showed a significantly lower level at the third month (192.39 ± 78.85 vs. 388.27 ± 263.10 pg/ml; $P < 0.001$) and at the sixth month (127.56 ± 90.87 vs. 249.85 ± 97.69 pg/ml; $P < 0.001$) in the niacin group.

Conclusion: Niacin caused a statistically significant decrease in levels of phosphate and PTH in dialysis patients.

Trial registration: Registered at ClinicalTrials.gov [NCT03163576](https://clinicaltrials.gov/ct2/show/study/NCT03163576). Trial registration date: 22 May 2017. Date of first patient's enrolment: 1 October 2018. Date of the ethical committee approval: 29 March 2017. Number of the ethical committee approval: 17100040.

Keywords: Hyperphosphatemia, Niacin, ESRD, Phosphorus

Background

Hyperphosphatemia is a frequent complication of end-stage renal disease (ESRD) and principally affects hemodialysis (HD) patients. Elevated serum phosphorus contributes to the development of secondary hyperparathyroidism, chronic kidney disease–mineral bone

disorder (CKD-MBD), metastatic calcifications, and calcific uremic arteriolopathy. There is a significant association between hyperphosphatemia and increased morbidity and mortality in ESRD patients including cardiovascular morbidity and mortality, also it is associated with the hospitalization of HD patients [1].

Although there are multiple lines of treatment of hyperphosphatemia in ESRD patients undergoing HD, they are still inadequate. Calcium-containing phosphate binders sometimes cause adverse effects such as

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hypercalcemia. Whereas the non-calcium-containing phosphate binders, such as sevelamer and lanthanum, is expensive. Moreover, aluminum-containing agents are efficient, but no longer widely used because of their toxicity. Several trials have shown that nicotinamide (NAM) and niacin can reduce serum phosphate levels markedly in patients undergoing HD [2].

Niacin was initially reported to lower plasma cholesterol [3]. The main clinical use of niacin has been to raise high-density lipoprotein (HDL) cholesterol and reduce triglyceride levels with potentially favorable cardiovascular effects. Recently, nicotinic acid and related compounds such as nicotinamide (NAM) have also shown to decrease phosphorus absorption in the gastrointestinal tracts of animals through a unique mechanism other than the that of the traditional phosphate binders [4]. In vitro studies have shown that NAM decreases phosphate uptake by inhibiting the co-transporter NaPi2a in the renal proximal tubule and the co-transporter NaPi2b in the intestine [5, 6]. As niacin is mainly converted to NAM, it also inhibits intestinal phosphate absorption [7]. *Edalat-Nejad et al.* (2012) suggested that niacin may emerge as a safe and low-cost therapy in combination with other phosphate binders for phosphate control [8]. The modest increase in HDL values may be considered as another beneficial effect of this treatment. Its major side effects are vasodilation and flushing, and prostaglandins seem to be the cause, thus can be attenuated by premedication with aspirin [9]. This study aimed to assess the efficacy of niacin in the management of hyperphosphatemia in ESRD patients undergoing HD.

Aim of study

Primary outcome

To assess the efficacy and safety of niacin in management of hyperphosphatemia in ESRD patients undergoing hemodialysis (HD).

Secondary outcome

Assess the effect of niacin on calcium and parathormone hormone.

Methods

After approval of the ethical committee of the Faculty of Medicine at Assiut University at 29 March 2017, complied with the tenets of 1964 Declaration of Helsinki and its later amendments (no.: 17100040). Before enrollment in our study, all participants signed a consent. Before signing, they informed in detail about our study aim.

Patients with end-stage renal disease (ESRD) were included if they met the following criteria: (1) age

between 18 and 60 years, (2) underwent HD for more than 6 months, and (3) serum phosphorus level > 5 mg/dL. The exclusion criteria were patients on sevelamer (non-calcium-based phosphate binder) or cinacalcet (Calcimimetic), patients with hepatitis C virus, connective tissue disease, active malignancy, pregnancy, active peptic ulcer disease, treatment with carbamazepine, or treatment with aluminum hydroxide.

Patient selection

Patients with end-stage renal disease (ESRD) were included if they met the following criteria: (1) age between 18 and 60 years, (2) underwent HD for more than 6 months, and (3) serum phosphorus level > 5 mg/dL. The exclusion criteria were patients on sevelamer (non-calcium-based phosphate binder) or cinacalcet (calcimimetic), patients with hepatitis C virus, connective tissue disease, active malignancy, pregnancy, active peptic ulcer disease, treatment with carbamazepine, or treatment with aluminum hydroxide.

Study design

This study employed a two-arm randomized controlled trial (RCT) design. Between October 2018 and October 2019 in a dedicated outpatient clinic at the Nephrology Unit of Internal Medicine Department and Dialysis Unit and outpatient clinic in University Hospital. Fifty ESRD patients on HD with hyperphosphatemia (serum phosphorus level > 5 mg/dl), received the same calcium-based phosphate binder, together with a not changed serum phosphorus in the last 2 weeks.

Subjects were assigned in a 1:1 ratio randomly into one of two treatment arms; group I (niacin group): 25 patients received one tablet of niacin daily (750 mg) titrated up to 2 tablets daily (1500 mg) at week 5 and continued till the end of the study, besides usual calcium-based phosphate binders for 6 months. Group II (control group): 25 patients received only calcium-based phosphate binders (calcium acetate or calcium carbonate) for 6 months.

Study population

We enrolled 50 consecutive patients who fulfilled the selection criteria for this study. Demographic characteristics and medical history to exclude any associated risk factors and serum Ca, PH, and PTH were assessed at the third and the sixth. Patients were regularly examined for any side effects, such as flushing and gastrointestinal symptoms. In case of flushing, patients were counseled to take 100 mg aspirin 1 h before niacin treatment.

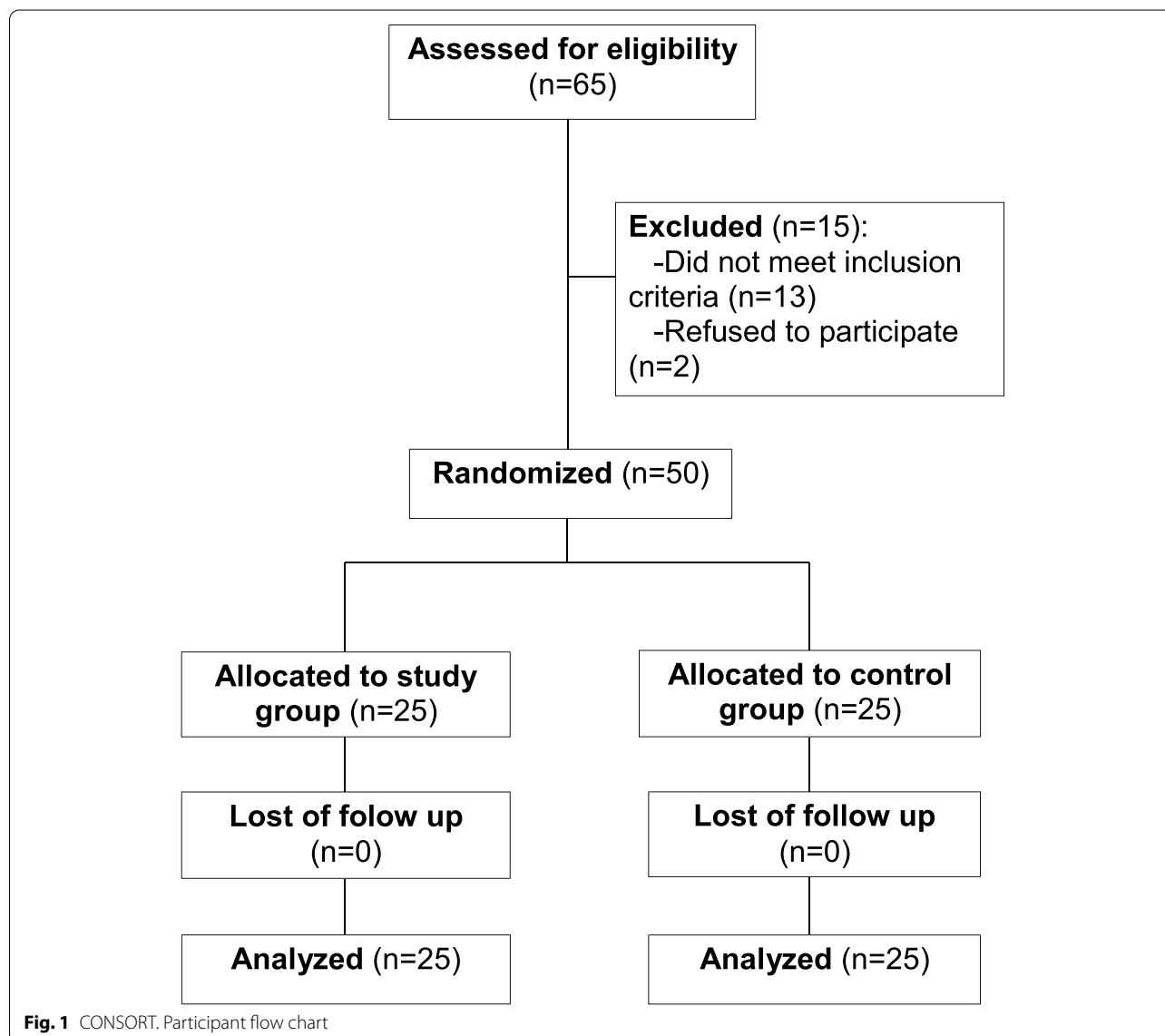
Sample size calculation

G*Power 3.1.9.2 software program (Franz Faul, Kiel University, Germany) was utilized for the sample size calculation. The trial was planned to have 80% power to recognize the difference between the study groups and α was 0.05. Based on a previous study by N. S. Zahed et al. [2], the mean phosphorus level in the niacin group was 5.8 ± 1 mg/dl; while in the control group, the mean phosphorus level was 6.9 ± 1.4 mg/dl at the end of the second month. This resulted in a minimum sample size of 21 patients in each treatment arm was needed. A drop rate of 10% was considered so we determined a total sample size of 46 patients and the figure was rounded up to 50 (25 in each group) (Fig. 1).

Pre-treatment evaluation**For each patient**

(1) Full history and clinical examination, about disease onset, course, and duration; physical examination; and follow-up for detection of any side effects of niacin.

(2) Laboratory investigations were performed at baseline and at the third and the sixth months for follow-up, including complete blood picture using the ADVIA 2120i Hematology System (Siemens Healthcare Diagnostics Inc. Tarrytown, NY 10591, USA), kidney function tests (blood urea, serum creatinine), liver function tests (ALT, AST, alkaline phosphatase), lipid profile (total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c)), and specific tests



(serum phosphorus, serum calcium, serum parathyroid hormone PTH, and serum magnesium), were done on the automated chemistry analyzer Dimension RxL Max.

(3) Imaging: radiological evaluation (chest X-ray, postero-anterior view) was done three times as a baseline and two follow-ups.

Statistical analysis

Analysis of the results was done by Statistical Package for the Social Sciences (SPSS) program windows (version 20, IBM, and Armonk, NY). Continuous data were expressed in form of mean \pm SD or median (range) while nominal data were expressed in form of frequency (percentage). A comparison of patients' properties was performed by the chi-squared test for categorical variables and the student t-test when the variables were continuous. For all tests, p values < 0.05 were considered significant.

Limitations

Small sample size was used in the study and there was noncompliance of some patients to the drug.

Results

In this study, 50 patients (29 male and 21 female) with a mean age of 44 ± 13.5 (range 30–58) years and the mean duration of dialysis 3 ± 2 years were evaluated. The difference in mean age between niacin and placebo groups was not significant (42.96 ± 12.4 and 47.12 ± 10.43 , respectively) ($P = 0.27$). Likewise, both groups had insignificant differences regarding sex, residence, the duration of dialysis, and etiology of kidney disease ($P = 0.75, 0.09, 0.49$, and 0.16 , respectively). Demographic data, the etiology of kidney disease, and the duration of dialysis of studied groups are shown in Tables 1 and 2.

Table 1 Demographic data of studied groups

	Niacin group (n = 25)	Control group (n = 25)	P value
Age (years)	42.96 ± 12.40	47.12 ± 10.43	0.27
Sex			0.75
Male	14 (56%)	15 (60%)	
Female	11 (44%)	10 (40%)	
Residence			0.09
Rural	17 (68%)	18 (72%)	
Urban	8 (32%)	7 (28%)	

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05

Table 2 Etiology of kidney disease and duration of dialysis among studied groups

	Niacin group (n = 25)	Control group (n = 25)	P value
Duration of dialysis (in years)	2.82 ± 1.78	2.28 ± 0.98	0.49
Range	1–5	1–4	
Etiology			0.16
HTN	11 (44%)	10 (40%)	
Obstructive uropathy	10 (40%)	7 (28%)	
Diabetes mellitus	3 (12%)	4 (16%)	
Glomerulonephritis	1 (4%)	3 (12%)	
Polycystic kidney	0	1 (4%)	

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05

Before the start of the study, there was an insignificant difference between both groups regarding itching, cholesterol, calcium, phosphorus, and PTH ($P = 0.51, 0.58, 0.37, 0.80$, and 0.40). At the end of the third and sixth months of follow-up, the difference between the two groups in itching, cholesterol, calcium, phosphorus, and PTH levels was significant (Tables 3, 5, and 6) (Figs. 7, 9, and 10). The mean difference in mineral bone disease (MBD) symptoms, low-density lipoprotein (LDL), high-density lipoprotein (HDL), AST, ALT, ALP, and triglyceride (TG) between the two groups was not significant at the end of the baseline, third, and sixth month ($P > 0.05$) (Tables 3, 4, 5, and 6). In the niacin group, the mean phosphorus level significantly decreased from 6.88 ± 0.86 mg/dl at the baseline to 5.90 ± 0.52 mg/dl at the end of the third month and 5.12 ± 0.41 mg/dl at the end of the sixth month ($P < 0.001$) (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10).

Only two patients developed flushing and were treated with 100 mg aspirin, while the majority of patients (92%) reported no side effects (Fig. 10).

Table 3 Clinical findings among studied patients

	Niacin group (n = 25)	Control group (n = 25)	P value
Itching			
Baseline	23 (92%)	22 (88%)	0.51
At 3rd month	3 (12%)	12 (48%)	< 0.001
At 6th month	2 (8%)	10 (40%)	< 0.001
Symptoms of MBD			
Baseline	16 (64%)	17 (68%)	0.50
At 3rd month	15 (60%)	17 (68%)	0.45
At 6th month	13 (52%)	15 (60%)	0.11

Data expressed as frequency (percentage). P value was significant if < 0.05 . MBD mineral bone disease

Table 4 Changes in lipid profile among studied groups

	Niacin group (n = 25)	Control group (n = 25)	P value
Cholesterol (mg/dl)			
Baseline	172.40 ± 43.89	179.56 ± 33.78	0.58
At 3rd month	150.52 ± 35.37	184.93 ± 37.19	< 0.001
At 6th month	136.88 ± 32.98	174.25 ± 28.41	< 0.001
HDL (mg/dl)			
Baseline	76.56 ± 16.23	80.68 ± 9.30	0.36
At 3rd month	82.44 ± 16.68	77.56 ± 13.56	0.33
At 6th month	82.20 ± 15.01	79.56 ± 14.20	0.57
LDL (mg/dl)			
Baseline	93.56 ± 13.99	91.50 ± 13.23	0.64
At 3rd month	86.80 ± 12.60	92.81 ± 9.23	0.10
At 6th month	78.40 ± 14.16	87.81 ± 16.31	0.06
Triglyceride (mg/dl)			
Baseline	139.36 ± 35.72	133.93 ± 21.64	0.58
At 3rd month	140.16 ± 42.58	130.12 ± 15.67	0.37
At 6th month	118.08 ± 36.27	125.25 ± 16.89	0.46

Data expressed as mean (SD). P value was significant if < 0.05. HDL high-density lipoprotein, LDL low-density protein

Discussion

Latterly, new phosphate-binding drugs, advanced membrane technology, and advancements in HD techniques are continuously upgrading. Still, control of hyperphosphatemia endures a major challenge in hemodialysis patients' care. Niacin and niacinamide

Table 5 Changes in serum electrolytes and PTH among studied patients

	Niacin group (n = 25)	Control group (n = 25)	P value
Calcium (mg/dl)			
Baseline	8.60 ± 0.96	8.86 ± 0.74	0.37
At 3rd month	8.87 ± 0.56	9.62 ± 0.54	< 0.001
At 6th month	8.92 ± 0.55	10.53 ± 0.77	< 0.001
Phosphorous (mEq/l)			
Baseline	6.88 ± 0.86	6.95 ± 0.92	0.80
At 3rd month	5.90 ± 0.52	6.42 ± 0.65	< 0.001
At 6th month	5.12 ± 0.41	5.76 ± 0.47	< 0.001
ALP (μ/l)			
Baseline	182.52 ± 67.89	299.25 ± 98.87	0.05
At 3rd month	216.52 ± 58.90	223.81 ± 47.08	0.88
At 6th month	169.96 ± 44.56	158.06 ± 65.10	0.68
PTH (pg/ml)			
Baseline	284.17 ± 98.46	312.87 ± 65.89	0.40
At 3rd month	192.39 ± 78.85	388.27 ± 263.10	< 0.001
At 6th month	127.56 ± 90.87	249.85 ± 97.69	0.01

Data expressed as mean (SD). P value was significant if < 0.05. PTH parathormone hormone

Table 6 Side effects of niacin

Side effects of niacin	N = 25
Flushing	2 (8%)
Pruritus	0
Anorexia	0
Nausea	0
Vomiting	0
Diarrhea	0
No side effects	23 (92%)

Data expressed as frequency (percentage)

derivatives as phosphate-binder agents have been used to control hyperphosphatemia in patients with CKD. Previous experiences have shown that nicotinamide inhibits sodium/phosphorous transport in both renal and intestinal brush borders and lowers phosphorus levels in patients on HD [4, 10]. Previous studies have examined the phosphate-lowering effect of these derivatives.

The present clinical trial evaluated the impact of one tablet of niacin (750 mg/day) titrated up to 2 tablets daily (1500 mg) at week 5 and continued for 6 months. It was noticed that after 12 weeks and at the end of 15 weeks, the mean serum phosphorus level in the niacin group was significantly different from the control group, with a decreasing trendline. In line with the results of this study, Takahashi et al. (2004) found a significant decrease in serum level of phosphorous of patients who were on regular HD and received nicotinamide for 12 weeks, at a starting dose of 500 mg/day, with titration every 2 weeks by 250 mg/day [11]. Rennick et al., in a meta-analysis, reviewed seven studies that assessed the effect of nicotinamide and nicotinic acid on phosphorus serum level in ESRD patients undergoing dialysis. They showed that out of the seven studies, three were using nicotinic acid as the therapeutic intervention and in four studies, there were using nicotinamide. Serum phosphorus level was significantly reduced with using nicotinic acid and nicotinamide [4]. Ahmadi et al. found that flat doses of 500 mg/day for niacin demonstrated a significant drop in serum phosphorus in comparison to the placebo group (2.2 ± 0.6 mg/dL, $P < 0.0001$ and 1.7 ± 1 mg/dL, $P = 0.004$, respectively) but no significant change in serum calcium level [12].

In the present study, at the end of the third and sixth months, significant changes were noted in the occurrence of itching, and levels of cholesterol, calcium, phosphorous, and PTH levels. The frequency of itching was significantly lower in the niacin group in the third month (12% vs. 48%; $P < 0.001$) and at the sixth month (8% vs.

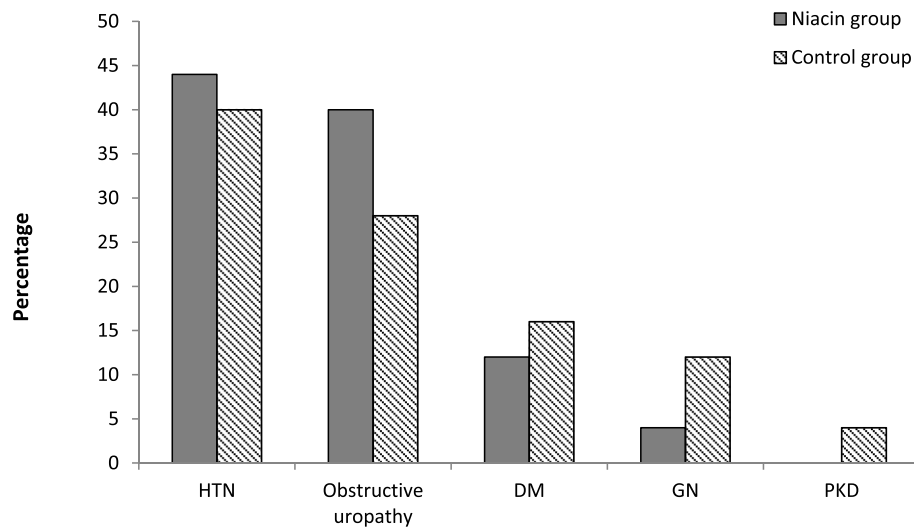


Fig. 2 Aetiology of kidney disease among the studied groups

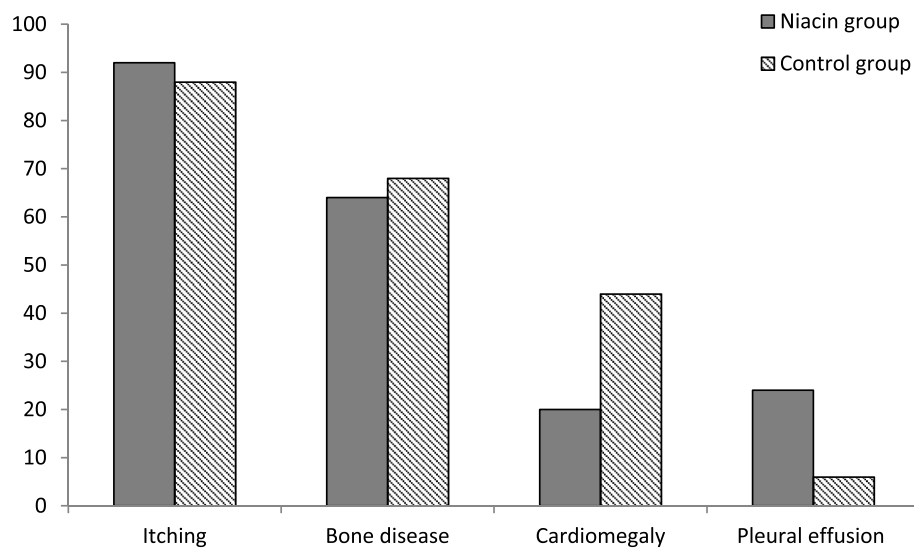
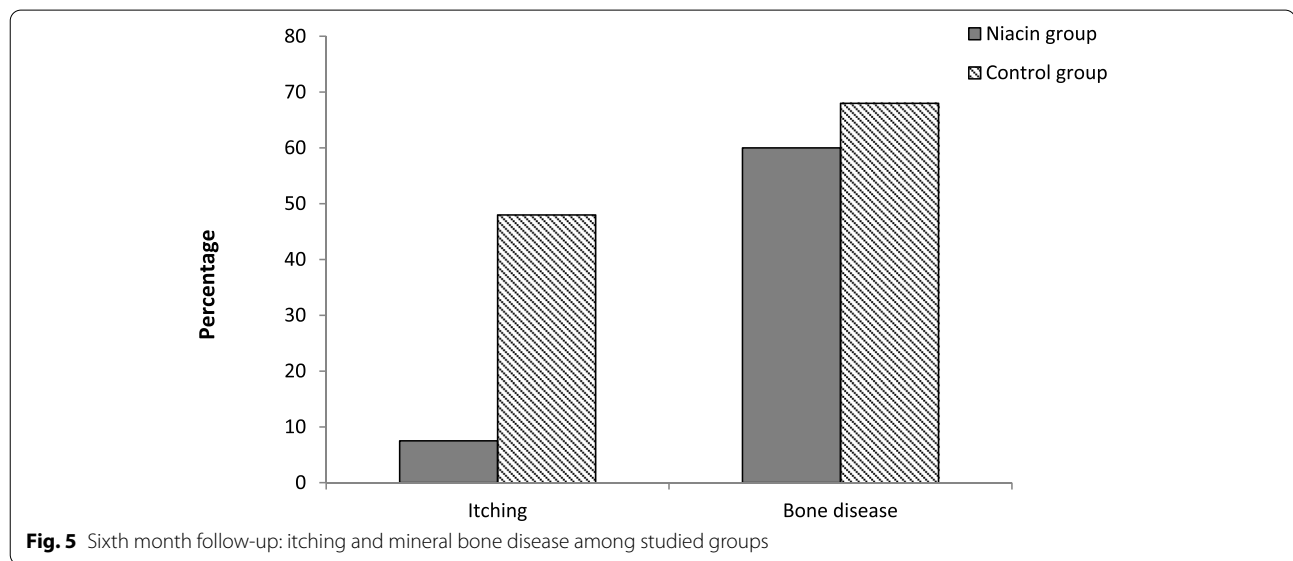
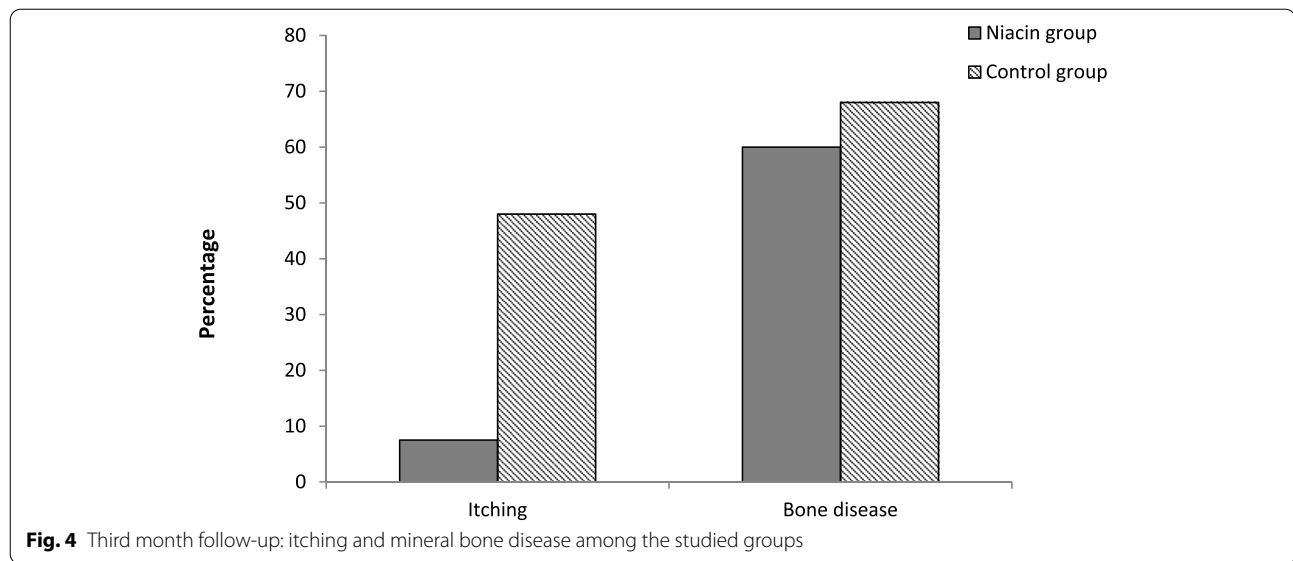


Fig. 3 Itching, bone disease and radiological findings among the studied groups

40%; $P < 0.001$). Despite failed to reach a significant level, the frequency of MBD was lower in the niacin group in the third month (60% vs. 68%; $P = 0.45$) and sixth month (52% vs. 60%; $P = 0.45$) compared to the control group. These effects of niacin on itching were attributed to its anti-inflammatory reaction, anti-xerosis, and mast-cell stabilizing effects. That is why it could be an effective treatment against itching in patients with CKD [13]. In agreement with our study, Namazi et al. reported that there was a significant difference between the reduction

of pruritus in the nicotinamide group compared to the control group. They concluded that increasing the time of application of nicotinamide sodium to over 4 weeks may be more effective than placebo in reducing itching in uremic patients [13]. In contrast to these results, Omidian et al. reported that analysis of repeated measurement showed no significant difference in the reduction of pruritus between the nicotinamide and the placebo groups [14], and they used a less dose of nicotinamide (500 mg twice daily) for a short duration (4 weeks), depending



on pruritus score. However, in our study, we used a large dose for a longer duration, and largely depend on the patient's history of itching and their laboratory investigations.

Regarding cholesterol level, the niacin group had significantly lower cholesterol at the third month (150.52 ± 35.37 vs. 184.93 ± 37.19 mg/dL; $P < 0.001$) and at sixth month (136.88 ± 32.98 vs. 174.25 ± 28.41 mg/dL; $P < 0.001$), but there was an insignificant difference between both groups as regarding changes in HDL, LDL, and TG at baseline, third month, and sixth month of

follow-up ($P > 0.05$). Nicotinic acid (NA) has been known for many years as a lipid-modifying drug. It has been very well documented that NA increases HDL cholesterol and decreases triglycerides and LDL cholesterol. In contrast with our study, Zhang et al. reported in a previous systematic review and meta-analysis that both groups have no significant differences between TG and LDL [15]. The disagreement point was the level of HDL, as they found HDL level significantly higher among the niacin group. A critical limitation of a meta-analysis was including few RCTs.

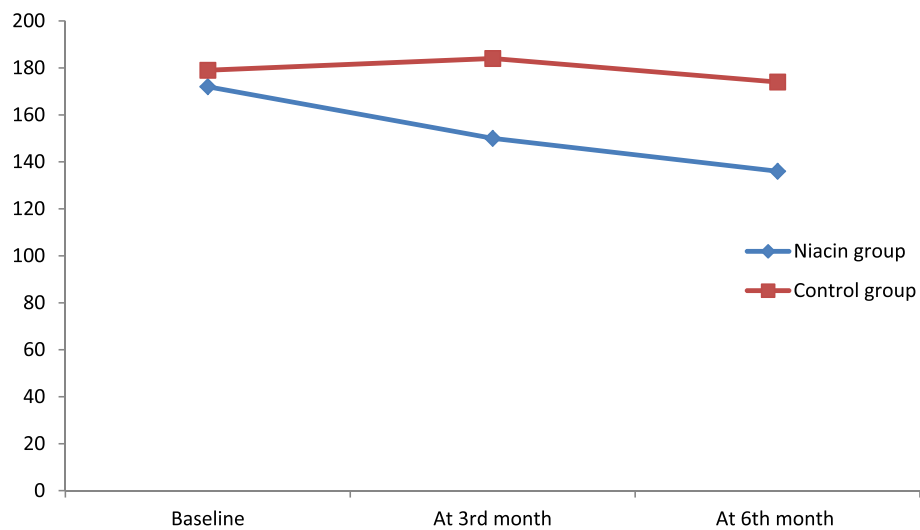


Fig. 6 Changes in level of cholesterol in both groups

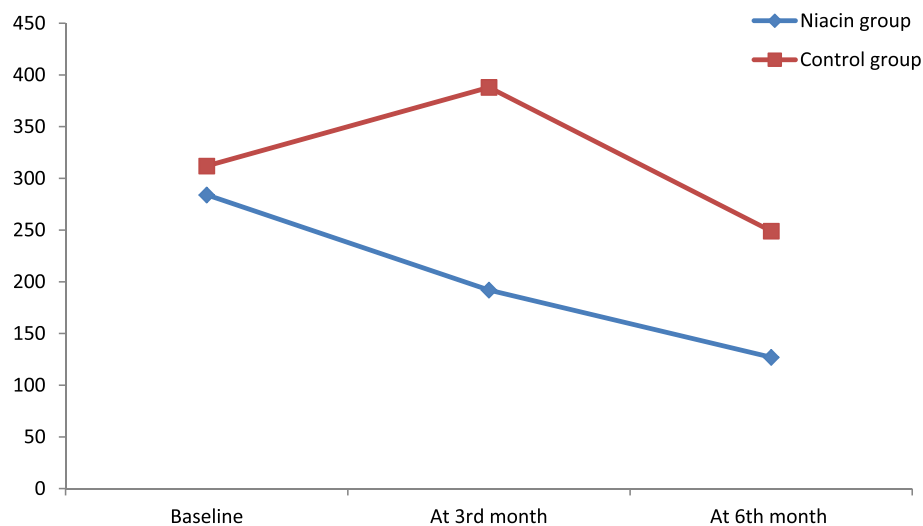
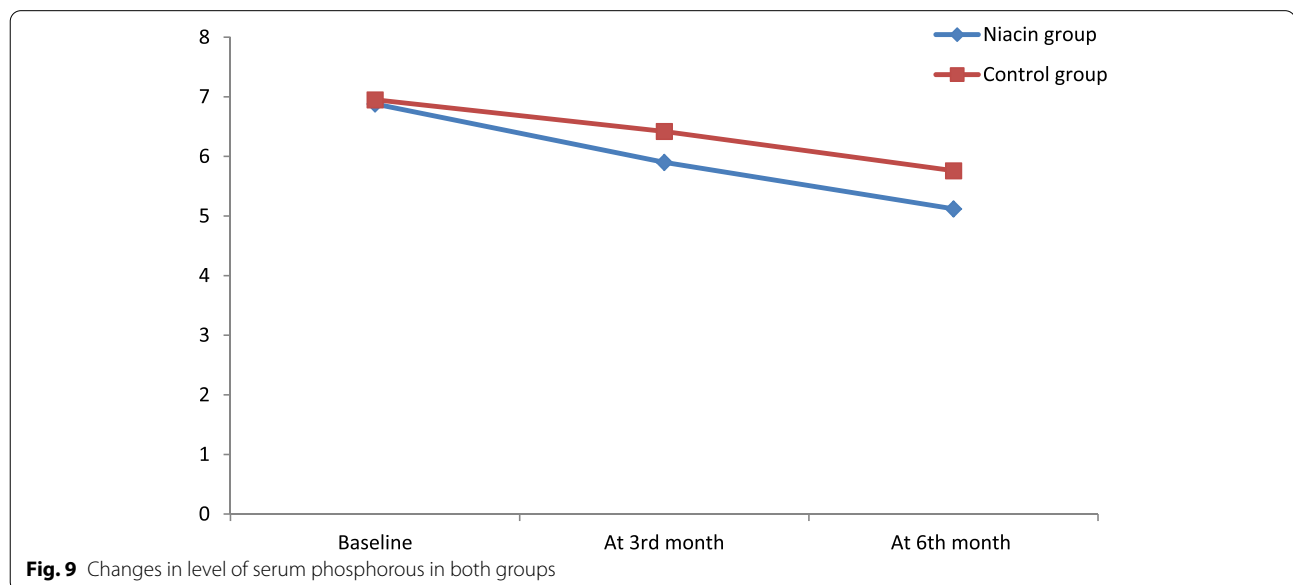
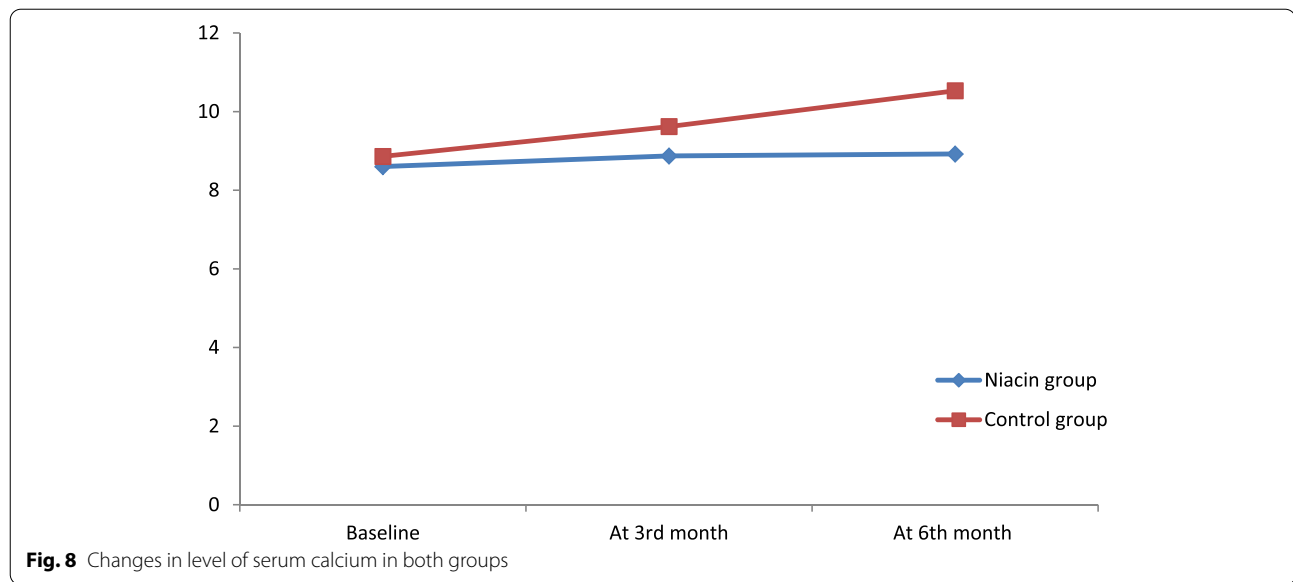


Fig. 7 Changes in level of parathormone in both groups

In our study, both groups had no significant difference regarding baseline PTH, though the niacin group had significantly lower PTH after 3 months of treatment (192.39 ± 78.85 vs. 388.27 ± 263.10 pg/ml; $P < 0.001$) and also after 6 months (127.56 ± 90.87 vs. 249.85 ± 97.69 pg/ml; $P < 0.001$). In this respect, our data were consistent with the results of Muller [16], Cheng et al. [17], Takahashi et al. [11], and Liu et al. [18] who reported that the level of PTH was significantly reduced in patients who received niacin therapy. Our results were different from Cheng et al. [17] and Malhotra et al. [19] as they

observed insignificant changes in serum PTH levels in the niacin group. The change in the PTH level is mainly secondary to the reduction in phosphate levels. The variations in changes of PTH among different studies may be attributed to different sample size, and this issue is still controversial.

Also, we detected an insignificant difference regarding baseline serum calcium, with a significant reduction in calcium at the third month of follow-up (8.87 ± 0.56 vs. 9.62 ± 0.54 mg/dL; $P < 0.001$) and also at the sixth month (8.92 ± 0.55 vs. 10.53 ± 0.77 mg/dL; $P < 0.001$). Similarly,



Kang et al. reported that calcium levels ($P = 0.001$) were significantly decreased at 24 weeks compared with baseline in the niacin group [11]. Inconsistent with our results, Malhotra et al. (2018) reported that niacin and control groups had insignificant differences regarding calcium level [10].

The main adverse events of niacin are vasodilation and flushing [9]; however, in the present study, we detected flushing only in two patients and controlled with 100 mg aspirin, those patients did not stop

niacin therapy during the study. El Borolossy et al. [1] reported eight cases of flushing during the second month of the nicotinamide treatment; all cases resolved spontaneously in the third month, with no need to stop nicotinamide treatment. In a randomized, double-blind placebo-controlled crossover trial, Cheng et al. [17] reported that one patient complained of a rash on his abdomen during week 8 of niacinamide, which resolved after 4 days, with no reports of flushing.

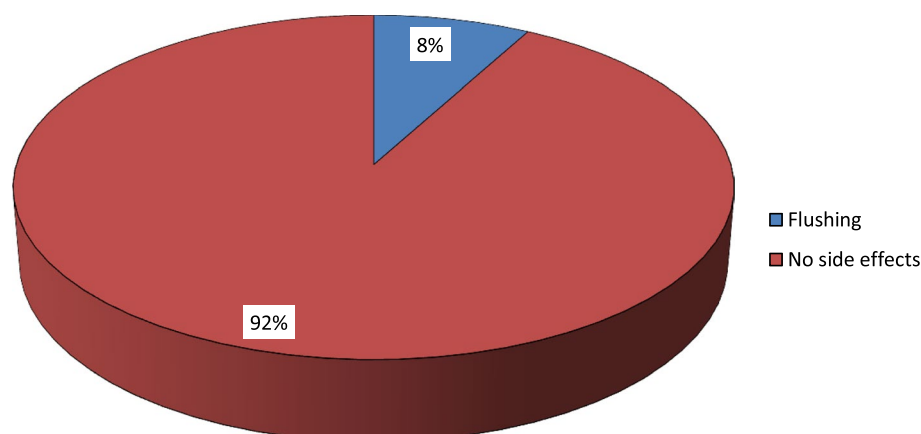


Fig. 10 Side effects among niacin group

Conclusions

The results of our study have confirmed that niacin is an effective drug in reducing blood phosphate levels in dialysis patients in combination with other phosphate binders. Niacin may be considered as a safe, low-cost therapy, with less side effects, and fewer tablets are required to achieve good compliance. The slight elevation in HDL values may be considered as an added beneficial effect.

Abbreviations

HD: Hemodialysis; ESRD: End-stage renal disease; CKD-MBD: Chronic kidney disease-mineral bone disease; NAM: Nicotinamide.

Acknowledgements

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Authors' contributions

EM made substantial contributions to the design of the work, the acquisition, analysis, interpretation of data and was a major contributor in revising the manuscript. HM made substantial contributions to the design of the work and supervising the work. AS made substantial contributions to analysis and interpretation of laboratory data. EY is the corresponding author, has a major role in collecting the data and laboratory investigations of the patients in the study, had a major role in writing the manuscript, and had a major role in doing the Statistical analysis of the data. All authors have read and approved the manuscript.

Funding

Nil.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study's protocol was approved by the institutional review board of the Faculty of Medicine in Assiut University and complied with the tenets of 1964 Declaration of Helsinki and its later amendments (no.: 17100040). Informed written consent was obtained from all participants.

Consent for publication

Applicable.

Competing interests

The authors declare that they have no competing interests.

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