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Nicotinamide suppresses hyperphosphatemia in hemodialysis patients

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Nicotinamide suppresses hyperphosphatemia in hemodialysis patients.

Background. The use of calcium- or aluminum-based phosphate binders against hyperphosphatemia is limited by the adverse effects of hypercalcemia or aluminum toxicity in long-term hemodialysis. Because nicotinamide is an inhibitor of sodium-dependent phosphate cotransport in rat renal tubule and small intestine, we examined whether nicotinamide reduces serum levels of phosphorus and intact parathyroid hormone (iPTH) in patients undergoing hemodialysis.

Methods. Sixty-five hemodialysis patients with a serum phosphorus level of more than 6.0 mg/dL after a 2-week washout of calcium carbonate were enrolled in this study. Nicotinamide was administered for 12 weeks. The starting dose was 500 mg/day, and the dose was increased by 250 mg/day every 2 weeks until serum phosphorus levels were well controlled at less than 6.0 mg/dL. A 2-week posttreatment washout period followed the cessation of nicotinamide. Blood samples were collected every week for measurement of serum calcium, phosphorus, lipids, iPTH, and blood nicotinamide adenine dinucleotide (NAD).

Results. The mean dose of nicotinamide was 1080 mg/day. The mean blood NAD concentration increased from 9.3 ± 1.9 nmol/10^5 erythrocytes before treatment to 13.2 ± 5.3 nmol/10^5 erythrocytes after treatment ($P < 0.01$). The serum phosphorus concentration increased from 5.4 ± 1.5 mg/dL to 6.9 ± 1.5 mg/dL with the pretreatment washout, then decreased to 5.4 ± 1.3 mg/dL after the 12-week nicotinamide treatment ($P < 0.0001$), and rose again to 6.7 ± 1.6 mg/dL after the posttreatment washout. Serum calcium levels decreased during the pretreatment washout from 9.1 ± 0.8 mg/dL to 8.7 ± 0.7 mg/dL with the cessation of calcium carbonate. No significant changes in serum calcium levels were observed during nicotinamide treatment. Median serum iPTH levels increased with pretreatment washout from 130.0 (32.8 to 394.0) pg/mL to 200.0 (92.5 to 535.0) pg/mL and then decreased from the maximum 230.0 (90.8 to 582.0) pg/mL to 150.0 (57.6 to 518.0) pg/mL after the 12-week nicotinamide treatment ($P < 0.05$). With nicotinamide, serum high-density lipoprotein (HDL) cholesterol concentrations increased from 47.4 ± 14.9 mg/dL to 67.2 ± 22.3 mg/dL ($P < 0.0001$) and serum low-density lipoprotein (LDL) cholesterol concentrations decreased from 78.9 ± 18.8 mg/dL to 70.1 ± 25.3 mg/dL ($P < 0.01$); serum triglyceride levels did not change significantly.

Conclusion. Nicotinamide may provide an alternative for controlling hyperphosphatemia and hyperparathyroidism without inducing hypercalcemia in hemodialysis patients.

Key words: nicotinamide, hyperphosphatemia, hemodialysis patients, nicotinamide adenine dinucleotide, parathyroid hormone, serum lipids.

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End-stage renal disease (ESRD) is associated with calcium and phosphate metabolism abnormalities that can result in severe bone disease and ectopic calcification of cardiovascular tissues [1, 2]. Phosphorus-restricted diets are essential for the prevention of these deleterious complications in ESRD patients. Weekly dietary absorption of phosphate is approximately 4200 mg, assuming fractional absorption of phosphate is 60% [3], whereas phosphate efflux is approximately 1057 mg per 4-hour dialysis session or 3171 mg per week [4], suggesting a positive phosphorus balance in dialysis patients. The common phosphate binders contain aluminum or calcium. Aluminum accumulates in the tissues and causes neurologic, skeletal, and hematologic toxicities [5, 6]. Ingestion of calcium carbonate, an effective phosphate binder, leads to hypercalcemia and increases the risk of vascular calcification in ESRD patients [7, 8].

Nicotinamide is a circulating form of nicotinic acid. The biologic function of nicotinamide derives from its active form, nicotinamide adenine dinucleotide (NAD). Administration of nicotinamide is reported to increase the concentration of renal cortical tissue NAD, which was shown to inhibit phosphate uptake by brush border membrane vesicles obtained from rat proximal tubules [9, 10]. A similar effect of nicotinamide has been reported on phosphate uptake by brush border membrane vesicles isolated from the rat small intestine [11], suggesting that nicotinamide is probably an effective inhibitor of phosphorus absorption in the intestine.

Table 1. Baseline characteristics of study patients ($N = 65$)

Gender *males/females*	38/27
Age *years*	57.0 ± 11.5
Vitamin D *users/nonusers*	17/48
Time on dialysis *years*	6.5 ± 5.2
Etiology of end-stage renal disease	
Chronic glomerulonephritis	31
Diabetes mellitus	24
Hypertension	5
Polycystic kidney disease	3
Other	2
Laboratory values	
Serum phosphorus *mg/dL*	5.4 ± 1.5
Serum calcium *mg/dL*	9.1 ± 0.8
Serum calcium-phosphorus product mg^2/dL^2	48.4 ± 13.6
Serum intact parathyroid hormone *pg/mL*	187.3 ± 204.4

Numbers are number of patients unless otherwise indicated.

The aim of the present study was to examine whether nicotinamide lowers serum levels of phosphorus and intact parathyroid hormone (iPTH) in long-term hemodialysis patients.

METHODS

Seventy-two hemodialysis patients were originally enrolled in the present study. All patients had been dialyzed three times weekly with a bicarbonate dialysate for 6.5 ± 5.2 years. The dialysate calcium concentration was 3.0 mEq/L. Patients with a history of serious gastrointestinal disease, malignancy, total parathyroidectomy, vasculitis, dementia, or poorly controlled diabetes mellitus were excluded. Inclusion criteria were stable dosage of calcium carbonate (2.9 ± 1.7 g/day) for at least 1 month and avoidance of intentional changes in diet throughout the study. Seventeen patients were being given vitamin D (0.4 ± 0.2 μg/day) at the start of the study. No changes in the dosage of vitamin D were made during the study.

We obtained written informed consent from each participant, and the study protocol was approved by the Human Research Ethics Committee of the Koto Hospital. Administration of calcium carbonate was discontinued during a 2-week pretreatment washout period (weeks −2 to 0). Sixty-five hemodialysis patients (38 men and 27 women; mean age, 57.0 years) with serum phosphorus levels of more than 6.0 mg/dL during the pretreatment washout period were eligible for nicotinamide treatment. Characteristics of these patients are shown in Table 1. The 65 patients received nicotinamide (Nippon Roche K.K., Tokyo, Japan) for 12 weeks (weeks 1 to 12). The starting dose of nicotinamide was 500 mg/day and was increased by 250 mg/day every 2 weeks if necessary to control the serum phosphorus concentration at less than 6.0 mg/dL. The nicotinamide was given twice daily in powder form immediately after meals. After 12 weeks of treatment, the patients were taken off nicotinamide (weeks 13 to 14, posttreatment washout period).

Blood samples were collected weekly prior to a hemodialysis session, and serum concentrations of phosphorus, calcium, and lipids were determined by standard clinical laboratory methods. The serum iPTH concentration was determined by immunochemilumetric assay (Intact PTH Kit) (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) (upper limit of normal, 65 pg/mL). The blood NAD concentration was determined according to the Shibata and Murata–modified [12] Nisselbaum and Green method [13]. Blood NAD concentrations were expressed as NAD per 10^5 erythrocytes (nmol/10^5 erythrocytes) because NAD was not detected in serum. Dietary intake was estimated every 2 weeks as the protein catabolic rate (PCR) [14]. We judged the avoidance of intentional changes in diet by no change in PCR. Compliance was confirmed by face-to-face interview.

Data are expressed as mean ± standard deviation (SD) or as median values when the data were highly skewed. The Wilcoxon signed-rank test was used to analyze differences in paired group data. The effects of nicotinamide administration on the serum phosphorus concentrations and other laboratory values were assessed by comparing the serum levels at the end of the pretreatment washout period to those at the end of the treatment period. Spearman's rank correlation coefficient was calculated to assess association between the changes in serum phosphorus and other laboratory values. Statistical analyses were based on two-tailed Student t test. iPTH levels were shown as median (10^{th} to 90th percentile) and expressed as box and whisker plots. The analysis of PTH data was based on Welch t test. A P value of less than 0.05 was considered statistically significant.

RESULTS

The mean dose of nicotinamide at the end of the 12-week treatment period was 1080 ± 370 mg/day. The minimum dose of nicotinamide was 500 mg/day (7.9 mg/kg body weight/day) and the maximum was 1750 mg/day (33.3 mg/kg body weight/day). Compliance was confirmed in all cases. No significant changes were observed in PCR with nicotinamide treatment (before treatment, 1.1 ± 0.2 g/kg/day vs. after treatment, 1.1 ± 0.2 g/kg/day).

The blood NAD concentration increased from 9.3 ± 1.9 nmol/10^5 erythrocytes to 13.2 ± 5.3 nmol/10^5 erythrocytes with nicotinamide treatment ($P < 0.01$) (Fig. 1). The doses of nicotinamide were significantly correlated with blood NAD concentrations ($r = 0.805$, $P < 0.0001$). After the posttreatment washout period, the blood NAD level decreased significantly to 8.4 ± 2.7 nmol/10^5 erythrocytes ($P < 0.005$). There was no significant difference in the NAD concentration between the pretreatment washout period and the posttreatment washout period.

Serum phosphorus levels changed significantly with nicotinamide treatment (Fig. 2). Serum phosphorus levels

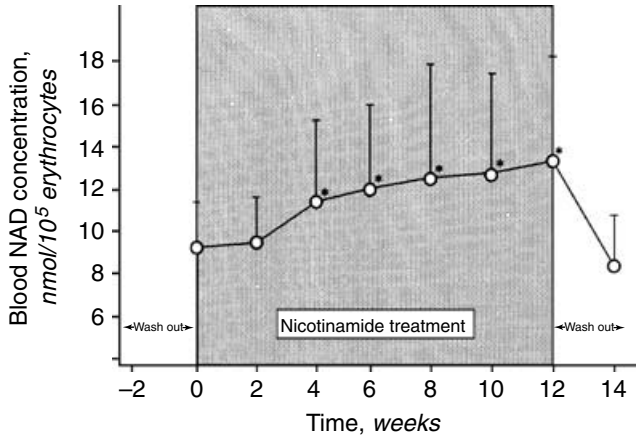

Fig. 1. Effect of nicotinamide on blood nicotinamide adenine dinucleotide (NAD) concentration in hemodialysis patients. −2 weeks indicates the start of pretreatment washout. *vs. 0 week, $P < 0.01$.

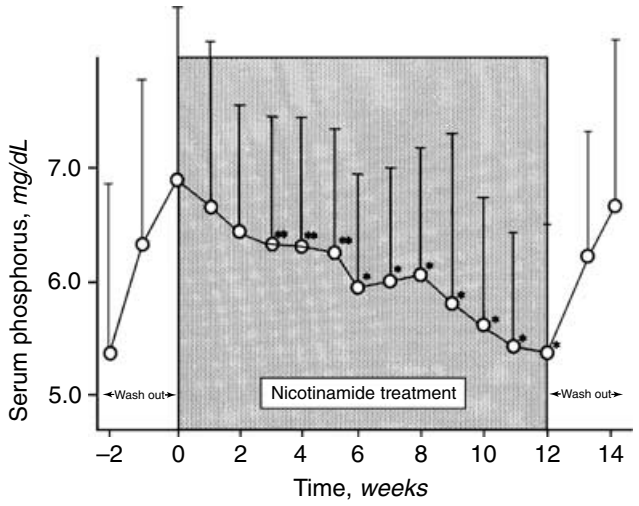

Fig. 2. Changes in serum phosphorus levels with nicotinamide treatment in hemodialysis patients. *vs. 0 week, $P < 0.001$; **vs. 0 week, $P < 0.01$.

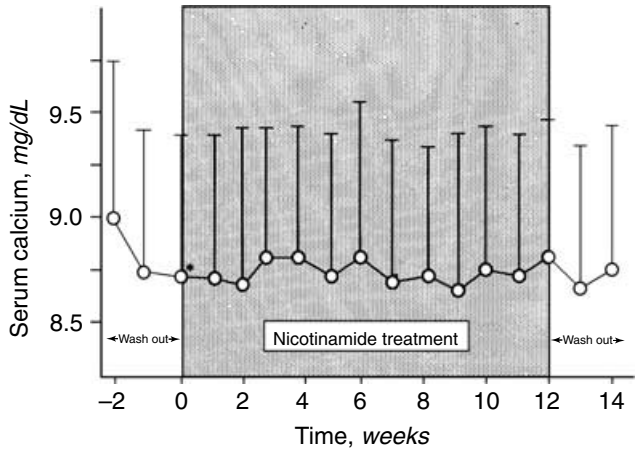

Fig. 3. Serum calcium levels in relation to nicotinamide treatment in hemodialysis patients.

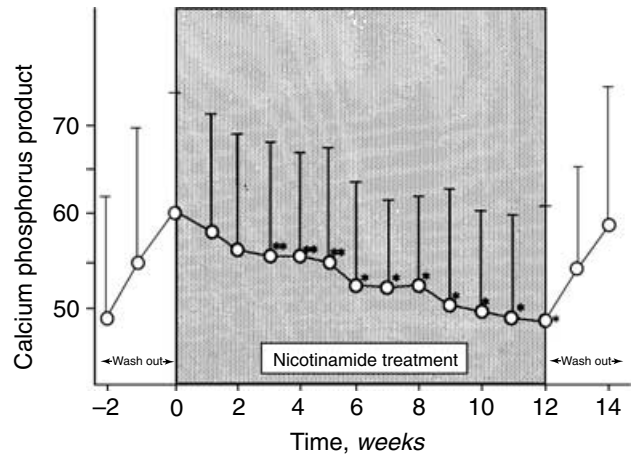

Fig. 4. Effect of nicotinamide treatment on calcium-phosphorus product in hemodialysis patients. *vs. 0 week, $P < 0.0001$; ** vs. 0 week, $P < 0.01$.

increased from 5.4 ± 1.5 mg/dL before the pretreatment washout period to 6.9 ± 1.5 mg/dL after the pretreatment washout period. Serum phosphorus levels decreased immediately after the start of nicotinamide treatment and continued to decrease until the cessation of treatment. Serum phosphorus levels decreased from 6.9 ± 1.5 mg/dL to 5.4 ± 1.3 mg/dL during the 12 weeks of nicotinamide treatment ($P < 0.0001$). After the posttreatment washout, serum phosphorus levels increased significantly to 6.7 ± 1.6 mg/dL ($P < 0.0001$). Reductions in serum phosphorus levels were comparable between vitamin D users and nonvitamin D users.

Serum calcium levels decreased from 9.1 ± 0.8 mg/dL before the pretreatment washout period to 8.7 ± 0.7 mg/dL after the pretreatment washout period ($P < 0.0001$) (Fig. 3). Serum calcium levels were unchanged during the 12 weeks of nicotinamide treatment (8.8 ± 0.7 mg/dL, $P = 0.4230$) and remained the same after the 2-week posttreatment washout period (8.8 ± 0.7 mg/dL). Serum calcium levels were similar between vitamin D users and nonvitamin D users.

The calcium-phosphate product increased significantly from 48.4 ± 13.6 mg^2/dL^2 to 59.8 ± 14.5 mg^2/dL^2 at the end of the pretreatment washout period ($P < 0.0001$) (Fig. 4). A calcium-phosphorus product decreased immediately and significantly to 47.3 ± 13.4 mg^2/dL^2 during the 12 weeks of nicotinamide treatment ($P < 0.0001$). With the cessation of nicotinamide, the serum calcium-phosphorus product increased gradually, reaching 58.7 ± 16.1 mg^2/dL^2 after the 2-week posttreatment washout period ($P < 0.0001$).

Median serum iPTH levels over the course of the study are shown in Figure 5. Median serum iPTH levels increased with the pretreatment washout from 130.0 (32.8 to 394.0) pg/mL to 200.0 (92.5 to 535.0) pg/mL ($P < 0.05$).

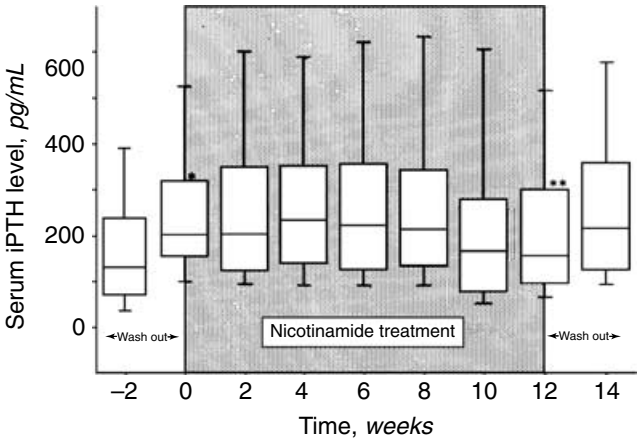

Fig. 5. Box and whisker plots showing serum intact parathyroid hormone (iPTH) levels in nicotinamide-treated hemodialysis patients. *vs. −2 weeks, $P < 0.05$; **vs. 4 weeks, $P < 0.05$.

With nicotinamide treatment, median serum iPTH levels reached 230.0 (90.8 to 582.0) pg/mL on week 4 and decreased, reaching 150.0 (57.6 to 518.0) pg/mL by the end of the 12 weeks of treatment ($P < 0.05$). After the 2-week posttreatment washout period, median serum iPTH levels were again increased to 220.0 (97.2 to 570.0) pg/mL. Median iPTH levels decreased with nicotinamide treatment in both vitamin D users and nonvitamin D users. Median serum iPTH levels after nicotinamide treatment did not differ significantly from those before the pretreatment washout. No changes were observed in serum magnesium concentrations with nicotinamide treatment. Serum alkaline phosphatase levels decreased significantly from 173.8 ± 79.3 IU/L to 159.3 ± 68.4 IU/L ($P < 0.01$) at 6 weeks and to 159.2 ± 58.6 IU/L ($P < 0.01$) at 12 weeks after the start of nicotinamide treatment and then increased significantly to 166.1 ± 59.8 IU/L ($P < 0.05$) at 2 weeks after the cessation of nicotinamide.

Serum high-density lipoprotein (HDL) cholesterol levels increased significantly from 47.4 ± 14.9 mg/dL before the pretreatment washout period to 67.2 ± 22.3 mg/dL ($P < 0.0001$) after the 12 weeks of nicotinamide treatment. In contrast, serum low-density lipoprotein (LDL) cholesterol levels decreased from 78.9 ± 18.8 mg/dL to 70.1 ± 25.3 mg/dL ($P < 0.01$). There were no changes in serum total cholesterol levels (before treatment, 160.9 ± 30.3 mg/dL vs. after treatment, 161.6 ± 33.9 mg/dL) or in serum triglyceride levels (before treatment, 145.7 ± 82.2 mg/dL vs. after treatment, 131.4 ± 69.6 mg/dL) throughout the study period. Changes in serum HDL cholesterol levels correlated significantly with changes in NAD concentrations ($r = 0.512$, $P < 0.01$).

There were no significant changes in other laboratory values during nicotinamide treatment. Serum albumin and total serum proteins did not change significantly during the study. Adverse events possibly related to treatment included diarrhea (five patients, 7.8%) and thrombocytopenia (one patient, 1.6%). The platelet count of the patient with thrombocytopenia decreased from 16.8 × 10^4/μL to 8.3 × 10^4/μL. Two weeks after discontinuance of nicotinamide, the platelet count increased to 18.0 × 10^4/μL. There were no changes in his erythrocyte or leucocyte count during nicotinamide treatment. All six patients with adverse effects had received more than 1500 mg/day of nicotinamide. The diarrhea and thrombocytopenia disappeared when the nicotinamide was reduced or discontinued.

DISCUSSION

Hyperphosphatemia is an important risk factor for the development of ectopic calcification and cardiovascular changes in patients undergoing hemodialysis. Although calcium- or aluminum-based phosphate binders are usually essential for avoiding hyperphosphatemia in long-term hemodialysis patients, certain adverse effects associated with the absorption of calcium and/or aluminum are inevitable. We showed in the present study that nicotinamide controls serum phosphorus levels in hemodialysis patients at levels similar to those achieved with currently available calcium- or aluminum-based phosphate binders.

A novel calcium- and aluminum-free phosphate binder, poly[allylamine hydrochloride] (RenaGel, GelTex Pharmaceuticals, Inc., Waltham, MA, USA), was recently reported to reduce serum phosphorus and iPTH concentrations without significant changes in serum calcium levels [15–17]. Total serum cholesterol and LDL cholesterol levels were also shown to be significantly reduced in RenaGel-treated patients without a reduction in HDL cholesterol [15–17].

Nicotinamide, a metabolite of nicotinic acid, stimulates biosynthesis of NAD, inhibits catabolism of NAD, and increases the ratio of NAD (oxidized) to NADH (reduced) [10]. The mechanism by which nicotinamide lowers serum phosphorus levels remains unknown. NAD is proposed to be an intracellular regulator of sodium-dependent phosphate transport [10]. Nicotinamide has been shown in rats to increase the renal cortical NAD concentration, inhibit phosphate uptake by brush border membrane vesicles of the renal proximal tubules in the rat kidney, and increase phosphate excretion in thyroparathyroidectomized rats [9, 10]. Intestinal phosphate transport is reported to occur by a sodium-independent, nonsaturable process and an active, sodium-dependent component of phosphate absorption in the duodenum and jejunum [18]. Katai et al [11] showed that nicotinamide inhibits phosphate uptake in the brush border membrane of rat small intestine. Furthermore, nicotinamide, apart from its inhibitory effect on poly(ADP-ribose) polymerase (PARP)-1 and its ability to restore intracellular NAD^+ pools, has recently been

suggested to act against the pathogenic process leading to insulin-dependent diabetes mellitus (IDDM). A recent meta-analysis showed nicotinamide, when given at the time of IDDM diagnosis, to have a protective effect on residual cell function of the pancreas as assessed by C-peptide secretion [19]. It is probable that nicotinamide improves insulin secretion and consequently decreases serum phosphorus levels by shifting phosphorus from the extracellular to the intracellular space.

Nicotinamide significantly reduced serum phosphorus levels in hemodialysis patients in the present study. Mean serum phosphorus levels decreased significantly during the 12 weeks of nicotinamide treatment and increased significantly to pretreatment levels after the 2-week posttreatment washout, suggesting the serum phosphorus-lowering effect to be due to nicotinamide. The onset of nicotinamide action was relatively rapid; the substantial reduction in serum phosphorus levels occurred within 2 weeks. This study proved that the serum phosphorus–lowering ability of nicotinamide is nearly equivalent to that of calcium-based phosphate binders.

Serum calcium levels declined after the pretreatment washout in our study, probably due to the removal of calcium carbonate. Nicotinamide treatment did not change serum calcium levels during the 12 weeks. The risk of vascular calcification increases with increases in serum calcium-phosphorus product. The mean increase in serum calcium-phosphorus product we observed after the pretreatment washout along with the remarkable reduction to below prewashout levels indicates that nicotinamide can reduce the risk of vascular calcification in hemodialysis patients.

Several investigators have shown that increased serum phosphorus levels increase the synthesis and secretion of PTH [20–22]. Evidence exists for a direct role of serum phosphorus as a regulator of parathyroid gland function [23]. In the present study, median serum iPTH levels gradually decreased after the start of nicotinamide treatment and showed significant reduction after 12 weeks of treatment. The increase in serum phosphorus and the decrease in serum calcium with pretreatment washout stimulated a corresponding increase in median serum iPTH levels. The decline in serum iPTH levels during the second half of nicotinamide treatment was associated with the decline in serum phosphorus.

Nicotinamide treatment significantly increased serum HDL cholesterol and decreased LDL cholesterol in our subjects. Shepherd et al [24] reported that nicotinic acid elevates the HDL_2-to-HDL_3 ratio because of a great increase in the absolute level of circulating HDL_2 and a small absolute decrease in circulating HDL_3. Cardiovascular diseases, including myocardial infarction, sudden death, and stroke, collectively account for approximately 50% of the mortality of ESRD patients [25, 26]. There are multiple abnormalities in the lipid profi1e of ESRD patients, and these may contribute to the high incidence of atherosclerosis [27]. Controlled clinical trials will ultimately determine whether an increase in HDL cholesterol will be of benefit to ESRD patients with atherosclerosis.

Nicotinamide treatment has a few adverse effects, including the possible occurrence of gastrointestinal disorders such as diarrhea. One patient showed a statistically significant decrease in platelet count during nicotinamide treatment. After the washout period, however, the platelet count returned to the pretreatment level. Nicotinamide has been used at 1500 mg/day to 3000 mg/day without adverse effects for protection of beta cells from end-stage destruction in patients with recent-onset IDDM [28]. However, we used a mean dose of 1080 mg/day. Rutkowski et al [29] reported recently that serum *N*-methyl-2-pyridine-5-carboxamide (2-PY), an end product of NAD degradation, was elevated in hemodialysis patients and that nicotinamide inhibited PARP-1 activity in vitro. In the present study, however, intracellular NAD levels in hemodialysis patients (9.3 $nmol/10^5$ erythrocytes) were nearly the same as levels in healthy subjects (9.0 $nmol/10^5$ erythrocytes) [12], suggesting that intracellular 2-PY concentrations may not be increased in chronic renal failure patients. Nicotinamide is a well-known inhibitor of PARP-1. Activation of PARP-1 has been implicated in the pathogenesis of stroke, myocardial ischemia, diabetes, cardiovascular dysfunction, shock, central nervous system injury, and various other forms of inflammation. Therefore, inhibition of PARP-1 by pharmacological agents may prove useful in the treatment of these diseases. Although blood NAD concentrations were increased up to 13.2 $nmol/10^5$ erythrocytes after nicotinamide administration in our study, it is not clear whether this concentration of intracellular NAD can inhibit PARP-1 activity. Further studies on adverse effects of long-term administration of nicotinamide are needed.

CONCLUSION

Nicotinamide may provide an alternative for controlling hyperphosphatemia and hyperparathyroidism in hemodialysis patients.

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