Nicotinic acid and related compounds
A meta-analysis of their use for hyperphosphatemia in dialysis patients
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Abstract
Background: Studies indicate that nicotinic acid and related compounds may decrease phosphorus concentrations effectively by reducing the absorption in the gastrointestinal tract. However, the efficacy and safety of oral niacin treatments have only been investigated in a limited number of small-scale studies.

Methods: We performed this meta-analysis by pooling 12 qualified relevant preclinical and clinical trials to evaluate the association of nicotinic acid (and its related compounds) treatment and hyperphosphatemia among dialysis patients. Baseline and after treatment data were collected from the studies to evaluate drug efficacy, effect on lipid profile, and drug safety. To evaluate drug efficacy, subgroups were created based on different exposure time (i.e., 4 wks, 8 wks, 12 wks, and 24 wks) and each subgroup was compared against baseline data. In the assessment of lipid profile and drug safety, results of 8-week treatment were compared against baseline data.

Results: Our study showed that in the efficacy assessment of drug treatment, serum phosphorus concentration was only significantly reduced in the 4-wk (SMD, 0.68; 95% CI, 0.40 to 0.97; P = .000; n = 8), and 8-wk (SMD, 1.05; 95% CI, 0.68 to 1.42; P = .000; n = 10) treatment groups. The calcium × phosphorus product showed significantly reduced concentration in all the drug exposure time settings, and no rebound was detected (4-wk treatment: SMD, 0.61; 95% CI, 0.18 to 1.04; P = .005; n = 5; 8-wk treatment: SMD, 0.76; 95% CI, 0.32 to 1.18, P = .001; n = 8; and 12-wk treatment: SMD, 0.28, 95% CI, −0.06 to 0.61; P = .103; n = 3). Lipid profile monitoring showed that high-density lipoprotein (HDL) and triglycerides (TG) significantly changed after 8 weeks of treatment (HDL: SMD, −0.63; 95% CI, −1.03 to 0.24; P = .002; n = 5) and TG: SMD, 0.25; 95% CI, 0.02 to 0.49; P = .033; n = 5). Assessment of drug safety detected significant association for incidence of diarrhea (8% incidence rate; 95% CI, 4% to 12%; P = .001) and total adverse event (41% incidence rate, 95% CI: 12% to 69%, P = .001).

Conclusion: Our study concludes that nicotinic acid and related compounds can significantly reduce serum phosphorus concentration with additive antilipemic effects. We also recommend that the safety of this drug be further studied, as our results suggest significant incidence of adverse events.

Abbreviations: CI = confidence interval, CKD = chronic kidney disease, HD = hemodialysis, HDL = high-density lipoprotein, iPTH = intact parathyroid hormone, LDL = low-density lipoproteins, MeSH = medical subject headings, NAD = nicotinamide adenine dinucleotide, OR = odds ratio, RCTs = randomized controlled trials, SMD = standardized mean difference, TG = triglycerides.

Keywords: dialysis patients, hyperphosphatemia, meta-analysis, nicotinic acid

1. Introduction

Hyperphosphatemia is a critical pathophysiologic feature of chronic kidney disease (CKD) patients undergoing maintenance hemodialysis (HD). The abnormalities of phosphate metabolism was reported to be linked to the development of secondary hyperparathyroidism, severe bone disease and cardiovascular complications.[1,2] The association between hyperphosphatemia and increased morbidity and mortality from cardiovascular disease in CKD patients has already been established.[3–6] A 1 mg/dL rise above normal range in serum phosphorus was reported to be linked to an estimated 23% increased risk of mortality.[3] Current National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend targeting serum phosphate values of 1.49 mmol/L (4.6 mg/dL) for patients with stages 3 and 4 CKD and 1.78 mmol/L (5.5 mg/dL) for stage 5 CKD patients. A total of 3 main clinical strategies are currently employed for hyperphosphatemia management in HD patients:

- Restriction of dietary phosphorus intake,
- Removal of phosphate by adequate dialysis (3 times weekly or daily and/or more prolonged dialysis sessions), and
- Reduction of intestinal phosphate absorption by using phosphate binders.

However, the efficacy of conventional phosphate binders is not reliable and they are associated with a range of limitations and side effects.[7,8] Nicotinic acid and related compounds such as nicotinamide have been shown to decrease phosphorus absorption in the...
The gastrointestinal tracts of animals by a different mechanism than the traditional phosphate binders. Several preliminary studies observed its effect in reducing serum phosphorus in HD patients, suggesting that it could be a useful pharmacological adjuvant to binder-based approaches. However, these once-daily oral niacin treatments for elevated serum phosphorus levels were only investigated in a limited number of small-scale studies. The clinical investigation of niacin’s novel effects is still in the early stages. Well-designed, larger clinical trials are awaited to validate its true function. We thus carried out this meta-analysis to pool the related preclinical and clinical trials to evaluate the efficacy and safety of nicotinic acid and related compounds on hyperphosphatemia with a focus on dialysis patients.

We collected baseline and after treatment data of serum phosphorus, calcium, calcium × phosphorus product and intact parathyroid hormone (iPTH) to assess the efficacy of drug treatment. Lipid profile including total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides (TG) were collected for lipid profile monitoring. Serum uric acid, platelet count, incidence rate of diarrhea, incidence rate thrombocytopenia and total adverse event were collected for drug safety evaluation. Data were subjected to pooled analysis to assess the efficacy and safety of nicotinic acid (its analogs or derivatives) in hyperphosphatemia HD patients.

2. Methods
All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy, data collection, extraction, and study design
Two investigators independently conducted a systematic literature search of PUBMED (1966 to November 24, 2015), EMBASE (1980 to November 24, 2015) and the Web of Science (1945 to November 24, 2015) for relevant studies. We used the search term based on a combination of Medical Subject Headings (MeSH) and key words “Nicotinic acid,” “Nicotinate,” “Nicotinat,” “Nicotinamide,” “hyperphosphatemia,” and “dialysis.” Primary reports identified were further screened using the following inclusion criteria:

1. study of the effect of niacin or its analogs or derivatives on hyperphosphatemia;
2. hyperphosphatemia must be caused by hemodialysis;
3. study published in English language; and
4. sufficient raw data could be extracted/obtained from primary studies.

All case reports, review articles, animal studies and duplicate publications were excluded from our study (Fig. 1).

![Data collection procedure](image-url)
The following information were extracted and tabulated from qualified studies by the same 2 investigators: first author and year of publication, study design, number of cases and controls, patient sex and age, washout period, serum phosphorus, drug, time, dose (the first weeks) mg/day. All controversial issues were resolved by discussion between authors.

2.2. Risk of bias

The risk of bias was quantitatively assessed using the checklist developed by Downs and Black, which can be used for both randomized and non-randomised studies. The studies were assessed based on reporting, external validity, internal validity - bias, selection bias, and power. The checklist could be answered with yes or no and most items could be given a value of 1 for yes and 0 for no or unable to determine (UTD). One question on reporting confounders could be scored 0 to 2, and the power question could have a value of 0 to 5. Of note, the power question could have a value of 0 to 5. Also, they could be scored 0 to 2, and the question on reporting confounders could be scored 0 to 2, and the power question could have a value of 0 to 5. As a result, the checklist could be assessed based on reporting, external validity, internal validity - bias, selection bias, and power. The checklist could be applied for OR estimation. When at least moderate statistical heterogeneity was detected, a Mantel-Haenszel random-effects model was selected. Begg’s funnel plot and Egger’s linear regression test was employed to check possible publication bias. The symmetric funnel plot is an indication of no publication bias. Subgroup analyses based on different drug exposure time (4 wks, 8 wks, 12 wks, and 24 wks) were carried out similarly.

2.3. Statistical analysis

Forest plots were constructed using STATA 12 software (STATA Corp LP, College Station, Texas, United States). Standardized Mean Difference (SMD) with 95% CIs for the appropriate effect size was estimated for each study. Heterogeneity across the studies was evaluated by I² test. When heterogeneity was small (I² < 50%), a Mantel-Haenszel fixed-effects model was applied for OR estimation. When at least moderate statistical heterogeneity (I² > 50%) was detected, a Mantel-Haenszel random-effects model was selected. Begg’s funnel plot and Egger’s linear regression test was employed to check possible publication bias. The symmetric funnel plot is an indication of no publication bias. Subgroup analyses based on different drug exposure time (4 wks, 8 wks, 12 wks, and 24 wks) were carried out similarly.

3. Results

A total of 26 publications from PUBMED, 66 publications from EMBASE and 41 publications from Web of science were retrieved from first round of search. After full text of the 81 primary identified reports by the inclusion criteria were reviewed, a total of 12 qualified articles including 352 patients were pooled in our meta-analysis. Out of the 12 studies, 6 were randomized controlled trials (RCTs), 1 was RCT with crossover, 1 was randomized comparative, and 4 were quasi-experimental studies (QES) (i.e., single arm studies). All the data in these 12 included studies were related to the association between nicotinic acid (and its related compounds) and hyperphosphatemia in dialysis patients. All studies had baseline information and did a drug exposure of a minimum of 4-week period. Single arm trials had baseline and post treatment data. Characteristics of included studies and quality score were summarized in Table 1 (also see Supplementary 1, http://links.lww.com/MD/C159).

3.1. Control of serum phosphorus, calcium and calcium × phosphorus product and iPTH by nicotinic acid (and its analogs or derivatives) in dialysis patients

The concentration changes of phosphorus, calcium and calcium × phosphorus product at different time points after nicotinic acid and analogs or derivatives treatment were pooled into 4 subgroups (4 wks, 8 wks, 12 wks, and 24 wks) and analyzed using forest plot.

The results of subgroup analysis showed that serum phosphorus concentrations did not have a continuous downward trend over time but had a lowest value at 8 weeks. From the 4 week group after treatment (SMD, 0.68; 95% CI, 0.40–0.97; P = .000; I² = 48.0%; n = 8), serum phosphorus concentration decreased and reached its lowest value at 8 weeks (SMD, 1.05; 95% CI, 0.68–1.42; P = .000; I² = 76.0%; n = 10) and then went upward after 12 weeks (SMD, 0.60; 95% CI, –0.04 to 1.24; P = .067; I² = 80.7%; n = 4) and 24 weeks of treatment (SMD, 0.03; 95% CI, –0.66 to 0.73, P = .924; I² = 64.3%; n = 2) (Table 2, Fig. 2A). Model used to estimate effect size was indicated in Table 2.

Meanwhile, the calcium concentration did not have significant difference at all time points: Baseline vs. 4 weeks treatment (SMD, –0.16; 95% CI, –0.42 to 0.09; P = .218; I² = 0.0%; n = 4), baseline versus 8 weeks subgroup (SMD, –0.11; 95% CI, –0.28 to 0.07, P = .233; I² = 10.1%; n = 9), baseline versus 12 (SMD, –0.18, 95% CI, –0.45 to 0.09; P = .203; I² = 0.0%).

Table 1

| Study                        | Design              | Subjects | Number of patients | Male | Age            | Disease        | Washout period | constant dosage of phosphate binders | serum phosphorus | drug | Time exposed | Dose (the first weeks) mg/day |
|------------------------------|---------------------|----------|--------------------|------|----------------|----------------|----------------|---------------------------------------|------------------|-----|---------------|-----------------------------|
| Yutaka Takahashi (2004)      | QES (Single-arm)    | 17       | 65                 | 56.46| 57 ± 11.5      | ESRD           | -              | 2 weeks 6.0mg/dL                      | nicotinamide     | 12 wks | 500           |
| Krishnaswamy                 | QES (Single-arm)    | 16       | 34                 | 86.24| 49 ± 13        | ESRD           | 8.7 ± 6.6 year| 1 week 6.0mg/dL                       | Nicotinamide     | 8 wks | 1125          |
| Sampathkumar                 | RCT with crossover | 24       | 63                 | 60.70| 52 ± 6         | ESRD           | >60 days      | 2 weeks 5.0mg/dL                      | nicotinamide     | 10wks | 500           |
| Carlos Guido Musso (2009)    | QES (Single-arm)    | 10       | 12                 | 71.43| 51 ± 13.3      | CKD            | -              | -                                     | hyperphosphatemic| Nicotinamide   | 6 mo | 500           |
| Daniel G. Youn (2009)        | RCT                 | 26       | 17                 | 71.43| 51 ± 13.3      | CKD            | >3 months     | 2 weeks 4.9mg/dL                      | nicotinamide     | 8 wks | 500           |
| J. Juncaloski (2011)         | QES (Single-arm)    | 14       | 30                 | 66.67| 54 ± 14.9      | ESRD           | >3 months     | 1 month 5.0mg/dl                      | nicotinamide     | 8 wks | 500           |
| H. Shahbazian (2011)         | RCT                 | 26       | 24                 | 58.33| 53 ± 10.6      | ESRD           | >2 months     | 2 weeks 5.0mg/dl                      | nicotinamide     | 8 wks | 500           |
| Pomieton Arambill (2012)     | RCT                 | 23       | 14                 | 71.43| 45 ± 11.4      | ESRD           | 6 months      | 5.5mg/dl                             | Niaspan 24 wks   | 800-1000 |              |
| M. Edalat Nejo (2012)        | RCT                 | 21       | 47                 | 38.30| 57 ± 11        | ESRD           | 3 months      | 2 weeks 5.0mg/dl                      | nicotinamide     | 8 wks | 500           |
| Farnazkhah                   | Randomized          | 23       | 20                 | 65.00| 57 ± 16.1      | ESRD           | -             | 6.0mg/dl                             | Nicotinamide     | 4 wks | 500           |
| Almawi (2012)                | comparative         |          |                    |      |                |                |              |                                       |                  |       |               |
| Magdy El-Sharkawy (2011)     | RCT                 | 19       | 30                 | 80.00| 51.63 ± 8.1    | ESRD           | 3 months      | 2 weeks 5.0mg/dl                      | nicotinamide     | 8 wks | 500           |
| Radeka E                      | RCT                 | 25       | 30                 | 53.30| 11.9 ± 2.9     | ESRD           | >3 months     | 1 month 5.0mg/dl                      | nicotinamide     | 24 wks | 1000 or 2000 |

*Quality score based on Downs and Black Assessment. Maximum score: 28.
Table 2: Meta-analysis of the efficacy by nicotinic acid (its analogs or derivatives) treatment.

| Time points | Model used | No. of studies (n) | SMD | Cl | P value | I² | P | P of Begg’s test | P of Egger’s test |
|-------------|------------|--------------------|-----|----|---------|----|---|-----------------|-----------------|
| Serum phosphorus concentration | 4 wks | Fixed-effect | 8 | 0.68 | -0.40 to 0.97 | 0.000 | 48.0% | 0.062 | 0.386 | 0.554 |
| 8 wks | Random-effects | 10 | 1.05 | -0.68 to 1.42 | 0.000 | 76.0% | 0.000 | 0.283 | 0.206 |
| 12 wks | Random-effects | 4 | 0.60 | -0.04 to 1.24 | 0.067 | 80.7% | 0.001 | 1.000 | 0.814 |
| 24 wks | Random-effects | 2 | 0.03 | -0.66 to 0.73 | 0.924 | 64.3% | 0.094 | 1.000 | - |
| Serum calcium concentrations | 4 wks | Fixed-effect | 4 | -0.16 | -0.42 to 0.09 | 0.218 | 0.50% | 0.528 | 1.000 | 0.996 |
| 8 wks | Random-effects | 9 | -0.11 | -0.28 to 0.07 | 0.233 | 10.1% | 0.351 | 0.348 | 0.458 |
| 12 wks | Fixed-effect | 3 | -0.18 | -0.45 to 0.09 | 0.203 | 0.0% | 0.951 | 0.296 | 0.084 |
| 24 wks | Fixed-effect | 2 | -0.34 | -0.74 to 0.06 | 0.098 | 0.0% | 0.770 | 1.000 | - |
| Serum calcium x phosphorus product concentration | 4 wks | Random-effects | 5 | 0.61 | 0.18 to 1.04 | 0.005 | 65.8% | 0.02 | 0.806 | 0.721 |
| 8 wks | Random-effects | 8 | 0.76 | 0.32 to 1.20 | 0.001 | 78.6% | 0.000 | 0.902 | 0.662 |
| 12 wks | Random-effects | 3 | 0.28 | -0.06 to 0.61 | 0.103 | 23.4% | 0.271 | 1.000 | 0.390 |
| iPTH concentration | 8 wks | Fixed-effect | 4 | -0.07 | -0.31 to 0.16 | 0.540 | <0.01% | 0.855 | 0.734 | 0.519 |

0.0%; n = 3), and baseline versus 24 weeks treatment (SMD, −0.34, 95% CI, −0.74 to 0.06; P = 0.098; I² = 0.0%; n = 2) (Table 2, Fig. 2B).

However, the calcium × phosphorus product concentration had significant reduction at all time points after drug treatment and no rebound was detected: baseline vs 4 weeks (SMD, 0.61; 95% CI, 0.18 to 1.04; P = 0.005; I² = 65.8%; n = 5), baseline versus 8 weeks (SMD, 0.76; 95% CI, 0.32 to 1.20; P = 0.001; I² = 78.6%; n = 8), baseline versus 12 weeks (SMD, 0.28, 95% CI, −0.05 to 0.61; P = 0.103; I² = 23.4% n = 3); no subgroup analysis was done after 24 weeks (Fig. 2C).

In addition, investigation of serum iPTH concentration at 8 weeks from 4 studies involving 134 hyperphosphatemia dialysis patients showed no significant association with niacin treatment (SMD, −0.07; 95% CI, −0.31 to 0.16, P = 0.540; I² < 0.01%; n = 4) (Table 2, Fig. 2D). Begg’s funnel plot and Egger’s linear regression analysis to assess the potential publication bias showed no evidence of obvious asymmetry in all the subgroup analyses (Table 2).

3.2. The effect of nicotinic acid (and its analogs or derivatives) on lipid profile in hyperphosphatemia dialysis patients

A total of 5 studies involving 141 hyperphosphatemia dialysis patients investigated lipid profile at 8 weeks after drug treatment. Results showed that after niacin drug treatment, there was no significant change on the concentration of serum LDL (SMD, −0.16; 95% CI, −0.78 to 0.45; P = 0.604; I² = 83.6%) and TC (SMD, −0.03; 95% CI, −0.20 to 0.26, P = 0.798; I² < 0.01%) but there were significant changes on the concentration of HDL (SMD, −0.63; 95% CI, −1.03 to 0.24; P = 0.002; I² = 58.8%) and TG (SMD, 0.25, 95% CI, 0.02 to 0.49; P = 0.033; I² < 0.01%) (Table 3, Fig. 3). Begg’s test and Egger’s test showed no evidence of publication bias (Table 3).

3.3. Side effect of nicotinic acid (and its analogs or derivatives)

Niacin drug treatment did not have significant effect on uric acid concentration (SMD, 0.14; 95% CI, −0.11 to 0.39; P = 2.77; I² = 0.01%; n = 5) and platelet count (SMD, 0.10; 95% CI, −0.48 to 0.68; P = 0.763; I² = 81.7%; n = 5) 8 weeks after treatment (Fig. 4A and B). No obvious asymmetry was detected in both analyses, indicating no potential publication bias (Table 4).

The occurrence of thrombocytopenia and diarrhea during treatment were reported with incidence rate of 17% for thrombocytopenia (95% CI, 0% to 37%; P = 0.001; I² = 88.1%; n = 3), 8% for diarrhea (95% CI, 4% to 12%; P = 0.001; I² = 48.5%; n = 5), and 41% for total adverse event (95% CI, 12% 69%; P = 0.001, I² = 88.3%; n = 3) (Fig. 4 C–E, respectively). No obvious asymmetry was detected, indicating no potential publication bias.

4. Discussion

Current orally administered phosphate binders, such as calcium (carbonate or acetate), magnesium (hydroxide or carbonate), aluminum hydroxide, sevelamer (hydrochloride and carbonate), lanthanum carbonate have major disadvantages. These include aluminum accumulation/intoxication, absorption of administered calcium, which might contribute to hypercalcemia, promote vascular calcification, gastrointestinal adverse events, and high cost. Thus, identifying an efficacious, well-tolerated, and cost-effective new phosphate binder is of great clinical significance. Nicotinic acid (or niacin) and nicotinamide (niacinamide or nicotinic amide) are the 2 major forms of vitamin B3. Nicotinic acid is converted to nicotinamide majorly through amidation. Nicotinamide is a central component of the coenzyme nicotinamide adenine dinucleotide (NAD). Study suggested that nicotinamide can reduce the phosphate level in dialysis patients by lowering its absorption from the GI tract. A recent meta-analysis also highlighted the effectiveness of both nicotinic acid and nicotinamide in reducing serum phosphorus concentrations for patients with ESRD on either hemodialysis or peritoneal dialysis. Results from animal model study suggested the absorption reduction might through inhibiting NaPi2b expression. Our meta-analysis from 12 qualified studies indicated that the serum level of phosphorus was significantly reduced in nicotinic acid (its analogs or derivatives) treated patients in 4 weeks, 8 weeks, and 12 weeks subgroups, and the 8 weeks group had the maximum reduction effect (Fig. 2A). 24 weeks treatment of the drug showed no significant difference. Limited exposure time (8 wks) of nicotinic acid (its analogs or derivatives) seems enough for serum phosphate management.
Significant reduction of the calcium × phosphorus product also was observed, and no rebound was detected (Fig. 2C). On the other hand, the serum calcium level showed no change after the drug treatment at all time points, distinguishing nicotinic acid (and its analogs or derivatives) from the calcium-based binder.

Declined renal function not only leads to phosphate retention, but also can elevate synthesis and secretion of parathyroid hormone.
hormone (PTH),[19] thus the effect on iPTH level following drug treatment was investigated. Intact parathyroid hormone (iPTH) is the first choice for the characterization of renal osteodystrophy in CKD suggested by Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines in 2003.[20] We pooled the data of 4 studies with a total of 134 hyperphosphatemia dialysis patients to investigate the iPTH level after 8 weeks of drug treatment, and the results did not show any statistical significant difference, which differed from previous studies that showed either an increase[14] or decrease[17] of iPTH level after drug treatment. This difference could be attributed to difference in sample size. Further research are required to clarify its function in iPTH level regulation.
Nonetheless, our results suggested that the reduction of plasma phosphate concentration by nicotinic acid (its analogs or derivatives) was achieved without increasing serum calcium levels, which might lead to renal bone disorder.

We also monitored the lipid profile change in drug treatment patients and results showed that it was also significantly affected by nicotinic acid treatment, particularly the levels of HDL and TG. Mean serum levels of HDL significantly increased (63%) while TG level significantly decreased (26%) (Fig. 3). Similar observation was reported by other studies,[13,17,21] suggesting its association with clinically important differences. The drug’s antilipemic effects were suggested to be via specific nicotinic acid receptors.[22,23]

The potential side effects of nicotinic acid (its analogs or derivatives) need to be carefully evaluated, and our meta-analysis revealed a significant effect in the incidence of diarrhea during drug treatment. Literature suggested nicotinic acid (its analogs or derivatives) may be uremic toxins.[24] Uric acid has been recognized as a potential risk factor in CKD development and progression.[25] Several studies reported the development of

| Study | Model used | No. of studies (n) | SMD  | CI    | P     | I²   | P of Begg’s test | P of Egger’s test |
|-------|------------|--------------------|------|-------|-------|------|------------------|-------------------|
| HDL   | Random-effects | 5                  | -0.63| -1.03 | -0.24 | 0.002| 58.8%            | 0.046             |
| LDL   | Random-effects | 5                  | -0.16| -0.78 | 0.45  | 0.604| 83.6%            | <0.001            |
| TC    | Fixed-effect | 5                  | 0.03 | -0.20 | 0.26  | 0.708| <0.01%           | 0.469             |
| TG    | Fixed-effect | 5                  | 0.25 | 0.02  | 0.49  | 0.033| <0.01%           | 0.724             |

Figure 3. Forest plots for association between serum lipid profile and different niacin treat time in hyperphosphatemia dialysis patient.
thrombocytopenia in some drug treated patients,[13,26] which might be attributed to drug induced low thyroxin-binding globulin level.[13] Gastrointestinal symptoms mainly diarrhea was reported[27] to be related to the treatment. Our meta-analysis revealed that at the clinical dose, no significant association was detected between the drug treatment and uric acid level or platelet count change (Fig. 4A and B). The incidence of thrombocytopenia thus was neither increased by the drug treatment (Fig. 4C). However, a significant increase of the incidence of diarrhea and total adverse event was observed in our analysis (Fig. 4D and E, respectively). More well-designed clinical studies are needed to fully assess the adverse drug reactions to nicotinic acid (its analogs or derivatives).

### 4.1. Limitations of the study

Findings from this study revealed and validated the effect of nicotinic acid in the treatment of hyperphosphatemia in dialysis patients, nonetheless certain limitations should be acknowledged. The limitations are

1. different study design,
2. inclusion of single-arm trials,
3. different dosage used in studies, and
4. small sample size in the subgroup analyses.

Although most of the included studies were RCTs, 4 studies were single arm studies with pre- and post-study design and one

| Study          | Model used | No. of studies | SMD | CI    | P value | $I^2$ | P    | P of Begg's test | P of Egger's test |
|----------------|------------|----------------|-----|-------|---------|------|------|-----------------|------------------|
| Uric acid      | Fixed-effect | 5              | 0.14 | -0.11 | 0.39    | 0.27 | 0.0% | 0.732           | 0.221            |
| Platelet count | Random-effects | 5              | 0.10 | -0.48 | 0.68    | 0.737| 81.7%| 0.000           | 0.806            |

Figure 4. Forest plots for association between (A) serum uric acid concentration, (B) serum platelet number, (C) the rate of thrombocytopenia, (D) the rate of diarrhea, and (E) the rate of any adverse event, and niacin treatment in hyperphosphatemia dialysis patient.
study was a randomized comparative trial. To maximize the sample size, all studies were included, however, pooled analyses of different study types may affect the weight of the validity of the conclusions. As reported, quality score of the single-arm studies were relatively lower than that of the RCTs. In addition, dosage of nicotinic acid and derivatives varied among the included studies. Though initial and subsequent drug dosage may have an impact on the efficacy of the drug; elucidation of this possible effect is beyond the scope of the present study. Of note, limited number of qualified studies were available even though studies other than RCTs were already included, some subgroups particularly in the efficacy assessment had few samples (n=4 in the 4-week treatment group and n=2 in the 24-week treatment group).

5. Conclusion
Our results suggest that nicotinic acid is probably effective in reducing serum phosphorus levels of dialysis patients. It can be a good alternative (or add on) to the traditional phosphate binders, with different action mechanism, requires limited exposure time, and has additive antilipemic effects. While the side effect such as the gastrointestinal symptoms detected in our study requires further investigation, it appears to be a potentially safe treatment for hyperphosphatemia. Well-designed large-scale clinical studies are recommended to assess the long-term drug safety and efficacy.

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References
[1] Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32(5 Suppl 3):S112–9.
[2] Ste I, Mazel J, Barreto FC, et al. Effects of phosphate on vascular function under normal conditions and influence of the uric acid state. Cardiovasc Res 2012;96:130–9.
[3] Kim WY, Lee JB, Kim HY, et al. Achievement of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative: recommended serum calcium, phosphate and parathyroid hormone values with parathyroidectomy in patients with secondary hyperparathyroidism. J Korean Surg Soc 2013;85:25–9.
[4] Mehrzad R, Peralta CA, Chen SC, et al. No independent association of serum phosphorus with risk for death or progression to end-stage renal disease in a large screen for chronic kidney disease. Kidney Int 2013;84:989–97.
[5] Block GA, Hulbert-Shearon TE, Levin NW, et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998;31:607–17.
[6] Savica V, Bellinghieri G, Calo LA. Association of serum phosphorus concentration with cardiovascular risk. Am J Kidney Dis 2009;54:389author reply 389–90.
[7] Moe SM, Block GA, Langman CB. Oral phosphate binders in patients with kidney failure. N Engl J Med 2010;363:990author reply 990.
[8] Jiang N, Fang W, Yang X, et al. Dietary phosphorus intake and distribution in Chinese peritoneal dialysis patients with and without hyperphosphatemia. Clin Exp Nephrol 2015;19:694–700.
[9] Katsi K, Tanaka H, Tatsusi S, et al. Nicotinamide inhibits sodium-dependent phosphate cotransport activity in rat small intestine. Nephrol Dial Transplant 1999;14:1195–201.
[10] Eto N, Miyata Y, Ohno H, et al. Nicotinamide prevents the development of hyperphosphatemia by suppressing intestinal sodium-dependent phosphate transporter in rats with adenine-induced renal failure. Nephrol Dial Transplant 2005;20:1378–84.
[11] Edalat-Nejad M, Zameni F, Talaei A. The effect of niacin on serum phosphorus levels in dialysis patients. Indian J Nephrol 2012;22:174–8.
[12] Yasantha J, Sounlararajan P, Vanitharani N, et al. Safety and efficacy of nicotinamide in the management of hyperphosphatemia in patients on hemodialysis. Indian J Nephrol 2011;21:245–9.
[13] Shahbaziian H, Zafar Moshahami A, Ghorbani A, et al. Oral nicotinamide reduces serum phosphorus, increases HDL, and induces thrombocytopenia in hemodialysis patients: a double-blind randomized clinical trial. Nefrologia 2011;31:58–65.
[14] Ahmad F, Shamskeli F, Lessan-Pezeeshki M, et al. Comparison of efficacy of the phosphate binders nicotinic acid and sevelamer hydrochloride in hemodialysis patients. Saudi J Kidney Dis Transplant 2012;23:934–8.
[15] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377–84.
[16] Lenglet A, Lielbeuf S, Guffroy P, et al. Use of nicotinamide to treat hyperphosphatemia in dialysis patients. Drugs R D 2013;13:165–73.
[17] Takahashi Y, Tanaka A, Nakamura T, et al. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. Kidney Int 2004;65:1099–104.
[18] Rennick A, Kalakeche R, Seel L, et al. Nicotinic acid and nicotinamide: a review of their use for hyperphosphatemia in dialysis patients. PharmacoTherapy 2013;33:683–90.
[19] Kestenbaum B, Sampson JN, Radser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16:520–8.
[20] Eknoyan G, Levin A, Levin NW. KDQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease - Foreword. Am J Kidney Dis 2003;42:57–201.
[21] Cheng SC, Young DO, Huang Y, et al. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. Clin J Am Soc Nephrol 2008;3:1131–8.
[22] Guyton JR. Niacin in cardiovascular prevention: mechanisms, efficacy, and safety. Curr Opin Lipidol 2007;18:415–20.
[23] Karpe F, Frayn KN. The nicotinic acid receptor—a new mechanism for an old drug. Lancet 2004;363:1892–4.
[24] Rutkowski B, Rutkowski P, Slominska E, et al. Cellular toxicity of nicotinamide metabolites. J Ren Nutr 2012;22:95–7.
[25] Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant 2013;28:2221–8.
[26] Rottembourg JB, Launay-Vacher V, Massard J. Thrombocytopenia induced by nicotinamide in hemodialysis patients. Kidney Int 2005;68:2911–2.
[27] Delanaye P, Weekers L, Krzesinski JM. Diarrhea induced by high doses of nicotinamide in dialysis patients. Kidney Int 2006;69:1914–1914.