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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-week (SMD, 0.68; 95% CI, 0.40 to 0.97; $P = .000$; n = 8), and 8-week (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-wks 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 = odd 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

gastrointestinal tracts of animals by a different mechanism than the traditional phosphate binders.[9,10] 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.[11–14] 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).
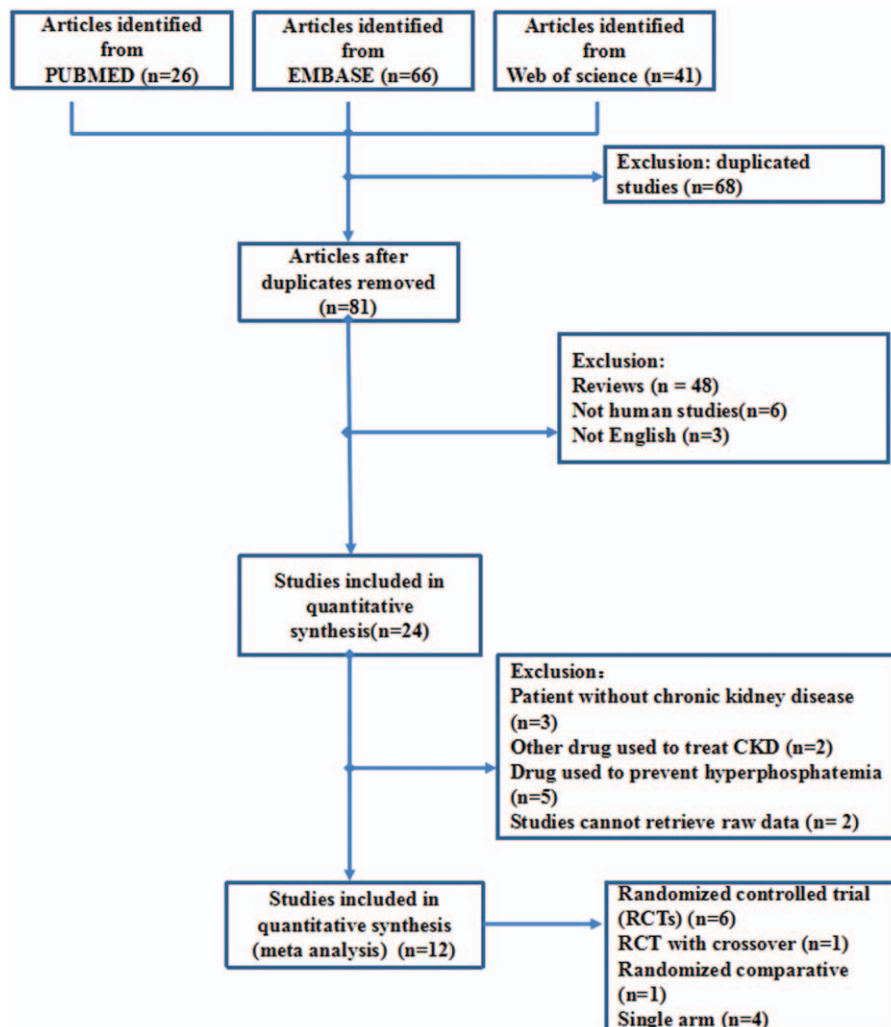

Figure 1. Data collection procedure. 81 literatures were retrieved from the first-round search. 12 qualified studies were included in the final meta-analysis.

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.[15] 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, we did a modification in answering the power question; study which included a power calculation was given 1, otherwise 0.

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 efficacy and safety of nicotinic acid (and its analogs or derivatives) were estimated for each study. Heterogeneity across the studies was evaluated by I^2 test. When heterogeneity was small ($I^2 < 50\%$), a Mantel–Haenszel fixed-effects model was applied for OR estimation. When at least moderate statistical heterogeneity ($I^2 > 50\%$) 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; $P = .000$; $I^2 = 48.0\%$; n = 8), serum phosphorus concentration decreased and reached its lowest value at 8 weeks (SMD, 1.05; 95% CI, 0.68–1.42; $P = .000$; $I^2 = 76.0\%$; n = 10) and then went upward after 12 weeks (SMD, 0.60; 95% CI, −0.04 to 1.24; $P = .067$; $I^2 = 80.7\%$; n = 4) and 24 weeks of treatment (SMD, 0.03; 95% CI, −0.66 to 0.73, $P = .924$; $I^2 = 64.3\%$; 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; $P = .218$; $I^2 = 0.0\%$; n = 4), baseline versus 8 weeks subgroup (SMD, −0.11; 95% CI, −0.28 to 0.07, $P = .233$; $I^2 = 10.1\%$; n = 9), baseline versus 12 (SMD, −0.18, 95% CI, −0.45 to 0.09; $P = .203$; $I^2 =$

Table 1

Summary of characteristics of included studies in the meta-analysis.

Study	Study design	Quality	Number of patients	Male	Age	Disease	Washout period HD time	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	58.46%	57.0±11.5	ESRD	-	2 weeks	6.0mg/dL	nicotinamide	12 wks	500
Krishnaswamy Sampathkumar (2006)	QES (Single-arm)	16	34	88.24%	48±13	ESRD	8.7±9.6 year	1 weeks	6.0mg/dL	Nicotinic acid	8 wks	1125
Steven C. Cheng (2008)	RCT with crossover	26	33	69.70%	52.6	ESRD	>90d	2 weeks	5.0mg/dL	nicotinamide	18wks	500
Carlos Guido Musso (2008)	QES (Single-arm)	12	18	-	-	CKD	-	-	hyperphosphatemic	Nicotinic acid	6 mo	500
Daniel O. Young (2009)	RCT	26	17	71.43%	51.1±10.3	CKD	> 3month	2 weeks	4.9mg/dL	nicotinamide	8 wks	500
J. Vasantha (2011)	QES (Single-arm)	18	30	66.67%	54 ± 14.9	ESRD	> 3month	1 month	5.0mg/dL	nicotinamide	8 wks	500
H. Shahbazian (2011)	RCT	26	24	58.33%	53.92 ± 11.06	CKD	>2 month	2 weeks	5.0mg/dL	nicotinamide	8 wks	500
Pornanong Aramwit (2012)	RCT	23	14	71.43%	45.52 ± 11.46	ESRD	6 month	-	5.5mg/dL	Niaspan	24 wks	800-1000
M. Edalat-Nejad (2012)	RCT	21	47	38.30%	57±11	ESRD	3 month	2 weeks	5.0mg/dL	niacin	8 wks	800-1000
Farrokhlagha Ahmadi (2012)	Randomized comparative	23	20	65.00%	51±16.1	ERSD	-	-	6.0mg/dL	Nicotinic acid	4 wks	500
Magdy El-Sharkawy (2013)	RCT	19	30	80.00%	51.63±8.1	ERSD	3 month	2 weeks	5.0mg/dL	nicotinamide	8 wks	500
Radwa El Borolossy (2015)	RCT	25	30	53.30%	11.9±2.9	ESRD	> 3month	1 month	5.0mg/dL	nicotinamide	24 wks	1000 or 2000

*Quality score based on Downs and Black Assessment. Maximum score: 28.

Meta-analysis of the efficacy by nicotinic acid (its analogs or derivatives) treatment.

	Time points	Model used	No. of studies (n)	SMD	CI		P value	I^2	P	P of Begg's test	P of Egger's test
Serum phosphorus concentration	4 wks	Fixed-effect	8	0.68	0.40	0.97	0.000	48.0%	0.062	0.386	0.554
	8 wks	Random-effects	10	1.05	0.68	1.42	0.000	76.0%	0.000	0.283	0.206
	12 wks	Random-effects	4	0.60	−0.04	1.24	0.067	80.7%	0.001	1.000	0.814
	24 wks	Random-effects	2	0.03	−0.66	0.73	0.924	64.3%	0.094	1.000	-
Serum calcium concentrations	4 wks	Fixed-effect	4	−0.16	−0.42	0.09	0.218	0.0%	0.528	1.000	0.996
	8 wks	Fixed-effect	9	−0.11	−0.28	0.07	0.233	10.1%	0.351	0.348	0.458
	12 wks	Fixed-effect	3	−0.18	−0.45	0.09	0.203	0.0%	0.951	0.296	0.084
	24 wks	Fixed-effect	2	−0.34	−0.74	0.06	0.098	0.0%	0.770	1.000	-
Serum calcium × phosphorus product concentration	4 wks	Random-effects	5	0.61	0.18	1.04	0.005	65.8%	0.02	0.806	0.721
	8 wks	Random-effects	8	0.76	0.32	1.20	0.001	78.6%	0.000	0.902	0.662
	12 wks	Fixed-effect	3	0.28	−0.06	0.61	0.103	23.4%	0.271	1.000	0.390
iPTH concentration	8 wks	Fixed-effect	4	−0.07	−0.31	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; $P=.098$; $I^2=0.0\%$; 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; $P=.005$; $I^2=65.8\%$; n=5), baseline versus 8 weeks (SMD, 0.76; 95% CI, 0.32 to 1.20, $P=.001$; $I^2=78.6\%$; n=8), baseline versus 12 weeks (SMD, 0.28, 95% CI, −0.05 to 0.61; $P=.103$; $I^2=23.4\%$ 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, $P=.540$; $I^2<0.01\%$; 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; $P=.604$; $I^2=83.6\%$) and TC (SMD, −0.03; 95% CI, −0.20 to 0.26, $P=.798$; $I^2<0.01\%$) but there were significant changes on the concentration of HDL (SMD, −0.63; 95% CI, −1.03 to 0.24; $P=.002$; $I^2=58.8\%$) and TG (SMD, 0.25; 95% CI, 0.02 to 0.49; $P=.033$; $I^2<0.01\%$) (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; $P=.277$; $I^2=0.01\%$; n=5) and platelet count (SMD, 0.10; 95% CI, −0.48 to 0.68; $P=.737$; $I^2=81.7\%$; 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%; $P=.001$; $I^2=88.1\%$; n=3), 8% for diarrhea (95% CI, 4% to 12%; $P=.001$; $I^2=48.5\%$; n=5), and 41% for total adverse event (95% CI, 12% 69%; $P=.001$, $I^2=88.3\%$; 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 oracetate), 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.[16] 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 nicotin-amide adenine dinucleotide (NAD). Study suggested that nicotinamide can reduce the phosphate level in dialysis patients by lowering its absorption from the GI tract.[17] 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.[18] Results from animal model study suggested the absorption reduction might through inhibiting NaPi2b expression.[10]

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.
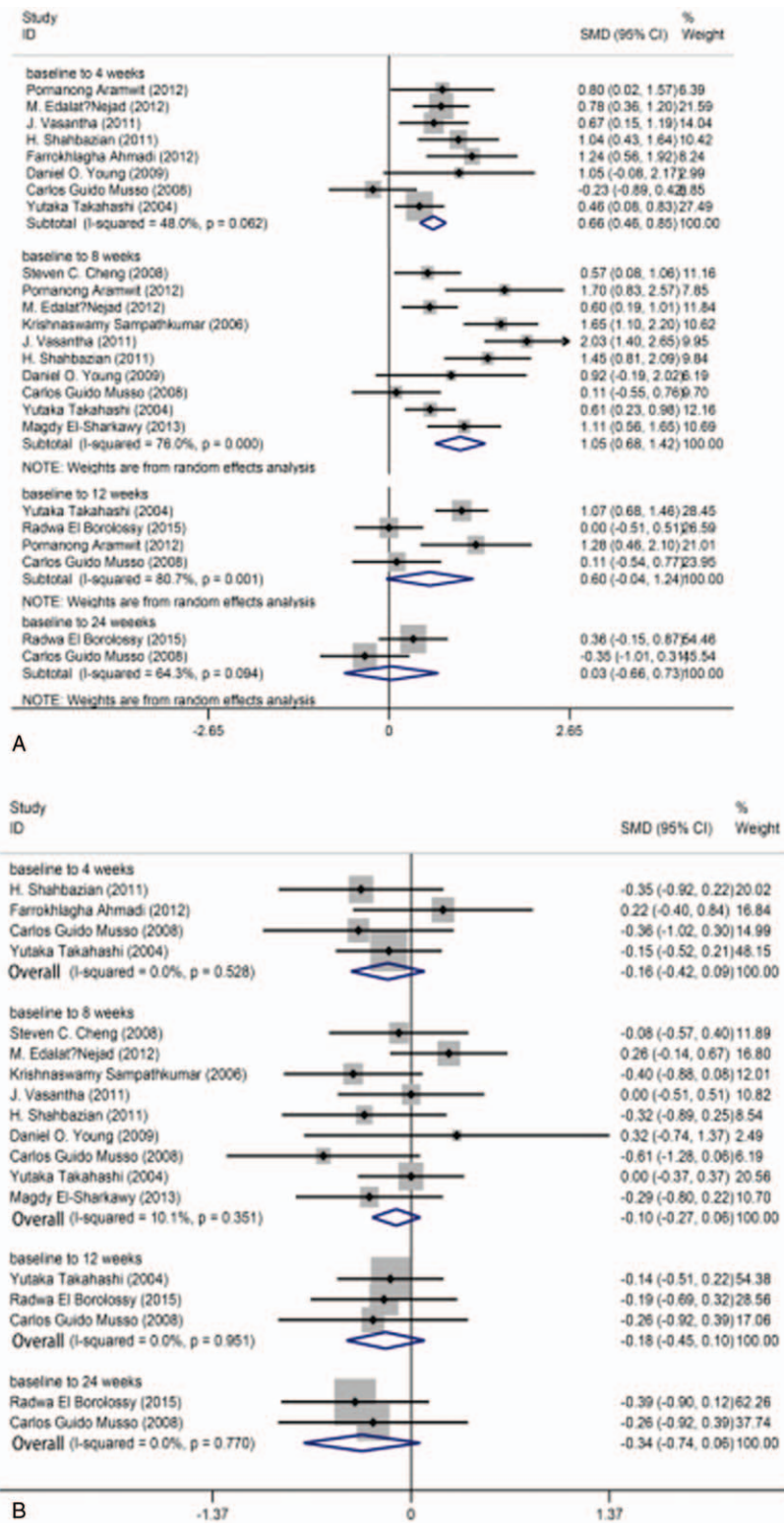
Figure 2. Forest plots for association between (A) serum phosphorus concentration, (B) serum calcium concentration, (C) serum calcium–phosphorus product [(mg/dL)^2] and (D) serum iPTH concentration and different niacin treat time in hyperphosphatemia dialysis patient.

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
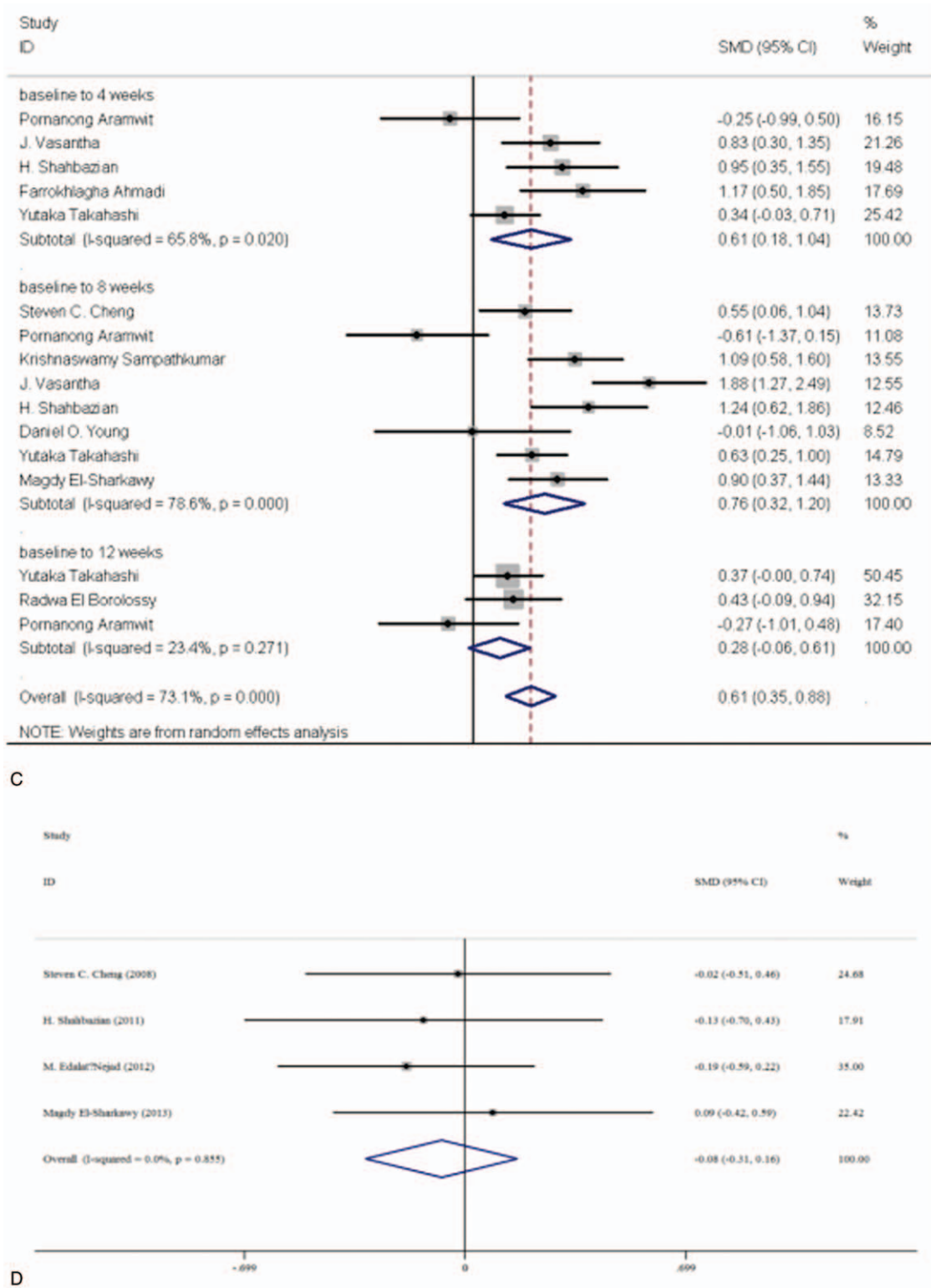
Figure 2. (Continued).

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.

Table 3

Meta-analysis of lipid profile change after 8 weeks treatment of nicotinic acid (its analogs or derivatives).

Study	Model used	No. of studies (n)	SMD	CI		P	I^2	P	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	0.806	0.981
LDL	Random-effects	5	−0.16	−0.78	0.45	0.604	83.6%	<0.001	0.806	0.59
TC	Fixed-effect	5	0.03	−0.20	0.26	0.798	<0.01%	0.469	0.806	0.585
TG	Fixed-effect	5	0.25	0.02	0.49	0.033	<0.01%	0.724	0.806	0.819

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
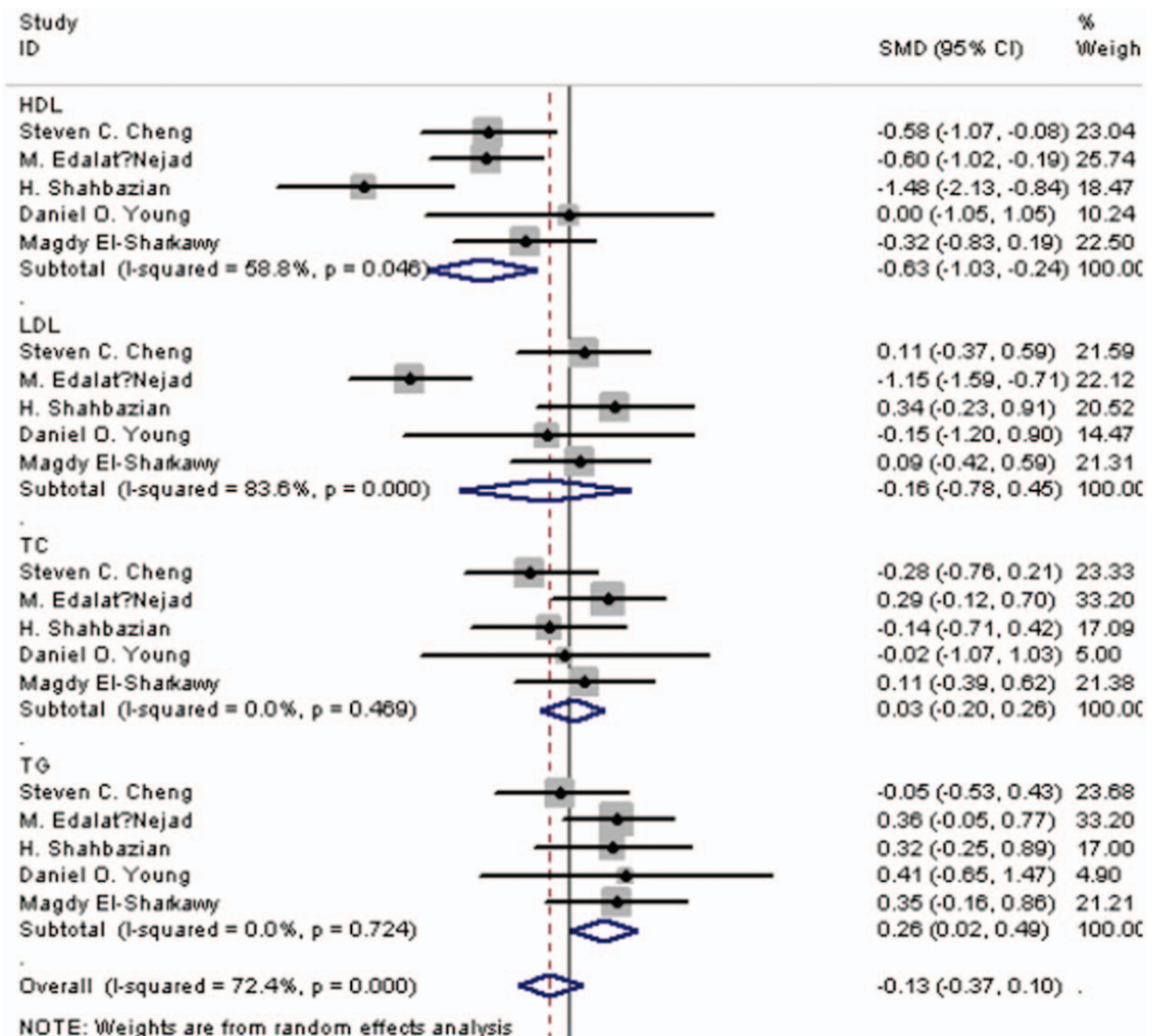

Figure 3. Forest plots for association between serum lipid profile and different niacin treat time in hyperphosphatemia dialysis patient.
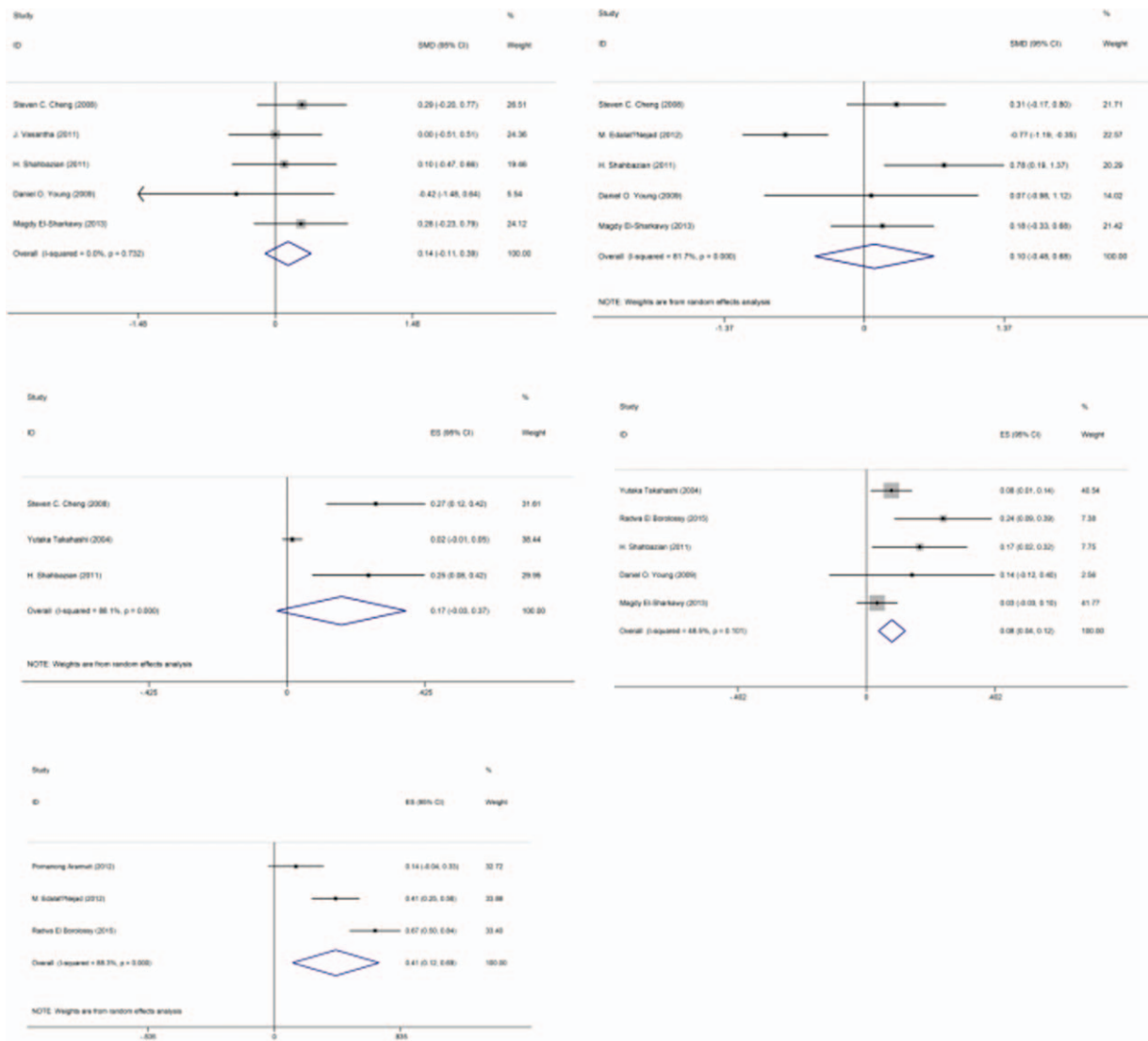
Figure 4. Forest plots for association between (A) serum uric acid concentration, (B) serum platelet number, (C) the rate of thrombocytopenia, (D) the rate of diarrhea, and (E) the rate of any adverse event, and niacin treatment in hyperphosphatemia dialysis patient.

thrombocytopenia in some drug treated patients,[13,26] which might be attributed to drug induced low thyroxin-biding 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

Table 4

Meta-analysis of the serum uric acid and platelet count change after 8 weeks treatment of nicotinic acid (its analogs or derivatives).

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	0.277	0.0%	0.732	0.221	0.11
Platelet count	Random-effects	5	0.10	−0.48	0.68	0.737	81.7%	0.000	0.806	0.484

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.

Author contributions

Formal analysis: R. Yang, H. Zhang.
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Software: N. Ma.
Validation: H. Zhang, J. Wang, N. Ma.
Writing – original draft: B. Dai.
Writing – review & editing: X. Liu, B. Dai.

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