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Nicotinamide and phosphate homeostasis in chronic kidney disease

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Abstract

Purpose of review—Higher serum phosphate concentration is a central driver of the chronic kidney disease (CKD) mineral bone disorder (MBD). Although phosphate binders are commonly used to lower phosphate, they are minimally effective in CKD. Nicotinamide (vitamin B3) decreases intestinal phosphate transport in animals. Its efficacy and safety in CKD is uncertain.

Recent findings—We review data differentiating nicotinamide from nicotinic acid (niacin) and compare the metabolism and side-effect profile of each. Several recent studies have tested the safety and efficacy of nicotinamide in patients with CKD and the general population. Available data on efficacy and safety, gaps in knowledge, and ongoing studies to address them are described.

Summary—Nicotinamide is a novel potential tool to treat hyperphosphatemia in patients with CKD, but additional data on safety and efficacy are required before widespread clinical use.

Keywords

kidney disease; mineral bone disorder; nicotinamide; osteodystrophy

INTRODUCTION

Phosphate homeostasis is regulated by an integrated mechanism involving the kidney, bone, intestine, and muscle [1]. In chronic kidney disease (CKD), multiple aspects of phosphate homeostasis are altered, and each is associated with higher mortality risk, coronary artery calcification, vascular stiffness, progression of CKD, and end-stage renal disease (ESRD) [2–5]. In response to higher serum phosphate concentrations, there are hormonal changes that serve to reduce phosphate concentrations. Serum concentrations of the phosphaturic hormones parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) are

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Conflicts of interest

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markedly increased in CKD, likely in response to dysregulated phosphate handling. 1,25-Dihydroxyvitamin D concentrations are lower in CKD, in part because of higher FGF-23, which, beyond inducing urinary phosphate excretion, also inhibits conversion of 25-hydroxy-vitamin D to 1,25-dihydroxyvitamin D. Interestingly, these hormonal alterations are evident in early CKD, even before development of hyper-phosphatemia [6,7▪].

Considering the consistent associations between hyperphosphatemia with morbidity and mortality in CKD, there is interest in lowering phosphate in clinical practice. Interestingly, although phosphate binders are widely used for phosphate lowering in CKD patients, and are recommended for use in CKD by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, they are only approved by the Food and Drug Administration (FDA) for use in ESRD patients [8]. Although phosphate binders are integral for the management of hyperphosphatemia in ESRD, their role in earlier stages of CKD remains controversial. Since the KDIGO CKD–MBD guidelines were published in 2009, a number of studies have questioned the efficacy and safety of binders in patients with CKD. For example, in a study of 148 patients with an estimated glomerular filtration rate (eGFR) of 20–45 ml/min/1.73 m^2 who were randomized to phosphate binders versus placebo for 9 months, serum phosphate concentrations declined by only 0.3 mg/dl relative to placebo [9]. In addition, the binder group had more rapid progression of vascular calcification compared to placebo, and serum FGF-23 concentrations were similar in both groups. Other randomized trials have had similar results, often with either smaller changes in serum phosphate, or no change at all relative to placebo [10–13].

Given limited efficacy, a novel proposed approach is to target the intestinal sodium phosphate cotransporter. Nicotinamide (vitamin B3) has been shown to decrease active intestinal phosphate transport in animal studies and represents one therapeutic option. The present review focuses on emerging data surrounding the use of nicotinamide for phosphate lowering in patients with CKD and ESRD.

EFFECTS OF NICOTINAMIDE ON INTESTINAL PHOSPHATE TRANSPORT

Intestinal phosphate absorption occurs via both sodium-dependent and sodium-independent mechanisms [14–16]. The majority of sodium-dependent absorption is through the sodium phosphate cotransporter 2b (Npt2b). Npt2b is located in the small intestine, but its expression in different segments varies across mammalian species [16–18]. To our knowledge, no study has evaluated Npt2b expression in different segments of the human intestine.

In the Npt2b knockout mouse, greater than 90% of all sodium-dependent phosphate absorption is abolished, thus Npt2b is the primary sodium-dependent phosphate transporter. The sodium-independent pathway was not increased in response to Npt2b deletion. In addition, phosphate concentrations were not affected when animals were on standard chow and in the absence of CKD, but there was a commensurate two-fold decrease in urinary phosphate excretion.

Considering no change in mean serum phosphate concentrations, further work was done to evaluate the Npt2b knockout effect on phosphate homeostasis in an adenine CKD model [19]. In this setting, Npt2b knockout mice had significantly lower serum phosphorus concentrations and 30% lower FGF23 concentrations compared to wild-type CKD control mice at 5 weeks. When a phosphate binder was added, an additional 12.5% reduction in serum phosphorus concentrations was noted in the Npt2b knockout, likely explained by a 36% increase in fecal phosphate excretion and concomitant 33% reduction in urinary phosphate excretion in binder-treated mice. Similarly, changes in FGF23 were amplified in the Npt2b CKD mouse treated with binders, with 50 and 22% reductions in FGF23 in the knockout and wild-type mice, respectively.

These studies provide an additional insight into intestinal phosphate handling. When the (wild-type) CKD animals were treated with phosphate binders, an increase in intestinal Npt2b expression was observed relative to mice not treated with binders. Similarly, Npt2b expression increases in rodents challenged by low phosphate diets [20]. Thus, upregulation of Npt2b in response to binder use or low phosphate intake may blunt the efficacy of intestinal phosphate binders in CKD [9,21▪▪]. In individuals taking phosphate binders, phosphate absorption may be enhanced at times when the binder is not in the intestinal lumen because of greater Npt2b expression. This may explain why binders appeared to be more effective in lowering serum phosphate concentrations when used in the Npt2b knockout CKD mouse compared to wild-type CKD mouse. It also suggests that combining a binder with a Npt2b inhibitor may provide greater phosphate lowering efficacy in patients with CKD.

NICOTINAMIDE AND PHOSPHATE HOMEOSTASIS IN ANIMAL MODELS

Nicotinamide decreases expression of the Npt2b cotransporter in the small intestine in animal models. This was first recognized by Katai *et al.* [17] who used niceritrol (an ester of niacin) in hemodialysis patients in Japan, and unexpectedly observed reductions in serum phosphate concentrations. They evaluated the effects of nicotinamide on intestinal brush border phosphate transport in rodents and found a two-fold reduction in sodium-dependent phosphate transport with nicotinamide relative to sham-treated animals. No change in intestinal sodium-independent phosphate transport was observed [17].

In the rodent model, intraperitoneal delivery was used. Unlike binders that act directly in the intestinal lumen, the intraperitoneal delivery implies that nicotinamide's effects on Npt2b were operable through a systemic delivery mechanism, and may not require direct exposure of nicotinamide to the intestinal lumen. Conversely, intraperitoneal delivery does not appear necessary as other studies have reported higher stool phosphate excretion with oral nicotinamide delivery [22].

Although the mechanism by which nicotinamide influences Npt2b expression and function is not completely understood, the aforementioned study by Katai *et al.* provided important clues. Ribonucleic acid (RNA) isolated from the jejunum from rats treated with nicotinamide vs. sham treated animals was injected it into Xenopus oocytes and phosphate transport was measured. In oocytes injected with RNA from nicotinamide treated rats,

phosphate transport was approximately two-fold lower than from sham treated animals [17]. These data suggest that nicotinamide may influence transcription or translation of Npt2b, or influence other intercellular regulatory factors that secondarily impact Npt2b function.

The aforementioned studies did not directly measure Npt2b expression or function. Eto *et al.* [23] used a rat adenine CKD model and treated with intraperitoneal nicotinamide. The investigators confirmed a decrease in intestinal phosphate absorption in nicotinamide-treated rats and demonstrated decreased Npt2b expression. The authors suggested specificity as nicotinamide did not affect expression of the sodium glucose transporter-1 [23].

An unanswered question is whether nicotinamide and its derivatives may also influence renal phosphate excretion, in which sodium phosphate cotransporters 2A and 2C (Npt2a and Npt2c) predominate [24]. Existing data are conflicting regarding nicotinamide action on these cotransporters. Wu *et al.* [25] reported that nicotinamide induced a 21% reduction in the sodium dependent phosphate reabsorption by the renal proximal tubule. Similarly, Kempson *et al.* [26] showed that nicotinamide increased urine phosphate excretion without changing urine creatinine, potassium, sodium, calcium, or urinary flow rates in rats. Similar observations were made in parathyroidectomized rats [27]. In contrast, in a rat CKD model, Eto *et al.* evaluated the blood clearance of phosphate, using timed measurements of radiolabeled phosphate after a small bowel phosphate lavage. Although nicotinamide induced lower intestinal phosphate, circulating radiolabeled phosphate disappearance rates were similar in nicotinamide versus vehicle treated rats. Thus, this group concluded renal excretion of phosphate was unlikely to be the dominant mechanism leading to lower serum phosphate concentrations [23].

NICOTINAMIDE METABOLISM IN HUMANS

There is increasing interest in the use of nicotinamide and niacin for inhibition of Npt2b in CKD. Shimoda *et al.* [28] first suggested that niceritrol decreased serum phosphate concentrations in 10 patients with ESRD. Compared to pretreatment concentrations, niceritrol 750 mg daily led to a mean 1.7 mg/dl decrease in serum phosphate concentrations at 4 weeks [28]. This study had no control group.

Understanding the different effects of nicotinamide versus nicotinic acid by literature review is challenging because historically the names have often been used interchangeably. The structure of nicotinamide (aka. vitamin B3) consists of a pyridine ring with an amide group in position three (Fig. 1). In contrast, nicotinic acid (aka. niacin) has a carboxyl group in position 3. Although nicotinamide and niacin have similar functions as vitamins, their pharmacologic and toxic properties differ [29]. For example, the flushing and pruritus experienced after ingestion of niacin are not observed with nicotinamide, and nicotinamide has much less, if any, effects on serum cholesterol concentrations. Unfortunately, the confounded use of these terms makes it difficult to discern with certainty the safety or toxicity profile of one or the other, especially for rare outcomes [30].

When niacin is taken orally, it is converted to nicotinamide [29]. In high doses, the exposure to niacin is sufficient to induce flushing and lipid lowering effects, before complete

conversion to nicotinamide, metabolism, or excretion. While rapid conversion of niacin to nicotinamide occurs, there appears to be little conversion of nicotinamide to niacin in humans. In rats, administration of very high doses of nicotinamide (250–500 mg/kg) results in a small increase in serum nicotinic acid concentrations, suggesting that there may be a small amount of conversion with extremely high doses [31]. Nicotinamide, in turn, is conjugated to nicotinuric acid and other metabolites by the liver, which are subsequently excreted in the urine [32].

Specific data on pharmacokinetics of nicotinamide in CKD are lacking, but given their interrelated metabolism, studies evaluating niacin are informative. Reiche *et al.* [32] compared the pharmacokinetics of extended release niacin in 10 patients with ESRD and eight CKD patients (mean eGFR 31 ml/min/1.73 m^2). Unfortunately, a non-CKD control group was not included. Patients were given niacin 500, 1000, and 1500 mg/day as single doses on weeks 1, 2, and 3. Patients with ESRD had lower total exposure [area under the curve (AUC)] of niacin and nicotinamide than CKD patients. Patients with CKD had AUCs and maximum concentrations (t_{max}) similar to those observed in patients without-CKD in prior studies, and it is probable that the lower AUC in ESRD was due to removal with dialysis. In contrast, the AUC for one of the niacin metabolites, nicotinuric acid, was four-fold higher in ESRD than in CKD [32]. Some side-effects reported with nicotinamide or niacin in ESRD have not been observed in large randomized trials of in the general population. It is, therefore, possible that nicotinuric acid or other metabolites may be retained and biologically active in ESRD, leading to unique side-effects. As most existing studies in kidney disease are small and have short-term follow-up, additional safety data are warranted before widespread clinical use.

NICOTINAMIDE AND PHOSPHATE HOMEOSTASIS IN HUMANS

Multiple small studies with varying study designs and relatively short-term follow-up have suggested that niacin and nicotinamide lower serum phosphate in CKD and ESRD. Takahashi *et al.* [33] evaluated 65 patients with ESRD, asking patients to discontinue phosphate binders and observed an increase in serum phosphate concentrations from 5.4 to 6.9 mg/dl over 2 weeks. Patients were then treated with 1080 mg (mean dose) of nicotinamide for 12 weeks. The mean phosphate decreased back to 5.4 mg/dl [33]. Although this study had no control group, it was the first study supporting the hypothesis that nicotinamide could influence phosphate homeostasis in patients with kidney disease.

Cheng *et al.* [34] published the first randomized cross-over trial of nicotinamide use in ESRD. Unlike the study by Takahashi *et al.* [33], patients were continued on stable phosphate binder dose and nicotinamide was used as add-on therapy. Thirty-three patients with ESRD with serum phosphate greater than 5 mg/dl were treated for 8 weeks with either placebo or nicotinamide, followed by a 2-week wash out period, and were then crossed over. The dose of nicotinamide was titrated up from 250 to 750 mg twice daily over 5 weeks unless serum phosphate fell below 3.5 mg/dl. During active treatment, serum phosphate concentrations were 1.54 mg/dl lower than placebo (P=0.0002). The investigators conducted a similar study in 15 peritoneal dialysis patients with similar phosphate lowering efficacy [35].

Recently, a trial evaluating nicotinamide in pediatric ESRD patients in Egypt was published [36▪]. This open label randomized trial evaluated 60 pediatric hemodialysis patients randomized to a phosphate binders or binders plus nicotinamide. Patients with serum phosphate 5–8 mg/dl received nicotinamde 100 mg twice daily, and those with phosphate greater than 8 mg/dl received 100 mg thrice daily. The control group experienced an increase in serum phosphate of 0.4 mg/dl, whereas the nicotinamide group experienced a 1.8 mg/dl reduction in serum phosphate at 6 months. There are several notable aspects of this study. First, the dose of nicotinamide was much lower than in other trials, even when considering differences in body weight. Second, although mean differences in serum phosphate concentrations across treatment groups were provided at the end of the trial (5 mg/dl in the nicotinamide arm and 8 mg/dl in the binder arm), standard errors and a *P*-values for across group differences were not. Third, the intervention group experienced greater flushing than the placebo group. This may suggest some impurity in the nicotinamide formulation, or perhaps a unique side-effect profile in the pediatric population.

Table 1 summarizes the experience with nicotinamide in patients with ESRD. Generally, the sample sizes are small and follow-up has uniformly been short. Moreover, although there is a growing experience for use of nicotinamide in patients with ESRD, little is known about its utility in patients with CKD. Retrospective analysis of dyslipidemia trials evaluating niacin has demonstrated that niacin similarly lowers phosphate and FGF23 in CKD stage 3 [39,40▪▪]. However, given the flushing and other side effects of niacin, nicotinamide may be a more promising approach. It should be noted that niacin is approved as a lipid-lowering medication in the United States and elsewhere and phosphate lowering is an off-label use. To address the utility of nictonamide in CKD, we are currently conducting the CKD Optimal Management with Binders and Nicotinamide (COMBINE) Trial. This is a randomized, placebo controlled trial comparing nicotinamide 1500 mg daily, lanthanum carbonate 1000 mg three times daily, combined therapy, or double placebo in 200 persons with baseline eGFR 20–45 ml/min/1.73 m^2. Participants will be treated for 12 months. The study is powered for dual primary end-points; changes in serum phosphate and FGF23 concentrations [21▪▪]. Preliminary results should be available in 2018.

POTENTIAL ADVERSE EFFECTS OF NICOTINAMIDE

The side-effect profile of niacin is well established. The intense flushing shortly after ingestion is nearly ubiquitous and is a major barrier to its tolerability. Other recognized side effects include risk of liver toxicity, hyperglycemia, and hyperuricemia. Studies with nicotinamide, in contrast, suggest it lacks many of these side effects [41], although it is difficult to know with certainty because of confounded use of terms in prior literature, and the possibility that side effect profiles may differ in kidney disease.

A case report published in 1973 reported elevated liver enzymes in a patient taking 3–9 g/day of nicotinamide [42]. However, impure mixtures with niacin may have confounded this report as, to our knowledge, liver toxicity has not been confirmed [30]. There is considerable experience with high-dose nicotinamide in non-CKD settings. The largest was a trial that enrolled 549 healthy adolescents randomized to nicotinamide or placebo, starting at 1200 mg/day, and titrating up to 3000 mg daily, for up to 5 years. The study was designed

to prevent type 1 diabetes, and failed to reach its primary efficacy endpoint. However, it provided important safety information. Liver toxicity was not observed, and side effects were similar in the active and the placebo arms [40▪▪].

Recently, Chen *et al.* [43▪▪] reported the results of a trial 386 patients at high risk of skin cancer randomized to nicotinamide vs. placebo. Participants received nicotinamide 500 mg twice daily vs. placebo for 5 years. Participants randomized to nicotinamide had significantly lower risk of skin cancer relative to placebo and there was no statistically significant difference in the safety profile between nicotinamide and placebo.

Potential side effects of nicotinamide in patients with CKD are summarized in Table 2. Among them, thrombocytopenia may be particularly important and is not recognized in the general population. The first case report described a patient with ESRD who developed leukopenia and thrombocytopenia while treated with niacin, which resolved upon discontinuation [44]. In the aforementioned Takahashi study, one case of thrombocytopenia occurred among the 65 patients [33]. Subsequently, Rottenbourg *et al.* [45] reported a small case series wherein significant decline in platelet count occurred in five of six patients with ESRD treated with nicotinamide 1 g/day. They observed a mean decline in platelet count of from 188 000 to 120 000/mm^3 [45]. In all cases, platelet count rebounded shortly after nicotinamide discontinuation. Recent clinical trials in patients with ESRD have closely monitored platelet concentrations. In the randomized trial by Cheng *et al.* [34], the nicotinamide arm experienced a mean decrease in platelet count of 17 000/mm^3; one patient had a more pronounced drop (196 000–61 000/mm^3). In the trial in patients with pediatric ESRD, a modest mean decrease in platelet count was observed (22 500/mm^3), but platelet count remained in the normal range in all patients [36▪]. Several other studies have not observed changes in platelet count [35,37]. Although thrombocytopenia is not a recognized side-effect in the general population, some metabolites of nicotinamide are elevated in persons with ESRD [32], and it is therefore important that platelet counts and other side effects be systematically evaluated in ongoing and future trials.

CONCLUSION

Despite widespread use of phosphate binders, management of hyperphosphatemia remains a major clinical challenge. Nicotinamide and its derivatives provide a new therapeutic opportunity as they lower intestinal phosphate absorption through a unique pathway. Preliminary studies consistent show serum phosphate lowering efficacy in animals and humans. Yet, additional safety and efficacy data are required. In CKD and ESRD, studies with larger sample sizes and longer follow-up are required to determine the safety, tolerability, and efficacy. Nonetheless, given its widespread availability and low cost, the opportunity to use nicotinamide to intervene on a novel mechanism contributing to intestinal phosphate transport represents an important opportunity which may ultimately improve care of CKD–MBD in patients living with kidney disease worldwide.

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KEY POINTS

- Because of limited efficacy of phosphate binders in early CKD, new therapies to lower phosphate in CKD are needed.
- Nicotinamide decreases serum phosphate concentrations by inhibiting sodium-dependent phosphate transport in the small intestine.
- Nicotinamide consistently lowers serum phosphate concentrations in ESRD.
- Larger studies with longer follow-up are needed to determine the safety and tolerability of nicotinamide in ESRD and CKD.

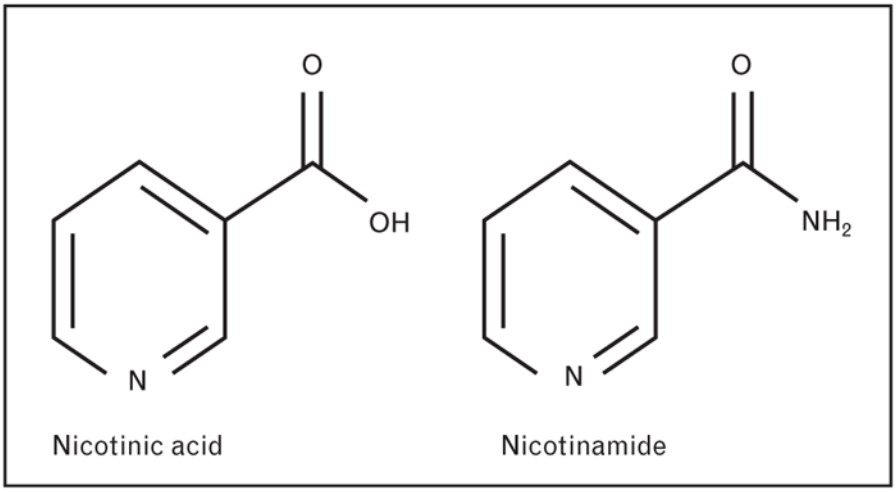

FIGURE 1.
Chemical structure of nicotinic acid and nicotinamide.

Table 1

Existing studies evaluating effects of nicotinamide on phosphorous concentrations in patients with ESRD

First author	Dialysis modality	No. of patients	Design	Placebo	Randomized	Maximum daily dose (mg/day)	Dosing interval	Treatment period (weeks)	Change in phosphate (mg/dl)
Takahashi [33]	HD	65	Open label	No	No	1750	BID	12	−1.5 ±1.4[a]
Cheng [34]	HD	33	Cross-over	Yes	Yes	1500	BID	8	−0.9 ±0.7[b]
Young [35]	PD	15	RCT	Yes	Yes	1500	BID	8	−1.1 ±0.6[b]
Vasantha [37]	HD	30	Open label	No	No	750	BID	8	−2.3 ±1.1[a]
Shahbazian [38]	HD	48	RCT	Yes	Yes	1000	Daily	8	−1.4 ±0.8[b]
El Borolossy [36▪]	HD	60	RCT	No	Yes	300 (pediatric patients)	BID	24	−2.2[a]

[a] $P<0.05$ compared to pretreatment concentrations.

[b] $P<0.05$ compared to placebo arm. BID, twice daily; ESRD, end stage renal disease; RCT, randomized clinical trial.

Table 2

Potential adverse effects of nicotinamide in patients with ESRD

First author	Maximum daily dose (mg/day)	Dosing interval	Treatment period (weeks)	Diarrhea (%)vs. placebo (%)	Thrombocytopenia (%)vs. placebo (%)	Other
Takahashi *et al.* [33]	1750	BID	12	7.8 vs. NA	1.6 vs. NA	None
Cheng *et al.* [34]	1500	BID	8	6.0 vs. 0	27 vs. 15	None
Young *et al.* [35]	1500	BID	8	12.5 vs. 0	0 vs. 0	Increased uric acid concentrations (0.4 mg/dl)
Vasantha *et al.* [37]	750	BID	8	23 vs. NA	0	None
Shahbazian *et al.* [38]	1000	Daily	8	16.6 vs. NR	25 vs. 0	Hyperglycemia
El Borolossy *et al.* [36▪]	300 (pediatric patients)	BID	24	24 vs. NR	0 vs. 0 (decreased mean platelet count noted in nicotinamide arm)	Flushing 32% Nausea 28%

BID, twice daily; NA, not applicable; NR, not reported.

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