Low Dose Nicotinamide as an Adjunctive Therapy to Calcium Carbonate for Control of Hyperphosphatemia in Hemodialysis Patients

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Abstract

Background: Hyperphosphatemia remains a common problem in patients on maintenance dialysis and contributes to the development of secondary hyperparathyroidism. Current therapies for the treatment of hyperphosphatemia are frequently insufficient to achieve the recommended K/DOQI goal of maintaining serum phosphorus level between 3.5 and 5.5 mg/dl. Niacinamide inhibits intestinal sodium/ phosphorus co transporters and reduces serum phosphorus level in some clinical studies. So, we aimed to evaluate the safety and the efficacy of nicotinamide as adjunctive therapy to calcium carbonate (as calcium based phosphate binder) in hemodialysis patients. **Methods:** Sixty hemodialysis patients with serum phosphorus level ≥ 5.0 mg/dl were randomly assigned to 8 weeks of the study. Patients were divided into two groups: **(group I) (control group):** 30 cases calcium carbonate only and **(group II) (study group):** 30 cases received a combination of calcium carbonate and nicotinamide. Nicotinamide dose was started as 500mg/day and increased on 8th day to 1000 mg/day. **Results:** *In the study group (nicotinamide group):* serum phosphorus level fell significantly *(p<0.001),* calcium × phosphorus product dropped significantly *(p<0.001),* with a significant elevation of serum calcium *(p<0.05). In the control group:* there was insignificant change in former parameters *(p values>0.05).* Intact parathyroid hormone, uric acid, platelet count, total cholesterol, hemoglobin, ASAT, and ALAT and lipid profile remained insignificantly changed **in both groups**. Diarrhea, flushing and skin rash were the major adverse effects seen with nicotinamide therapy resulting in early withdrawal of 4 patients from the study. **Conclusion:** In hemodialysis patients, 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 reported.

Key words: Nicotinamide- Hyperphosphatemia- Hemodialysis

Introduction

Chronic kidney disease (CKD) is a worldwide epidemic and escalating problem. 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 renal disease (ESRD), 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 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 mean both substances. Niacin is abundant in 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 phosphate binders found that doses up to 1750 mg/day decreased serum phosphorus from 6.9 to 5.4 mg/dl *(22).* In addition, HDL cholesterol increased and LDL cholesterol declined during the 12 week of treatment.

Dialysis patients in Egypt have poorer phosphorus control and might benefit from the addition of nicotinamide to their calcium based binder regimen taking into consideration, the other effects and side effects of the drug. So, we **aimed to** evaluate the safety and the efficacy of nicotinamide as adjunctive therapy to calcium carbonate (as calcium based phosphate binder) in hemodialysis patients

Patients and Methods

In this prospective, interventional study, **sixty patients (46♂ and 14♀) with age range of 30-60 years** with end stage renal disease (ESRD) on regular hemodialysis in the dialysis center of Ain Shams University Specialized Hospital and Al Motamyez hemodialysis center, Cairo, Egypt,

were included. All cases were scheduled to three sessions of hemodialysis per week (4 hours each). Patients were dialyzed using bicarbonate dialysate containing calcium concentration 3 mEq/L, polysulfon membrane dialyzers of surface area 1.3 to1.7 m² on volumetric machines (Fresenius 4008 B or Gambro AK 90).Urea reduction ratio (URR) was performed before the study to ensure adequate dialysis. All cases had serum inorganic phosphorus level > 5.0 mg/dl.

Patients were classified randomly into **two groups** depending on their medication; **group I (control group):** composed of 30 patients (**22♂ and 8♀**) who received ,only, calcium carbonate tablets containing 1.5 to 3 grams of elemental calcium per day. And **group II (study group):** composed of 30 patients (**24♂ and 6♀**) who received the same dose of calcium carbonate **plus** nicotinamide for **8 weeks**. Nicotinamide was administered at a starting dose of 500 mg once daily for one week (to ensure tolerance), then the dose was increased to 1000 mg once daily at week two and continued till the end of the study. Side effects of nicotinamide therapy caused 4 patients to withdraw early from the study. This made the number of cases of **group II (study group)** to fall to 26 patients (**22♂ and 4♀**). Statistical analysis ensured homogeneity of both groups and all patients gave consent.

Inclusion criteria: Patients on regular hemodialysis for more than three months who were receiving stable dosage of calcium carbonate during the previous two weeks prior to study and who had serum inorganic phosphorus level ≥ 5.0 mg/ dl on the most recent monthly laboratory data.

Exclusion criteria: Pregnant females were excluded from the study. Patients with history of chronic liver disease and those with peptic ulcer disease or on treatment with carbamazepine were also excluded. Patients on Sevelamer treatment, incompliant patients on dialysis, patients on regular hemodialysis for less than

three months and those who refused to give consent were excluded from the study.

Patients were subjected to full history taking and clinical examination to ensure the absence of exclusion criteria. Blood samples were taken **twice**, just before dialysis session on the first dialysis treatment of the week 1 and 9 for **measurement of** serum calcium, phosphorus, ca× ph product and intact parathyroid hormone (iPTH) to assess the efficacy of treatment. Serum uric acid, ASAT (aspartate aminotransferase) and ALAT (alanine aminotransferase), complete blood count to evaluate the safety of using nicotinamide were also measured. Lipid profile including total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides (TGD) were also measured to figure out the effect of nicotinamide on lipid profile.

Statistical analysis:

IBM compatible laptop and SPSS program (V. 19.0, IBM Corp., USA, 2010) were used for data analysis. Collective quantitative parametric data were expressed as *Mean± SD*. For comparison between two independent means for parametric data we used the *Student t test*. For comparison between 2 dependent groups for parametric data we used the *paired t test*. *Pearson correlation* test was used to study the possible association between each two variables among each group for parametric data. *Chi square test* was used to compare binomial 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 that 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: *Delta change (dC)* = (Post-Pre)/Pre

P value ≤ 0.05 was considered significant, while *≤ 0.01 and 0.001* were considered highly significant.

Results

Sixty cases of ESRD on regular hemodialysis were randomly 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 8 weeks 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).** Both tables show the homogeneity of *group I* and *group II* and hence, the liability for comparison.

- *Serum level of phosphorus, calcium, iPTH, and calcium × phosphorus product:*

As we can see from **table (3)**, patients of *group I* showed insignificant changes in the mean serum phosphorus, serum calcium and calcium×phosphorus product (p *values were > 0.05)*. In patients treated with nicotinamide *(group II),* there was a highly significant fall in the mean serum phosphorus from 6.75 to 5.47 mg/dl ($p < 0.001$) accompanied by a significant drop in calcium×phosphorus product from 58.7 to 48.5 mg/dl ($p < 0.001$), and a significant increase in serum calcium level from 8.6 to 8.91 mg/dl ($p < 0.05$). There was insignificant change in iPTH level in both groups during study period *(p values were > 0.05).*

To evaluate these changes in the levels of calcium phosphorus profile, we compared *group I* to *group II* as shown in **figures (1&2).** A highly significant decrease in serum phosphorus ($p < 0.001$), with a concurrent significant fall in calcium× phosphorus product ($p < 0.01$) were reported in favor of the nicotinamide group. Changes in serum calcium and iPTH showed insignificant differences between two groups *(p values were > 0.05).*

For more evaluation, comparison of the *degree of change* in these parameters *(dc)* was, also, done and shown in **figure (3).** The degree

of change reflects the actual difference change through the study. In this figure there were highly significant differences in the degree of change of phosphorus level *(p < 0.01),* ph×Ca product *(p < 0.01),* and significant in iPTH *(p < 0.05),* all in favor of the nicotinamide group, whereas the degree of change of ca level was insignificant ($p > 0.05$).

- *The effect of nicotinamide on the lipid profile of patients:*

Although nicotinamide lacks the hypolipidmic 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 (from249.5 to 234.5 mg/dl) were reported in this study. The changes observed in those variables were statistically insignificant *(p values > 0.05).*

- *Hepatotoxicity, thrombocytopenia, and hypeuricemia as side effect of nicotinamide:*

In this study, there was no significant change neither in liver enzymes (ASAT and ALAT), nor in uric acid at the end of study *(p values > 0.05).* Platelet count tended to reduced insignificantly upon nicotinamide treatment *(p values > 0.05).* Laboratory results at the end of study of control and nicotinamide groups are summarized in table (4).

- *Gastrointestinal disturbance, flushing, rash, and blurred vision:*

We started nicotinamide in a dose of 500 mg/d. No side effects appeared, but when we increased the dose to 1000 mg/day, two patients in *group II* developed flushing and abdominal rash and discontinued nicotinamide. At day 9, three patients developed gastrointestinal disturbances and diarrhea. Two of them withdrew and the one who 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 group.

Discussion

Niacin, or nicotinic acid, is also known as vitamin B3. Niacin is a water-soluble vitamin critical for cell energy metabolism. Niacinamide (or nicotinamide) is the corresponding amide form of niacin. Niacinamide is thought to possess lesser 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 trail by *Cheng et al (21)* demonstrated that niacinamide lowers serum phosphorus levels in maintenance hemodialysis patients when used in high dosage (1750 mg/d) and the traditional binding agents were withheld. In our 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 hemodialysis at Ain Shams specialized hospital- based hemodialysis unit and AL Motamayez Hemodialysis center.

After 8 weeks of therapy, our patients in nicotinamide arm had highly significant drop in **serum phosphorus** (6.75 to 5.47 mg/dl) *(p<0.001)* with concomitant fall in **calcium ×
phosphorus product** from 58.7 to 48.55 mg^2/dl^2

(p<0.001). Also **serum calcium** increased significantly from 8.68 to 8.91 mg/dl *(p<0.05).* Despite of using lower dose of nicotinamide in this study, our findings agreed with previous studies which stated that nicotinamide can effectively reduce serum phosphorus in hemodialysis patients *(22,27,21).*

In the present study, **HDL** and decreasing **LDL**, total **cholesterol** and **triglycerides were statistically insignificant.** 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),* also, 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 triglycerides and LDL with clinical significance but without noticeable change of total cholesterol level *(30).* Moreover, we have to consider that in previous studies, they were using higher doses of nicotinamide for longer durations than in our study, which may explain why we could not reach *significant p values.*

In our study, a slight decrease in **platelet count** (from 213.46 to 207.2 1000/mm$^{3)}$) was reported in nicotinamide group. This change was statistically insignificant, *(p>0.05),* when compared to change in the control group. Nevertheless, no clinical manifestations of thrombocytopenia complicated the administration of nicotinamide in our 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 in spite of the fact that

nicotinamide was administered in higher doses and for longer durations than in our study. *(21,31)*. Also there were no episodes of decreasing platelet counts reported in *Young's* study *(32)*..

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

In the current 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 hemodialysis patients neglected its effect on **hemoglobin level *(21,22).*** However, a trend towards reduced mean hemoglobin in nicotinamide treated group was demonstrated by *Young et al (32).* In the present study, there was insignificant change in hemoglobin level in nicotinamide treated group when compared to control group**.**

Nicotinamide lacks the vasodilator effect of nicotinic acid **(35).** In accordance with this fact, only one case of **flushing** and another case of **abdominal rash** were reported in our study at the second week at the beginning of higher dose. The two patients withdrew from the study. Our findings agreed with previous studies *(21,32).* In *Cheng et al,* and *Young et al.* only one case of abdominal rash and another case of pruritic rash were reported respectively. In both studies none of patients randomized to nicotinamide treatment developed flushing *(21,32).*

Nicotinamide seems to be well tolerated in general population *(36).* In the current study the percentages of **GI disturbances and diarrhea** were 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 with other studies which reported that much higher percentage of patients suffered diarrhea on nicotinamide therapy *(18,21,22)*, explained by co administration of phosphate binders with high dose of nicotinamide *(21).*

Conclusion

This study supports that nicotinamide in low dose of 1000 mg/d is effective in controlling serum phosphorus when co-administered with calcium carbonate as a phosphate binder in hemodialysis patients and it has beneficial effect on lipid profile with mild potential side effects.

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 1000mg daily.
- Nicotinamide companies with which phosphate binder to result in a novel treatment for hyperphosphatemia in hemodialysis patients.
- Whether nicotinamide reduces serum phosphorus level effectively in hemodialysis patients when used alone.
- Nicotinamide effects on platelet count, hemoglobin and 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.

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Table (1): Patient characteristics of *group I* and *group II*

	Group I (n =30)	Group II (n =30)	P
Age (years)	50.2 ± 9.87	51.63 ± 8.10	0.54
Dry wt. (kg)	74.18 ± 6.20	73.81± 5.80	0.81
Duration of dialysis (months)	58±22	62±24	0.52
Male : Female ratio	22:8	24:6	0.54

Table (2): Biochemical data of *group I* and *group II* at baseline (NB: patients withdrawn from the study were cancelled)

	Group I (n= 30)	**Group II** (n=26)	**P**
S. phosphorus level (mg/dl)	6.46±0.81	6.75±1.02	0.25
S. calcium level (mg/dl)	8.87 ± 1.17	8.68± 0.72	0.45
S. Ca× Ph product (mg^2/dl^2)	57.8 ± 12.96	58.70± 10.9	0.77
S. iPTH (pg/ml)	674.50± 318.2	585.5± 378.5	0.35
S. cholesterol (mg/dl)	238.2± 133.1	249.5± 134.5	0.71
S. triglycerides (mg/dl)	326.87± 159	332.73± 182	0.92
S. HDL (mg/dl)	39.07± 7.3	39.31± 7.2	0.93
S. LDL (mg/dl)	123.9± 62.67	125.40± 65.35	0.94
Hemoglobin (g /dl)	11.65± 1.96	11.24± 1.23	0.22
S. uric acid (mg/dl)	7.55± 1.7	7.56± 1.82	0.98
Platelet count ($1000/mm^3$)	210± 33.20	213.4± 34.43	0.79
S. AST (mg/dl)	38.23± 15.68	38.58± 16.33	0.96
S. ALT (mg/dl)	28.77± 15.18	29.54± 15.71	0.86

Table (3): Serum level of phosphorus, calcium, Ca× ph product and iPTH in *Group I* and *Group II* at the start and at the end of the study

	Group I (n= 30)			Group II (n = 26)		
	Week 1	**Week 9**	**P**	**Week 1**	**Week 9**	**P**
S. phosphorus (mg/dl)	6.46±0.81	6.53±0.81	0.56	6.75±1.02	5.47±1.28	0.001
S. calcium (mg/dl)	8.87±1.17	8.71±1.02	0.43	8.68±0.72	8.91±0.87	0.05
S. CaxPh product (mg^2/dl^2)	57.8±12.96	57.3 ±2.40	0.76	58.70±10.9	48.55±11.53	0.001
S. iPTH (pg/dl)	674±318.2	697±302	0.09	585.5±378	547.6±477	0.46

Table (4): laboratory results of *Group I* and *Group II* at the end of the study

	Group I (n= 30)	**Group II** (n=26)	**P**
S. cholesterol (mg/dl)	235.30± 123	234.5± 130.15	0.99
S. triglycerides (mg/dl)	281.60± 165.16	272.60± 162.55	0.84
S. HDL (mg/dl)	42.27± 8.06	42.38± 8.21	0.98
S. LDL (mg/dl)	118.2± 52.26	120.22± 53.76	0.90
Hemoglobin (g /dl)	12.43± 2.44	12.31± 0.87	0.81
S. uric acid (mg/dl)	7.02± 1.57	7.09± 1.57	0.90
Platelet count ($1000/mm^3$)	220.5± 29.60	207.26± 34.66	0.061
S. AST (mg/dl)	38.23± 15.80	38.65± 16.52	0.94
S. ALT (mg/dl)	28.90± 14.93	29.62± 15.42	0.89
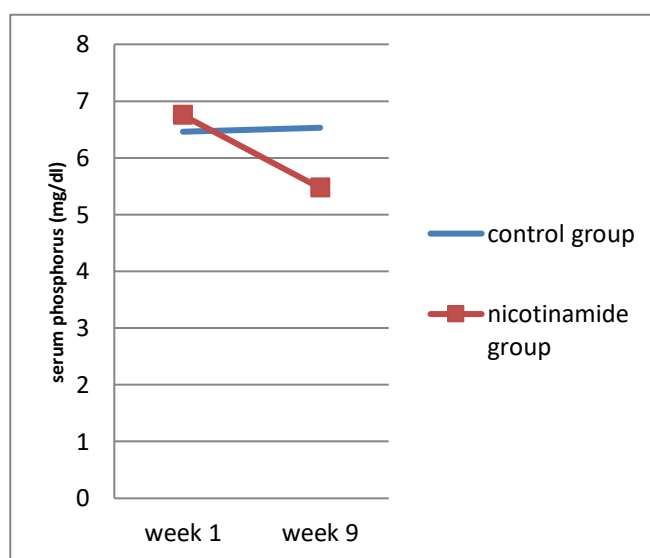
Figure (1): The serum level of phosphorus in in *Group I* and *Group II* on the start and at the end of the study.
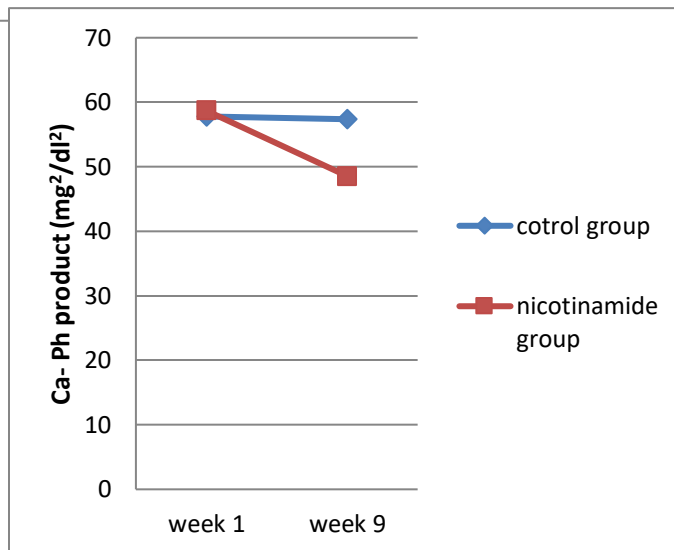
Figure (2): The serum level of calcium× phosphorus product in in *Group I* and *Group II* on the start and at the end of the study.

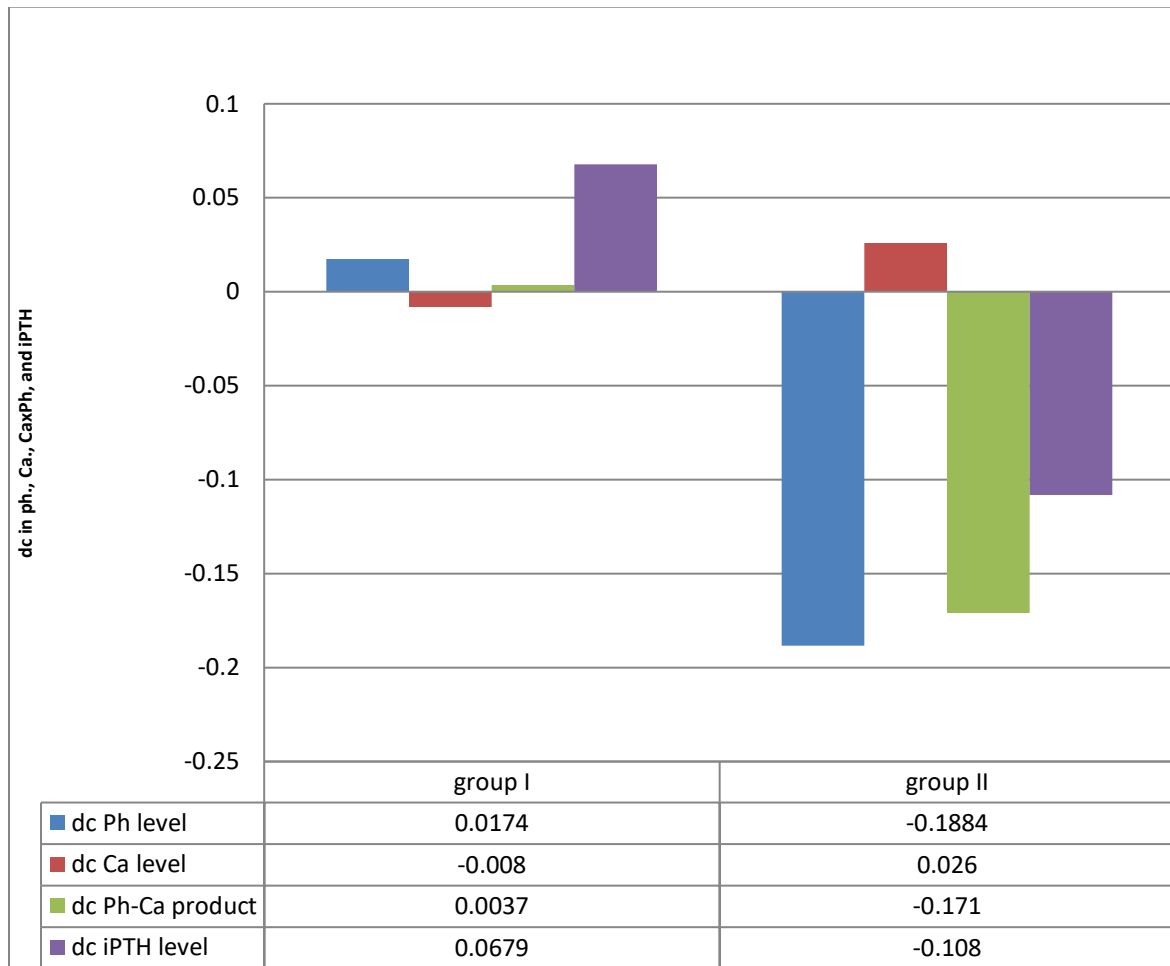|	group I	group II
■ dc Ph level	0.0174	-0.1884
■ dc Ca level	-0.008	0.026
■ dc Ph-Ca product	0.0037	-0.171
■ dc iPTH level	0.0679	-0.108

Figure (3): **The degree of change in serum level of Phosphorus, Calcium, Calcium x Phosphorus product, and iPTH in *Group I* and *Group II***