

The Effect of Coadministration of Nicotinamide and Calcium-based Phosphate Binder on Hyperphosphatemia in Patients Undergoing Hemodialysis

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Abstract

Background: Hyperphosphatemia remains a common problem in patients receiving maintenance dialysis. Nicotinamide inhibits intestinal sodium/phosphorus co transporters and reduces serum phosphorus level in some clinical studies.

Objective: Assessment the safety and the efficacy of nicotinamide as adjunctive therapy to calcium carbonate (as phosphate binder).

Study design and setting: A prospective, interventional, open-labeled, case control randomized trial was performed at Ain Shams University Specialized Hospital and Al Motamayz hemodialysis center, Cairo, Egypt, from August 2010 to December 2010.

Patients and methods: Sixty hemodialysis patients with serum phosphorus level ≥ 5.0 mg/dl were classified into two groups; group I (control group) in which patients received calcium carbonate tablets in dose of 500 mg to 1000 mg three t.i.d. And group II (study group) in which patients received calcium carbonate in dose of 500 mg to 1000 mg t.i.d. and nicotinamide tablets in a dose titrated to 1000 mg/day for 8 weeks. Serum calcium, phosphorus and intact parathyroid hormone were measured at week 1 and 9 to assess the efficacy of treatment.

Results: Fifty six patients successfully completed the trial. Serum phosphorus level falls significantly from 6.75 to 5.47 mg/dl with group II and not with group I (from 6.46 to 6.53 mg/dl). A concurrent fall in calcium-

phosphorus product was seen with nicotinamide treatment (from 58.7 to 48.55 mg^2/dl^2), whereas serum calcium, intact parathyroid hormone, uric acid, platelet count, total cholesterol, hemoglobin, AST, and ALT remained stable in both arms. A trend toward increasing HDL and reducing LDL and triglycerides were reported in nicotinamide group however the overall changes were statistically non significant. Diarrhea and other gastrointestinal disturbances symptoms were the major adverse effects seen with nicotinamide treatment.

Conclusion: Nicotinamide in single dose of 1000 mg daily can effectively reduce serum phosphorus level when administered with calcium carbonate (as phosphate binder) with less potential side effects.

Key words: Hyperphosphatemia; Hemodialysis; Nicotinamide; Phosphate binder

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide epidemic and escalating. Approximately 20 million adults in the United States are in various stages of CKD, with more than 400,000 individuals with end-stage kidney disease and over 300,000 individuals requiring maintenance hemodialysis. It has been projected that by 2030, more than 2 million individuals will need dialysis or transplantation for kidney failure as a result of an aging population and the increasing prevalence of type 2 diabetes. The gradual failure of kidney function is accompanied by an increase in cardiovascular disease and a number of metabolic abnormalities, including disordered

phosphorus and calcium metabolism. In patients with CKD, these abnormalities cause significant morbidity and directly influence the mortality associated with end-stage kidney disease. Indeed, cardiovascular mortality is 15 times greater in patients undergoing hemodialysis than in the general population^[1, 2, 3, 4].

As glomerular filtration rate (GFR) declines, there is a decrease in phosphate excretion resulting in phosphate retention, while serum calcium decreases and the production of calcitriol (1, 25-dihydroxyvitamin D) is suppressed. These metabolic changes cause the stimulation of parathyroid hormone production as an adaptive response to maintain normal serum phosphate and calcium concentrations^[5, 6]. Reduced calcitriol levels lead to impaired gastrointestinal calcium absorption, thereby leading to hypocalcaemia. Hyperphosphatemia, hypocalcaemia, and reduced calcitriol synthesis all promote the production of parathyroid hormone and the proliferation of parathyroid cells, resulting in secondary hyperparathyroidism^[7].

Hyperphosphatemia is a common complication of end-stage kidney disease, affecting up to 70% of patients on dialysis, despite dietary restrictions and the use of phosphate-binders^[8]. The clinical consequences of hyperphosphatemia are well documented and include cardiovascular and metastatic calcifications, secondary hyperparathyroidism, and renal bone disease^[9, 10, 11]. In hemodialysis patients, serum phosphate levels >6.5 mg/dl are associated with significantly increased mortality risk^[3, 6, 12]. Because dietary restriction of phosphorus and conventional dialysis are unable to maintain serum phosphorus within recommended range (2.7–5.5 mg/dl)^[13], phosphate binding agents are indicated for treating elevated phosphorus levels in the vast majority of patients undergoing hemodialysis^[14].

Oral phosphate binders play the central role in the control of hyperphosphatemia. Effective binders are available; however, aluminum-based binding exerts bone and brain damage in high-dose and long term use, on the other side, calcium (Ca)-containing binders may even contribute to cardiovascular calcification progression when administered in high doses. Non-aluminum-, non-calcium-based binders such as sevelamer hydrochloride (SEV) and lanthanum carbonate (La) seem to offer advantages in this context, but are also closely observed with regard to their gastrointestinal tolerability and to potential hepatic accumulation respectively^[15].

Nicotinamide is a water-soluble vitamin of the B complex, which together with nicotinic acid belongs to vitamin B3 or vitamin PP. Nicotinamide and nicotinic acid are also called niacinamide and niacin, respectively. However, the term of niacin in the open literature often refers to both substances. Sources of niacin are among others grains, meat and milk^[16]. Despite structural similarities and equivalent nutritional properties, niacinamide and niacin have differing actions and adverse effect profiles. Although

niacinamide can cause gastrointestinal discomfort and reportedly lowers platelet counts, it does not cause flushing, which is commonly seen with niacin^[17, 18]. *In vitro* studies have shown that Niacinamide decreases phosphate uptake by inhibiting sodium/phosphorus co-transporters in the renal proximal tubule (Na/Pi2a) and intestine (Na/Pi2b)^[19, 20, 21]. An open-label study of Niacinamide in Japanese hemodialysis patients who were not taking phosphorus binders found that dosages up to 1750 mg/d decreased serum phosphorus from 6.9 to 5.4 mg/dl, in addition, HDL cholesterol increased and LDL cholesterol declined during the 12 wk of treatment^[22].

AIM OF THE STUDY

To assess the safety and the efficacy of nicotinamide as adjunctive therapy to calcium carbonate (as calcium based phosphate binder).

PATIENTS AND METHODS

Study Design

The study was intended to be prospective, interventional, case control randomized trial.

Enrollment and Setting

Patients were recruited at Ain Shams University Specialized Hospital and Al Motamyz hemodialysis center, Cairo, Egypt. A total of sixty hemodialysis patients with a serum inorganic phosphorus level ≥ 5.0 mg/dl were enrolled in the trial during the period from August 2010 to December 2010. Patients ranged in age from 30 to 66 years. Each patient received hemodialysis regularly for three to four times per week. All patients gave an informed verbal consent.

Inclusion Criteria

1. Patients on regular hemodialysis for more than three months.
2. Stable dosage of calcium carbonate during the previous two week period.
3. Age above 21 years.
4. Serum inorganic phosphorus level equal to or greater than 5.0 mg/dl on the most recent monthly laboratory data.

Exclusion Criteria

1. Pregnancy
2. History of liver disease
3. Active peptic ulcer disease
4. Treatment with carbamazepine
5. Patients on niacin therapy; and Non compliant patients.

Study Medication and Randomization

Sixty hemodialysis patients with serum phosphorus level

≥ 5.0 mg/dl were classified randomly into two groups depending on their medication; group I (control group) in which patients received calcium carbonate tablets in dose of 500 mg to 1000 mg three times daily. And group II (study group) in which patients received calcium carbonate in dose of 500mg to 1000 mg three times daily and nicotinamide tablets in a dose titrated to 1000 mg/day for 8 weeks.

Samples

Five ml blood sample was taken twice (before and after study treatment) from each patient upon enrollment into study. Serum calcium, phosphorus and intact parathyroid hormone were measured at week 1 and 9 to assess the efficacy of treatment. Additionally, serum uric acid, liver enzymes (AST and ALT), and complete blood count were obtained at week 1 and 9 to evaluate the safety of using nicotinamide. Lipid panels were drawn at week 1 and 9 to figure out the effect of nicotinamide on lipid profile. All laboratory values were drawn just before dialysis session on the first dialysis treatment of the week.

Dosage Titration

Nicotinamide was administered at a starting dosage of one tablet (500 mg) once daily for one week. Then the dosage was increased to 1000 mg (two tablets) once daily at week two and continued till the end of the study.

Statistical Analysis

IBM SPSS statistics (V. 19.0, IBM Corp., USA, 2010) was used for data analysis. Data were expressed as Mean $\pm$ SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data.

The Following Tests Were Done

1. Comparison between two independent mean groups for parametric data using Student t test.
2. Comparison between 2 dependent groups for parametric data using Paired t test.
3. Pearson correlation test to study the possible association between each two variables among each group for parametric data.

For Follow-up Study

The degree of change due to follow-up study (delta change or dC) reflects the actual difference changed through the follow-up study can be calculated for each patient and from which, the mean delta change can be calculated. It is used for follow-up study and for comparison between the subgroups, also for correlation with other variables. It is

defined as follow:

$$\text{Delta change (dC)} = (\text{Post-Pre})/\text{Pre}$$

Or the difference between post and pre as regards pre values for each patient.

The probability of error at 0.05 was considered significant while at 0.01 and 0.001 are highly significant.

RESULTS

A total of 75 patients underwent screening, and sixty were randomly assigned into trial. They were categorized into two groups; group I (control) and group II (study or nicotinamide group). Each group included 30 patients. Only 4 patients withdrew the study group and a total 26 patients completed the 8weeks study in group II. All patients in two arms were compliant with medication. Patients characteristics are shown in table 1 and biochemical data are displayed in table 2.

Dosing Characteristics

In accordance with our protocol, the dosage of all medication, prescribed to patients, were not changed for any patients during the study. All control patients completed the study weeks receiving 500 to 1000 mg of calcium carbonate tablets three times daily. However, a total of 26 patients in the study group were successfully completed the trial receiving calcium carbonate tablets in the same dose of control group in addition to 500 mg nicotinamide tablets once daily for the first week. Then dose increased to 1000 mg once daily at week 2 to week 9.

1. First End Point for Evaluating the Efficacy of Nicotinamide

Serum Level of Phosphorus, Calcium, Intact Parathyroid Hormone, and Calcium Phosphorus Product

Among all patients, treatment in group I resulted in an insignificant rise in the mean serum phosphorus from 6.46 to 6.53 mg/dl ($p = 0.56$). However the treatment with nicotinamide resulted in highly significant fall in the mean serum phosphorus from 6.75 to 5.47 mg/dl ($p = 0$). Also, there were no significant difference in serum calcium, and calcium-phosphorus product of control group ($p = 0.43$), ($p = 0.76$), respectively. Otherwise, a significant decrease in calcium-phosphorus product (from 58.7 to 48.5 mg/dl; $p = 0$), and a significant increase in serum calcium level (from 8.6 to 8.91 mg/dl; $p = 0.005$) were reported with nicotinamide group. There were no significant changes in intact parathyroid hormone level in both arms during study period (table 3).

Table 1
Patient Characteristics of the Studied Groups I and Group II

Parameter	Group Number	Group I (n =30)	Group II (n =26)	P-value	Sig
*Age (years) Mean ± SD		50.2 ± 9.87	51.63 ± 8.10	0.54	NS
*Dry wt. (kg) Mean ± SD		74.18 ± 6.20	73.81± 5.80	0.81	NS
*Duration of dialysis (years) Mean ± SD		4.83 ± 1.82	5.16 ± 2.03	0.51	NS
**Male : Female ratio		22:8	24:6	0.54	NS

SD: standard deviation; n: number of patient; NS: non significant;*: using one way ANOVA test; **: using chi square test.

Table 2
Biochemical Data of the Studied Groups at Baseline

Parameters	Group I (n= 30)	Group II (n=26)	P- value	Sig
	6.46±0.81	6.75±1.02	0.25	NS
*Ca.level (mg/dl)	8.87 ± 1.17	8.68± 0.72	0.45	NS
*Ca- Ph product(mg ² /dl ²)	57.8 ± 12.96	58.70± 10.9	0.77	NS
*iPTH(pg/ml)	674.50± 318.2	585.5± 378.5	0.35	NS
*Chol.(mg/dl)	238.2± 133.1	249.5± 134.5	0.71	NS
*TRG(mg/dl)	326.87± 159	332.73± 182	0.92	NS
*HDL(mg/dl)	39.07± 7.3	39.31± 7.2	0.93	NS
*LDL (mg/dl)	123.9± 62.67	125.40± 65.35	0.94	NS
*Hgb(g /dl)	11.65± 1.96	11.24± 1.23	0.22	NS
*Uric acid(mg/dl)	7.55± 1.7	7.56± 1.82	0.98	NS
*Plt count(1000/mm ³)	210± 33.20	213.4± 34.43	0.79	NS
*SGOT(mg/dl)	38.23± 15.68	38.58± 16.33	0.96	NS
*SGPT(mg/dl)	28.77± 15.18	29.54± 15.71	0.86	NS

Values are expressed as mean ±SD

n: number of patients; **Ph. Level:** inorganic phosphate level; **Ca. level:** Calcium level; **Ph-Ca product:** calcium x phosphorous product; **iPTH level:** intact parathyroid hormone level; **Serum Chol.:** serum total cholesterol level; **Serum TRG:** serum triglyceride level; **Serum HDL:** serum high density lipoprotein level; **Serum LDL:** serum low density lipoprotein level; **Hgb:** hemoglobin level; **Plt counts:** platelet counts; **SGOT:** serum glutamate oxaloacetic transaminase; **SGPT:** serum glutamic pyruvate transaminase; **NS:** insignificant;*:using student t-test

Table 3
Serum Level of ph. Level, ca. Level, ph×Ca Product, and PTH in the Studied Groups Before (week 1), and After (week 9) the Study

Parameter	Group I n= 30				Group II n = 26			
	Week 1	Week 9	P- value	Sig.	Week 1	Week 9	P- value	Sig.
*Serum Ph. (mg/dl) Mean ± SD	6.46± 0.81	6.53± 0.81	0.56	NS	6.75± 1.02	5.47± 1.28	0.001	HS
*Serum Ca. (mg/dl) Mean ± SD	8.87± 1.17	8.71± 1.02	0.43	NS	8.68± 0.72	8.91± 0.87	0.005	S
*Serum Ca x Ph product (mg ² /dl ²) Mean ± SD	57.8± 12.96	57.3 ± 12.40	0.76	NS	58.70± 10.9	48.55± 11.53	0.001	HS
*Serum iPTH (pg/dl) Mean ± SD	674± 318.2	697± 302	0.09	NS	585.5± 378	547.6± 477	0.46	NS

n: number of patients; **Ph. Level:** inorganic phosphate level; **Ca. level:** Calcium level; **Ca-Ph product:** calcium x phosphorous product; **iPTH level:** intact parathyroid hormone level; **NS:** statistically non significant values; **HS:** highly statistically significant value; **S:** statistically significant value; * comparison carried using paired t-test

When changes in those variables in nicotinamide group (group II) compared to those of control group as shown in figure (1&2), a highly significant decrease in serum phosphorus ($p = 0.001$), with a concurrent significant fall in calcium-phosphorus product ($p = 0.008$)

were reported in nicotinamide group. Serum calcium and intact parathyroid hormone showed no significant difference between two groups ($p = 0.43$), ($p = 0.17$), respectively.

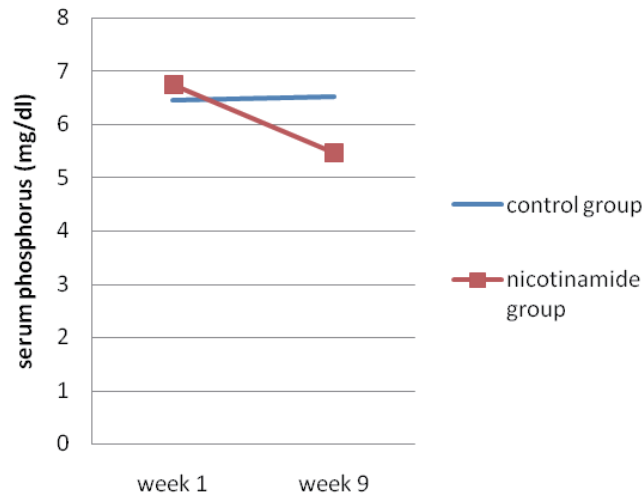


Figure 1
The Serum Level of Phosphorus in the Studied Groups at the End of Study

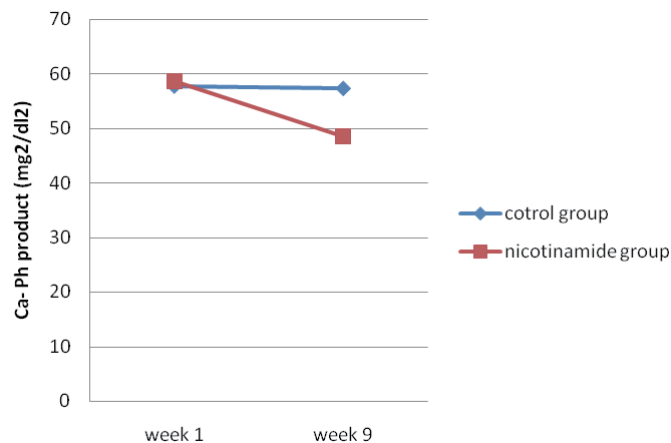


Figure 2
The Serum Level of Calcium-Phosphorus Product in the Studied Groups at the End of Study

A comparison of the degree of changes in ph. Level, ca. level, $ph \times Ca$ product, and iPTH in both groups was shown in figure (3). The degree of change reflects the actual difference changed through the study. In this figure there were significant difference in the degree of change of phosphorus level ($p = 0$) in the study group, $ph \times Ca$ product ($p = 0$), and iPTH ($p = 0.044$) whereas the degree of change of ca level was insignificant ($p = 0.158$).

2. Secondary End Point for Evaluating the Safety of Using Nicotinamide

During 8 weeks of study, the following side effects of nicotinamide were observed.

Gastrointestinal Disturbance, Flushing, Rash, and Blurred Vision

During the study, two patient in nicotinamide group discontinued medication because of flushing and

abdominal rash that started with the higher dose of nicotinamide. At day 9, three patients developed gastrointestinal disturbances and diarrhea. Two of them withdrew the study and the one completed the study was

advised to take the total daily dose in two divided doses. This patient had spontaneous resolution of his symptoms without a reduction in dosage. Such adverse effects were not reported in control arm.

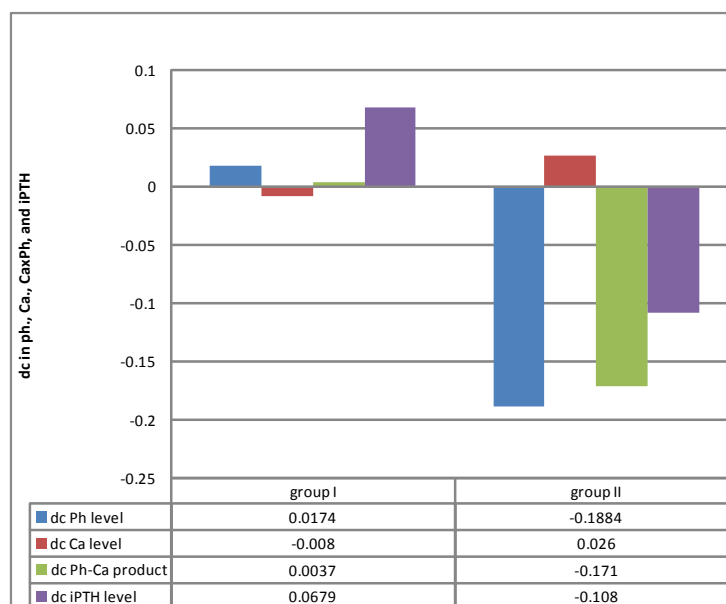


Figure 3
The Degree of Change in Serum Level of Phosphorus, Calcium, Phosphorus-Calcium Product, and IPTH in the Studied Group

The Effect of Nicotinamide on the Lipid Profile of Patients

Although nicotinamide lacks the hypolipidemic action of nicotinic acid, a trend toward increasing HDL (from 39.3 to 42.3 mg/dl), and decreasing LDL (from 125.4 to 123.2 mg/dl) and total cholesterol (from 249.5 to 234.5 mg/dl) were reported in this study. The changes observed in those variables were statistically insignificant ($p=0.21$), ($p=0.52$), and ($p=0.20$), respectively.

Hepatotoxicity, Thrombocytopenia, and Uricemia as Side Effect of Nicotinamide

In this study, there were not any significant changes in liver enzymes (AST and ALT), and uric acid at the end of study treatment between control group and nicotinamide group. Platelet count tended to reduced insignificantly upon nicotinamide treatment. Laboratory results at the completion of study of control and nicotinamide are summarized in table 4.

Table 4
Laboratory Results of the Studied Groups at the End of the Study

Parameters	Group I (n= 30)	Group II (n=26)	P- value	Sig
Chol.(mg/dl)	235.30± 123	234.5± 130.15	0.99	NS
TRG(mg/dl)	281.60± 165.16	272.60± 162.55	0.84	NS
HDL(mg/dl)	42.27± 8.06	42.38± 8.21	0.98	NS
LDL (mg/dl)	118.2± 52.26	120.22± 53.76	0.90	NS
Hgb(g /dl)	12.43± 2.44	12.31± 0.87	0.81	NS
Uric acid(mg/dl)	7.02± 1.57	7.09± 1.57	0.90	NS
Plt count(1000/mm ³)	220.5± 29.60	207.26± 34.66	0.061	NS
SGOT(mg/dl)	38.23± 15.80	38.65± 16.52	0.94	NS
SGPT(mg/dl)	28.90± 14.93	29.62± 15.42	0.89	NS

n: number of patients; **Serum Chol.:** serum total cholesterol level; **Serum TRG:** serum triglyceride level; **Serum HDL:** serum high density lipoprotein level; **Serum LDL:** serum low density lipoprotein level; **Hgb:** hemoglobin level; **Plt counts:** platelet counts; **SGOT:** serum glutamate oxaloacetic transaminase; **SGPT:** serum glutamic pyruvate transaminase; **NS:** insignificant. *using student t-test

DISCUSSION

Niacinamide (or nicotinamide) is the corresponding amide form of niacin. Niacinamide is thought to possess less potential for side effects, namely flushing, than niacin. Animal studies have suggested that niacinamide may decrease brush border uptake of phosphate by blocking the sodium phosphate co transporter in the small intestine^[19]. In large, multicenter studies, elevated serum phosphorus has been associated with an increase in morbidity and mortality in patients with ESRD^[3, 23]. Hyperphosphatemia is linked to cardiovascular risk as well as bone disease^[24, 25], and the hyperphosphatemic milieu may promote vascular calcification through cellular changes in vascular smooth muscle cells^[26]. Previous open-label studies by Takahashi *et al.*, Sampathkumar *et al.*^[22, 27] and a double-blind trial by Cheng *et al.*^[21] demonstrated that niacinamide lowers serum phosphorus levels in maintenance hemodialysis patients when used in high dosage and the traditional binding agents were withheld. In present study, the efficacy of nicotinamide on phosphorus reduction using lower dose (1000 mg daily) in conjunction with calcium carbonate was assessed on hyperphosphatemic patients undergoing haemodialysis at Ain Shams specialized hospital- based hemodialysis unit and AL Motamayz Hemodialysis center.

After 8 weeks of therapy, our patients in nicotinamide arm had highly statistically and clinically significant drop in serum phosphorus (6.75 to 5.47 mg/dl; $p=0$) with concomitant fall in calcium phosphorus product from 58.7 to 48.55 mg²/dl²; $p=0$. Also serum calcium increased significantly from 8.68 to 8.91 mg/dl; $p=0.005$. Despite of using lower dose of nicotinamide in this study, our findings are agreed with previous studies which stated that nicotinamide can effectively reduce serum phosphorus in hemodialysis patients^[22, 27, 21].

Trends toward increasing HDL and decreasing LDL, total cholesterol, triglycerides have been reported in the present study upon nicotinamide treatment. However, the overall changes in those variables were not statistically significant. In fact, nicotinic acid, but not nicotinamide, is known to decrease plasma fatty acids, triglyceride, and LDL by reducing lipase effects in adipose tissue and presumably increase HDL concentration by increasing apoA-1 which is the main lipoprotein of HDL^[28, 29]. In some studies, significant or considerable changes in HDL and LDL had been reported. Takahashi *et al.*, showed that nicotinamide can increase HDL and decrease LDL in hemodialysis patients^[22]. And a significant increase in HDL, but no change in LDL and triglyceride has been found in a recent randomized clinical trial^[21]. Another recent study showed that nicotinamide can increase HDL, and decrease the values of triglyceride and LDL with clinical significance. No noticeable changes were found in cholesterol levels in that study^[30]. At least in our population, nicotinamide was able to cause considerable changes in

lipid profile. Although those changes were not statistically significant, the cumulative effect of nicotinamide on lipid metabolism reported in this study may have important benefits on chronic kidney disease and dialysis patients.

Thrombocytopenia has been a concern from previous studies^[21]. In our study, a few decrease in platelet count (from 213.46 to 207.2 1000/mm³) was reported in nicotinamide group. This change was statistically insignificant ($p = 0.8$) when compared to those changes of control group. Nevertheless, no clinical manifestations of thrombocytopenia complicated the administration of study drug in the present study. This finding is in accordance with other authors' findings. In their studies, they stated that there was a trend toward decreasing platelet count in nicotinamide group. Additionally, although nicotinamide was administered in higher dose and for longer duration than used in the current study, that decrease was insignificant^[21, 31]. Also there were no episodes of decreasing platelet counts reported in Young's study^[32]. Although reduction in platelet counts is non significant in this study, it is still of great clinical importance. And for now, monitoring for thrombocytopenia in dialysis patients on nicotinamide is a must.

Agreed with the most previous studies which mentioned that nicotinamide had no effect on **uric acid** level^[21, 27, 30, 33, 34], our study showed no changes in uric acid level upon nicotinamide therapy.

In the current study, during the 8 wk of study, no **hepatotoxicity** cases were reported and no significant changes in liver enzymes were noted. This finding is explained by the fact that both nicotinic acid and nicotinamide are relatively safe and cause no liver enzymes abnormalities when used in dosage lower than 3g/day^[35].

Most of previous studies concerning the effect of nicotinamide on hyperphosphatemia in HD patients didn't mention the changes in **hemoglobin** upon the therapy^[21, 22]. However, a trend toward reduced mean hemoglobin in nicotinamide treated group was demonstrated in Young *et al.*^[32]. In the present study, there are not any significant changes in hemoglobin level of nicotinamide treated group when compared to those of control group.

Nicotinamide lacks the vasodilator action of nicotinic acid^[35]. In accordance with this fact, only one case of **flushing** and another case of **abdominal rash** were reported in this study at second week with the beginning of higher dose. The two patients withdrew study. Our findings are agreed with those reported in previous studies^[21, 32]. In Cheng *et al.*, and Young *et al.* only a case of abdominal rash and another case of pruritic rash were reported respectively. In both studies no one of patients randomized to nicotinamide treatment developed flushing (Cheng, 2008; Young *et al.*, 2009).

Nicotinamide seems to be well tolerated in general population^[36]. In the current study the percentages of **GI disturbances and diarrhea** are 10% (3 of 30) and 3.3% (1

of 30) of the total study population respectively. And they were 3.6% (1 of 26) and 0% (0 of 26) of study population completed the study. These findings are consistent with Young's study, in which low percentage of patients developed diarrhea^[32]. But our results are in a marked contrast to those reported in other studies. The authors in those studies reported that much higher percentage of patients suffered from diarrhea upon nicotinamide therapy^[18, 21, 22]. The authors speculated that the higher percentage of diarrhea was a result of co administration of phosphorus binders with high dose of nicotinamide^[21].

CONCLUSION

Icotinamide is effective in controlling serum phosphorus when co-administered with calcium carbonate in hemodialysis patients. Not only reducing serum phosphorus, but also nicotinamide provide beneficial changes in lipid profiles of hemodialysis patients when co administered with calcium carbonate.

All those advantages were reported in this study with less potential side effects noticed.

Dialysis patients in Egypt have poorer phosphorus control and might benefit from the addition of nicotinamide to their binder regimen.

RECOMMENDATION

Further studies in larger randomized trials for longer duration and other chronic kidney disease populations are indicated to assess the following:

The efficacy of nicotinamide when used in a dose less than 1000 mg daily.

Whether nicotinamide reduces serum phosphorus level effectively in hemodialysis patients when used alone.

Nicotinamide effects on platelet count, hemoglobin, liver enzymes.

If diarrhea and thrombocytopenia are a dose related side effects of nicotinamide! And if yes, which dose is safe.

The actual effect of nicotinamide on lipid profile of hemodialysis patients using different dosage of nicotinamide for different durations.

REFERENCES

- [1] Coresh J., Astor B. C., Greene T., Eknoyan G. & Levey A.S. (2003). Prevalence of Chronic Kidney Disease and Decreased Kidney Function in the Adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.*, 41, 1-12.
- [2] US Renal Data System. USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, Maryland: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003.
- [3] Block G. A., Klassen P. S., Lazarus J. M., Ofsthun N., Lowrie E.G. & Chertow G.M. (2004). Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. *J Am Soc Nephrol*, 15, 2208- 2218.
- [4] US Renal Data System. USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, Maryland: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005.
- [5] Malluche H. H., Mawad H. & Monier-Faugere M. C. (2004). The Importance of Bone Health in End-Stage Renal Disease: Out of the Frying Pan, into the Fire?. *Nephrol Dial Transplant*, 19, i9- i13.
- [6] Levin A. & Li Y.C. (2005). Vitamin D and Its Analogues: Do They Protect Against Cardiovascular Disease in Patients with Kidney Disease?. *Kidney Int.*, 68, 1973-1981.
- [7] Slatopolsky E., Brown A. & Dusso A. (1999). Pathogenesis of Secondary Hyperparathyroidism. *Kidney Int Suppl.*, 73, S14-S19.
- [8] Block G. A., Hulbert-Shearon T.E., Levin N.W. & Port F.K. (1998). Association of Serum Phosphate and Calcium X Phosphate Product with Mortality Risk in Chronic Haemodialysis Patients: A National Study. *Am J Kidney Dis.*, 31, 607-617.
- [9] Drücke T.B. (1996). A Clinical Approach to the Uraemic Patient with Extraskkeletal Calcifications. *Nephrol Dial Transplant*, 11(Suppl 3), 37-42.
- [10] Goodman W. G., Goldin J., Kuizon B.D., et al.(2000). Coronary-artery Calcification in Young Adults with End-Stage Renal Disease Who Are Undergoing Dialysis. *N Engl J Med.*, 342, 1478-1483.
- [11] Locatelli F., Cannata-Andia J. B., Drueke T.B., et al. (2002). Management of Disturbances of Calcium and Phosphate Metabolism in Chronic Renal Insufficiency, with Emphasis of the Control of Hyperphosphatemia. *Nephrol Dial Transplant*, 17, 723-731.
- [12] Ganesh S.K., Stack A.G., Levin N.W., Hulbert-Shearon T. & Port F.K. (2001). Association of Elevated Serum PO(4), Ca x PO(4) Product, and Parathyroid Hormone with Cardiac Mortality Risk in Chronic Hemodialysis Patients. *J Am Soc Nephrol*, 12, 2131-2138.
- [13] National Kidney Foundation (2003). National Kidney Foundation: K/ DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *AM J Kidney Dis.*, 42 (Suppl 3), S1- S 201.
- [14] Bleyer A.J. (2003). Phosphate Binder Usage in Kidney Failure Patients. *Expert Opin Pharmacother*, 4, 941-947.
- [15] Ketteler M (2007). Phosphorous Control in Chronic Kidney Disease. *European Nephrology*, (1), 24-6.
- [16] SIDS Initial Assessment Report for SIAM: 3-Pyridinecarboxamide (Nicotinamide). Boston, Massachusetts, 22-25 October 2002.
- [17] O'Brien T., Silverberg J & Nguyen T. (1992). Nicotinic Acid Induced Toxicity Associated with Cytopenia and Decrease Level of Thyroxin- Binding Globulin. *Mayo Clin Proc.*, 67, 465- 468.

- [18] Delanaye P., Weekers L. & Krzesinski J. (2006). Diarrhea Induced by High Doses of Nicotinamide in Dialysis Patients. *Kidney Int*, 69, 1914 .
- [19] Katai K., Tanaka H., Tatsumi S., Fukunaga Y., Genjida K., Morita K., *et al.* (1999). Nicotinamide Inhibits Sodium-Dependant Phosphate Cotransport Activity in Rat Small Intestine. *Nephrol Dial Transplant*, 14, 1195-1201.
- [20] Eto N., Miyata Y., Ohno H. & Yamashita T. (2005). Nicotinamide Prevents the Development of Hyperphosphatemia by Suppressing Intestinal Sodium-Dependent Phosphate Transporter in Rats With a Denin-Induced Renal Failure. *Nephrol Dial Transplant*, 20, 1378-1384.
- [21] Cheng S.C., Young D.O., Huang Y., Delmez J.A. & Coyne D.W. (2008). A Randomized, Double-Blind, Placebo-Controlled Trail of Niacinamide for Reduction of Phosphorus In Hemodialysis Patients. *Clin J AM SOC Nephrol*, 3, 1131- 1138.
- [22] Takahashi Y., Tanaka K., Nakamura T., Fukuwatari T., Shibata K., Shimada N., *et al.* (2004). Nicotinamide Suppress Hyperphosphatemia in Hemodialysis Patients. *Kidney Int.*, 65, 1099-1104.
- [23] Kalantar-Zadeh K., Kuwae N., Regidor D., Kovesdy C.P., Kilpatrick R.D., Shinaberger C.S., McAllister C.J., Budoff M.J., Salusky I.B., Kopple J.D. (2006). Survival Predictability of Time-Varying Indicators of Bone Disease in Maintenance Hemodialysis Patients. *Kidney Int.*, 70, 771-780.
- [24] DeBoer I.H., Gorodetskaya I., Young B., Hsu C.Y., Chertow GM (2002). The Severity of Secondary Hyperparathyroidism in Chronic Renal Insufficiency Is Gfr-Dependent, Race-Dependent, and Associated with Cardiovascular Disease. *J Am Soc Nephrol*, 13, 2762-2769.
- [25] Saleh F.N., Schirmer H., Sundsfjord J. & Jorde R. (2003). Parathyroid Hormone and Left Ventricular Hypertrophy. *Eur Heart J*, 24, 2054-2060.
- [26] Shalhoub V., Shatzken E., Henley C., Boedigheimer M., McNinch J., Manoukian R., Damore M., Fitzpatrick D., Haas K., Twomey B., Kiaei P., Ward S., Lacey D.L., Martin D. (2006). Calcification Inhibitors and WNT Signaling Proteins Are Implicated in Bovine Artery Smooth Muscle Cell Calcification in the Presence of Phosphate and Vitamin D Sterols. *Calcif Tissue Int.*, 79, 431-442.
- [27] Sampathkumar K., Selvam M., Sooraj Y.S., Gowthaman S. & Ajeshkumar R.N. (2006). Extended Release Nicotinic Acid: A Novel Oral Agent for Phosphate Control. *Int Urol Nephro*, 138, 171-174.
- [28] Carlson L. (2005). Nicotinic Acid: The Broad Spectrum Lipid Drug. A 50th Anniversary Review. *J Intern Med*, 258, 94-114.
- [29] Trevor A., Katzung B., Masters S. (2008). *Katzung & Trevor's Pharmacology Examinations and Board Review* (8th ed.). New York: Mc Graw-Hill.
- [30] Shahbazian H., Mohtashami A., Ghorbani A., Abbaspour M., Musavi S., Hayati F., Lashkarana G. (2011). Oral Nicotinamide Reduces Serum Level of Phosphorus, Increase HDL, and Induces Thrombocytopenia in Hemodialysis Patients: A Double-Blind, Randomized Clinical Trial. *Nefrologia*, 31(1), 58-65.
- [31] Rottembourg J, Launay-Vacher V & Massard J (2005). Thrombocytopenia Induced by Nicotinamide in Hemodialysis Patients. *Kidney Int.*, 68(6), 2911-2912.
- [32] Young D., Cheng S., Delmez A., Coyne D., *et al.* (2009). The Effect of Oral Nicotinamide on Plasma Phosphorus Level in Peritoneal Dialysis Patients. *Perit Dial Int.*, 29, 562-567.
- [33] Muller D., Mehling H., Otto B., Bergmann-Lips R., Luft F., Jordan J., Kettritz R. (2007). Niacin Lowers Serum Phosphorus and Increases HDL Cholesterol in Dialysis Patients. *Clin J Am Soc Nephro*, 12, 1249-1254.
- [34] Restrepo V. & Cruz J. (2008). Safety and Effectiveness of Nicotinic Acid in the Management of Patients with Chronic Renal Disease with Hyperlipidemia Associated to Hyperphosphatemia. *Nephrologia*, 28(1), 61-66.
- [35] Knip M., Douek I.F., Moore W.P., Gillmor H., Mclean A., Bingley P., *et al.* (2000). Safety of High Doses Nicotinamide: A Review. *Diabetologia*, 43(11), 1337-1345.
- [36] Gale E., Bingley P., Emmett C., Collier T., European Nicotinamide Diabetes Intervention Trial (ENDIT) Group (2004). European Nicotinamide Diabetes Intervention Trial (ENDIT): A Randomized Controlled Trial of Intervention Before the Onset of Type 1 Diabetes. *Lancet*, 363, 925-931.