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Effects of low-dose niacin on dyslipidemia and serum phosphorus in patients with chronic kidney disease

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Abstract

Background: Niacin supplementation improves dyslipidemia and lowers serum phosphorus levels in patients with chronic kidney disease (CKD). We evaluated whether low-dose niacin supplementation can improve dyslipidemia, lower serum phosphorus levels, and be administered with a low frequency of adverse effects in patients with CKD.

Methods: We retrospectively analyzed the clinical records of patients with CKD who had taken niacin from January 2009 to June 2011. We excluded patients with CKD stage 1 and 5. We then enrolled 31 patients with CKD who had taken niacin at a fixed dose of 500 mg/day for 6 months. We also randomly selected 30 patients with CKD who had been taking statin for 9 months as a control group.

Results: Among the 34 patients with CKD who were prescribed niacin, five (14%) complained of adverse effects, and three (8%) discontinued niacin. The proportion of patients in the niacin group who had been taking a statin or omega-3 fatty acids was 67.7% and 48.8%, respectively. In the niacin group, high-density lipoprotein cholesterol level was significantly increased and triglyceride level was significantly decreased at 12 and 24 weeks compared with baseline levels ($P < 0.05$). In the niacin group, phosphorous level ($P < 0.05$) was significantly decreased, and glomerular filtration rate (GFR) was significantly increased ($P < 0.05$) at 24 weeks compared with baseline values.

Conclusion: Low-dose niacin had a low frequency of adverse effects and also improved dyslipidemia, lowered serum phosphorus level, and increased GFR in patients with CKD. Further studies are needed to evaluate the long-term effects of low-dose niacin for renal progression of CKD.

Introduction

Niacin is a water-soluble vitamin, which is critical for cellular metabolism [1]. As a broad-spectrum drug that can affect lipid levels, niacin reduces levels of total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol, while increasing high-density lipoprotein (HDL) cholesterol levels when administered at a dose of 1–3 g/day [2–4]. Niacin

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also lowers serum phosphorus levels in patients with chronic kidney disease (CKD), dyslipidemia, and diabetes mellitus [4,5]. Furthermore, niacin plays a key role in cardiovascular diseases and cardiovascular-related mortality by modifying both dyslipidemia and phosphorus levels [6–9].

Despite these positive roles of niacin, physicians hesitate to prescribe niacin because of its various adverse effects such as hot flushing, liver function test disruption, and thrombocytopenia. Although some of these adverse effects are slight and easily controlled by symptomatic care, some effects such as hot flushing necessitate cessation of niacin administration [3,4]. Therefore, it is necessary to judge whether the benefits of low-dose niacin administration outweigh its adverse effects.

In this study, we retrospectively analyzed whether low-dose niacin supplementation improves dyslipidemia and lowers serum phosphorus levels with less adverse effects in patients with CKD.

Methods

Study population

We retrospectively analyzed the clinical records of 45 patients with CKD who had maintained dosing with an extended release formulation of fixed low-dose (500 mg) niacin (Niaspanor; Merck KGaA, Darmstadt, Germany) at Dong-A University Hospital between January 2009 and June 2011. We excluded eight patients with CKD stage 1 and 5. We also excluded three patients who had additional prescriptions such as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statin) or omega-3 fatty acid (FA) during the investigational period. Among the 34 enrolled patients, we additionally excluded three patients who had quit taking niacin due to adverse drug reactions. Finally, we enrolled 31 patients with CKD who had taken niacin at a fixed dose of 500 mg/day for 6 months and analyzed 34 patients for adverse effects. Niacin was prescribed for reducing triglyceride and increasing HDL levels in the enrolled 31 patients with CKD. There were no patients who were hospitalized during the investigational period in the niacin group. We randomly selected 60 patients with CKD who had been taking a statin for 9 months or more as a control group. We defined baseline point of control group as the point after using statin for 3 months because the control group should be having controlling levels of cholesterol similar to the niacin group. We excluded 14 patients with CKD stage 1 and 5. We also excluded five patients whose baseline HDL level was >40 mg/dL in men, and >50 mg/dL in women so as to match with the niacin group. We excluded three more patients who were hospitalized and seven who had prescription changes such as addition of omega-3 FA during the investigational period. Finally, we enrolled 30 patients with CKD who had been taking a statin for 9 months or more as the control group.

Laboratory tests and clinical findings

We defined baseline as the first prescription point of niacin in the niacin group and as the point after receiving a 3-month statin prescription in the control group. The following

Table 1. Baseline characteristics of the study populations

	Control group ($n=30$)	Niacin group ($n=31$)	*P*
Age (y)	59.3 ± 17.8	55.8 ± 14.8	0.245
Male gender (%)	19 (61.3)	12 (38.7)	0.074
Smoking history (%)	9 (30.0)	4 (12.9)	0.127
Body mass index (kg/m^2)	24.6 ± 3.8	23.9 ± 2.8	0.564
Systolic blood pressure (mmHg)	129.4 ± 25.0	124.8 ± 20.8	0.613
Diastolic blood pressure (mmHg)	77.1 ± 15.4	77.3 ± 12.0	0.760
Diabetes (%)	13 (43.3)	10 (32.3)	0.434
Coronary artery disease (%)	7 (23.3)	7 (22.6)	1.000
Peripheral artery disease (%)	9 (30.0)	5 (16.1)	0.235
Cerebrovascular disease (%)	9 (30.0)	5 (16.1)	0.286
Chronic kidney disease			
Stage 2 (%)	11 (36.7)	12 (38.7)	–
Stage 3 (%)	13 (43.3)	13 (41.9)	–
Stage 4 (%)	6 (20.0)	6 (19.4)	–
Medications			
Calcium channel blocker (%)	16 (53.3)	12 (38.7)	0.309
Beta-blocker (%)	10 (16.4)	10 (16.4)	1.000
Furosemide (%)	11 (36.7)	12 (38.7)	1.000
Spironolactone (%)	3 (10)	4 (12.9)	1.000
ACEI (%)	14 (46.7)	5 (16.1)	0.013
ARB (%)	19 (63.3)	19 (61.3)	1.000
Digoxin (%)	3 (10)	4 (12.9)	1.000
Aspirin (%)	8 (26.7)	8 (25.8)	1.000
Clopidogrel (%)	14 (46.7)	8 (25.8)	0.114
Allopurinol (%)	2 (6.7)	6 (19.4)	0.255
Omega-3 fatty acid (%)	11 (36.7)	15 (48.4)	0.440
Statin (%)	30 (100)	21 (67.7)	0.001
Fluvastatin (%)	12 (40)	9 (42)	–
Pravastatin (%)	9 (30)	7 (33)	–
Atorvastatin (%)	6 (20)	4 (19)	–
Rosuvastatin (%)	3 (10)	1 (6)	–
Hypertension medication count	2.5 ± 1.1	2.0 ± 1.4	0.198

Data are expressed as mean ± SD.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

demographic characteristics and comorbidities were collected: age, gender, smoking history, body mass index, and underlying comorbidities including diabetes mellitus, coronary artery disease, peripheral arterial disease, and cerebrovascular disease. We defined coronary artery disease as those with previous diagnosis by coronary angiography, echocardiography, electrocardiography changes, elevated levels of troponin I, or myocardial single-photon emission computed tomography scans. We defined cerebrovascular disease as those with previous ischemic stroke and brain hemorrhages diagnosed by clinical manifestation and magnetic resonance imaging. We defined peripheral arterial disease as those with previous amputation of extremities or diagnosis by Doppler ultrasonography of extremities.

We investigated systolic and diastolic blood pressures at baseline and after 12 and 24 weeks. We analyzed the following laboratory findings at the same intervals: hemoglobin, platelet count, calcium, phosphorus, blood urea nitrogen, creatinine, glomerular filtration rate (GFR), albumin, uric acid, aspartate aminotransferases, alanine aminotransferase, alkaline phosphatase (ALP), total cholesterol, triglyceride, HDL, LDL, C-reactive protein, HbA1c, random urine protein-to-creatinine ratio, and random urine microalbumin-to-creatinine ratio. We could not investigate serum parathyroid hormone, urine sodium, and urine phosphorus levels because these data were missing in most of the enrolled patients. GFR was estimated using the modification of diet in a renal disease study formula. The patients who were taking calcium-channel blockers, beta blockers, nitrates, furosemide, spironolactone, digoxin, low-dose aspirin, clopidogrel, allopurinol, omega-3 FA (Omacor; Pronova, Sandefjord, Norway), statins, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin II receptor blockers (ARBs) during the follow-up period were noted.

Statistical analysis

Descriptive statistics that used means and standard deviations are presented as continuous variables, with the exceptions of the urine albumin-to-creatinine ratio and urine protein-to-creatinine ratio, which used means and standard error. The nonparametric Mann–Whitney *U* test was used to compare baseline data between the control and the niacin groups. The Fisher exact test was used to compare categorical data between the two groups. The nonparametric Wilcoxon rank-sum test was applied to compare baseline data with 12- and 24-week data. A P value ≤ 0.05 was considered to be statistically significant for all the tests. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of study populations

The baseline characteristics were similar between the two groups (Tables 1 and 2). The mean age, lipid profiles, phosphorous levels, creatinine, and GFR were not significantly different between the niacin group and the control group.

In the niacin group, the percentage of patients already treated with a statin, omega-3 FA, both niacin and omega-3 FA, and neither of the medications was 67.7%, 48.8%, 38.7%, and 19.6%, respectively. The percentage of patient taking omega-3 FA was 36.7% in the control group. The percentage of patient taking ACEI in the niacin group was significantly lower than that in the control group, but administration of ARB medication was similar between the two groups. The percentage of patients taking both an ACEI and an ARB in the niacin group was significantly lower than that in the control group (6.5% vs. 26.7%, $P=0.043$).

Adverse effects of niacin

Among the 34 patients with CKD who were prescribed niacin, five patients (14%) complained of adverse effects of niacin and three patients (8%) discontinued niacin. Three patients (8%) experienced flushing, one had flushing with itching, and another

Table 2. Baseline laboratory findings of study populations

	Control group ($n=30$)	Niacin group ($n=31$)	P
Hemoglobin (g/dL)	12.9 ± 2.2	12.9 ± 1.8	0.729
Platelet count ($10^3/\mu L$)	216.0 ± 65.2	231.5 ± 56.9	0.264
Calcium (mg/dL)	9.0 ± 0.4	9.1 ± 0.5	0.439
Phosphorus (mg/dL)	3.6 ± 0.5	3.7 ± 0.6	0.406
Calcium–phosphorus product (mg^2/dL^2)	32.3 ± 4.8	33.8 ± 5.8	0.341
Blood urea nitrogen (mg/dL)	24.3 ± 11.0	22.0 ± 11.1	0.348
Creatinine (mg/dL)	1.6 ± 0.7	1.5 ± 0.7	0.405
GFR ($mL/min/1.73m^2$)	51.0 ± 19.6	53.4 ± 22.0	0.692
Albumin (g/dL)	4.2 ± 0.3	4.3 ± 0.3	0.174
Uric acid (mg/dL)	7.0 ± 1.6	6.8 ± 2.0	0.862
SGOT (IU/L)	22.3 ± 8.0	21.5 ± 8.9	0.366
SGPT (IU/L)	23.0 ± 11.5	20.9 ± 11.4	0.347
Alkaline phosphatase (IU/L)	241.4 ± 99.2	254.9 ± 71.2	0.306
Total cholesterol (mg/dL)	182.4 ± 48.2	178.5 ± 34.2	0.851
Triglyceride (mg/dL)	239.4 ± 192.1	221.1 ± 112.9	0.484
HDL (mg/dL)	39.3 ± 7.4	37.0 ± 8.2	0.079
LDL (mg/dL)	98.5 ± 33.0	93.5 ± 26.7	0.479
C-reactive protein (mg/dL)	0.1 ± 0.1	0.3 ± 0.6	0.603
HbA1c (%)	6.8 ± 2.1	7.0 ± 1.7	0.593
RU P/C ratio (g/g)	1.3 ± 0.4	1.1 ± 0.5	0.832
RU A/C ratio (mg/g)	209.4 ± 70.5	227.1 ± 54.9	0.872

Data are expressed as mean ± SD, except random urine P/C ratio and random urine A/C ratio, which were expressed as mean ± SE.
GFR, MDRD-estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MDRD, modification of diet in a renal disease study; RU A/C ratio, random urine albumin-to-creatinine ratio; RU P/C ratio, random urine protein-to-creatinine ratio; SGOT, serum glutamic oxaloacetic transaminase (aminotransferases); SGPT, serum glutamic pyruvic transaminase (alanine aminotransferase).

Table 3. Changes in biochemical data by niacin supplementation

	Control group (baseline)	Control group (24 wks)	Niacin group (baseline)	Niacin group (24 wks)
Systolic BP (mmHg)	129.4 ± 2 5.0	124.6 ± 15.2	124.8 ± 20.8	124.5 ± 18.0
Diastolic BP (mmHg)	77.1 ± 15.4	77.6 ± 12.4	77.3 ± 12.0	72.3 ± 17.8
Hemoglobin (g/dL)	12.9 ± 2.2	12.7 ± 2.2	12.9 ± 1.8	12.8 ± 1.8
Platelet count (10^3/μL)	216.0 ± 65.2	219.0 ± 60.9	231.5 ± 56.9	221.0 ± 62.6*
Calcium (mg/dL)	9.0 ± 0.4	8.8 ± 0.4*	9.1 ± 0.5	9.0 ± 0.4
Phosphorus (mg/dL)	3.6 ± 0.5	3.6 ± 0.6	3.7 ± 0.6	3.2 ± 0.7*
Calcium–phosphorus product (mg^2/dL^2)	32.3 ± 4.8	32.1 ± 5.3	33.8 ± 5.8	28.9 ± 6.0*
Blood urea nitrogen (mg/dL)	24.3 ± 11.0	24.5 ± 11.8	22.0 ± 11.1	23.1 ± 6.5
Creatinine (mg/dL)	1.6 ± 0.7	2.0 ± 2.0	1.5 ± 0.7	1.4 ± 0.7
GFR (mL/min/1.73 m^2)	51.0 ± 19.6	52.0 ± 22.2	53.4 ± 22.0	56.6 ± 24.3*
Albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.4	4.3 ± 0.3	4.4 ± 0.2
Uric acid (mg/dL)	7.0 ± 1.6	7.4 ± 1.6	6.8 ± 2.0	6.4 ± 1.8*
SGOT (IU/L)	22.3 ± 8.0	23.1 ± 8.6	21.5 ± 8.9	23.5 ± 10.7
SGPT (IU/L)	23.0 ± 11.5	24.9 ± 16.1	20.9 ± 11.4	22.7 ± 17.4
Alkaline phosphatase (IU/L)	241.4 ± 99.2	246.7 ± 66.3	254.9 ± 71.2	274.4 ± 82.2*
Total cholesterol (mg/dL)	182.4 ± 48.2	173.1 ± 47.9	178.5 ± 34.2	162.0 ± 28.5
Triglyceride (mg/dL)	239.4 ± 192.1	173.0 ± 101.9*	221.1 ± 1 12.9	168.4 ± 100.2*
HDL (mg/dL)	39.3 ± 7.4	43.2 ± 9.1*	37.0 ± 8.2	42.6 ± 8.2*
LDL (mg/dL)	98.5 ± 33.0	91.3 ± 33.9	93.5 ± 26.7	87.2 ± 24.7
C-reactive protein (mg/dL)	0.1 ± 0.1	0.1 ± 0.1	0.3 ± 0.6	0.3 ± 0.5
HbA1c	6.8 ± 2.1	6.9 ± 1.5	7.0 ± 1.7	6.6 ± 0.8
RU P/C ratio (g/g)	1.3 ± 0.4	1.4 ± 0.4	1.1 ± 0.5	1.2 ± 0.5
RU A/C ratio (mg/g)	209.4 ± 70.5	169.8 ± 62.0	227.1 ± 54.9	195.5 ± 63.3

* $P < 0.05$ (mean values are significantly different from baseline).
Data are expressed as mean ± SD.
BP, blood pressure; GFR, MDRD-estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MDRD, modification of diet in a renal disease study; RU A/C ratio, random urine albumin-to-creatinine ratio; RU P/C ratio, random urine protein-to-creatinine ratio; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

had anorexia. Two patients (5%) who experienced mild flushing found the side effect tolerable and continued to take niacin throughout the 24-week period without cessation. The mean platelet counts were significantly decreased at 12 and 24 weeks in the niacin group, but the counts remained within normal ranges.

Changes in biochemical data and clinical findings

There were no changes in statin dose, ACEI, or ARB medications during the investigational period in either the niacin group or the control group. There were no significant changes in blood pressure, creatinine, LDL cholesterol, C-reactive protein, random urine protein-to-creatinine ratio, and random urine microalbumin-to-creatinine ratio in both groups (Table 3).

HDL cholesterol was significantly increased at 12 ($P=0.003$) and 24 weeks ($P<0.001$) compared with baseline in the niacin group, but HDL cholesterol was significantly increased at only 24 weeks ($P=0.001$) compared with baseline in the control group (Fig. 1A). Triglyceride level was significantly decreased at 12 ($P=0.016$) and 24 weeks ($P=0.001$) compared with baseline in the niacin group, but was significantly decreased at only 24 weeks ($P=0.007$) compared with baseline in the control group (Fig. 1B).

Serum phosphorus levels ($P=0.006$) and calcium–phosphorus product ($P=0.001$) were significantly decreased at 24 weeks compared with baseline in the niacin group, but there was no change in serum phosphorus levels (Fig. 1C) and calcium–phosphorus product at 24 weeks compared with baseline in the control group. GFR ($P=0.016$) was significantly increased at 24 weeks compared with baseline in the niacin group, although serum creatinine was not significantly changed in the niacin group (Fig. 1D). GFR was significantly increased (55.4 ± 24.5 mL/min/1.73 m^2 vs. 62.8 ± 28.3 mL/min/1.73 m^2, $P=0.016$) and serum creatinine was significantly decreased (1.5 ± 0.8 mg/dL vs. 1.3 ± 0.7 mg/dL, $P=0.021$) at 24 weeks compared with baseline in the niacin subgroup without statin medication. There were no significant changes in GFR and serum creatinine at 24 weeks compared with baseline in the niacin subgroup taking statin. Uric acid level was significantly decreased ($P=0.033$) and ALP level was significantly increased ($P=0.019$) at 24 weeks compared with baseline in the niacin group.

Discussion

In this study, significant changes in HDL, triglyceride, and phosphorus levels were found by administering low-dose niacin in patients with CKD. In addition, the frequency and severity of the adverse effects were lower than in previous studies, which used routine doses of niacin in patients with CKD. The prevalence rate of adverse effects was 14% and compliance rate was 92% for a 6-month period in this study. Recent studies using niacin showed that a typical starting dose of niacin was 500 mg or 1 g/day, and the dose was advanced in phases to reach a given target dose to accommodate the drug's adverse effects [3,4,10,11]. Compliance rates in these studies were reported to be 57–80% [11–13]. Thrombocytopenia is one of the adverse effects caused by niacin supplementation. In our study, platelet count was significantly decreased after 12 weeks, but remained in the normal range. We suspect that only a mild decrease of platelet count rather than severe thrombocytopenia may be caused by administration of low-dose niacin. In addition, there were no specific adverse effects in 38.7% of patients who were managed with triple antilipid therapy (statin, omega-3 FA, and low-dose niacin). Therefore, our study supports that low-dose niacin (500 mg/day) administered for control of dyslipidemia is a relatively safe and effective dose in patients with CKD stage 2-4.

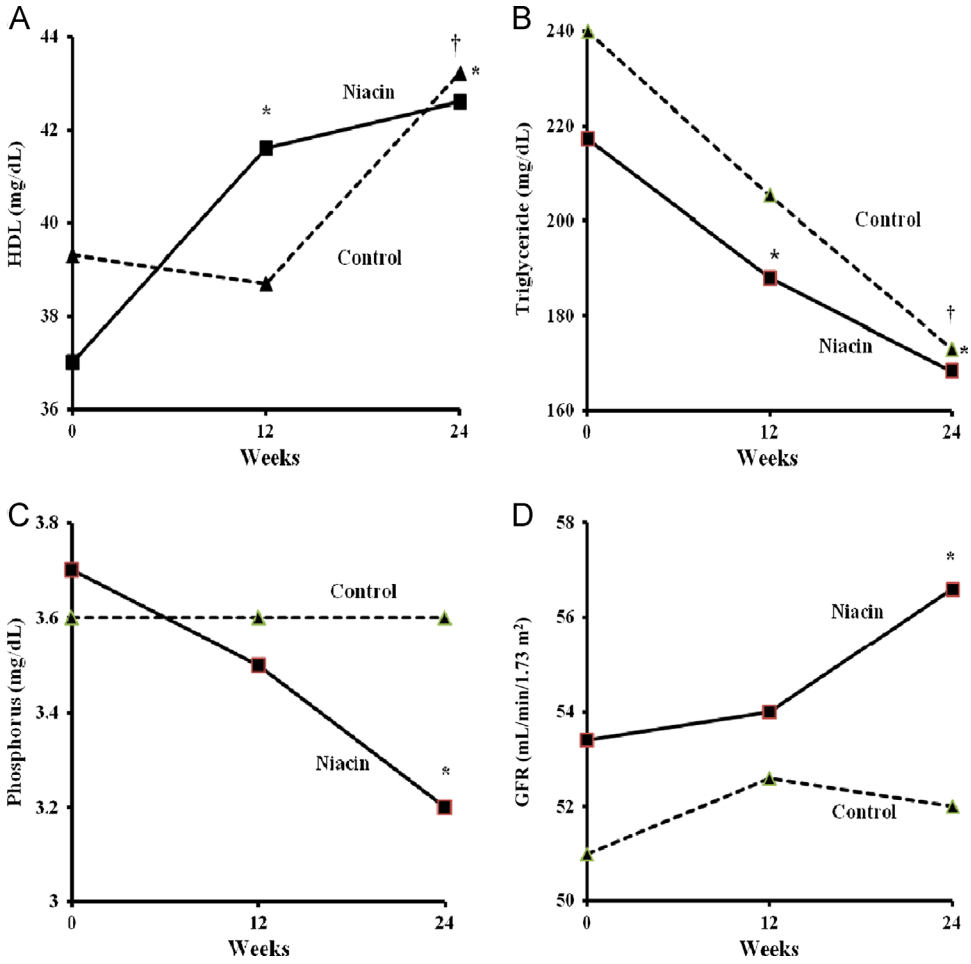

Figure. 1. Changes in the levels of HDL (A), triglyceride (B), phosphorus (C), and GFR (D) after niacin administration. GFR, glomerular filtration rate; HDL, high-density lipoprotein cholesterol. *$P < 0.05$ (mean values are significantly different from baseline in niacin group). †$P < 0.05$ (mean values are significantly different from baseline in control group).

Management of dyslipidemia by increasing HDL and decreasing triglyceride levels was also noted in this study by administering the low-dose niacin. It is not clear as to why a low dose of niacin effectively controls dyslipidemia in patients with CKD. Results of a previous study showed that treatment with a low dose of pravastatin showed primary prevention of cardiovascular disease in a Japanese population [14]. Therefore, further studies are necessary to confirm the effect of low-dose niacin in other ethnic populations, such as a cohort of Western population.

Niacin is now known to inhibit sodium/phosphorous co-transporters in both renal proximal tubules and intestinal brush borders [15,16]. Hyperphosphatemia is one of the main features of CKD-mineral and bone disorder and is linked to cardiovascular risk as well as bone disease [17]. The hyperphosphatemic milieu may promote vascular calcification through cellular changes in vascular smooth muscle cells [18]. Therefore, a low dose of niacin may be helpful not only for the control of dyslipidemia, but also for the early prevention of hyperphosphatemia in patients with CKD. Meanwhile, a comparison with baseline revealed increased ALP level after niacin supplementation in our study. Increased ALP level after niacin supplementation was also found in animal and human studies [19,20]. It is unknown which source of ALP was increased, but the effect may have been a compensatory response caused by decreased phosphorous levels. In contrast, decreased ALP level after niacin supplementation was shown in hemodialysis patients with hyperphosphatemia [21,22]. Further studies will be needed to evaluate the effects of niacin on ALP according to phosphorous and parathyroid hormone levels.

In this study, GFR was significantly improved by niacin supplementation after 24 weeks in patients with CKD. In addition, significantly decreased level of serum creatinine was found after 24 weeks in the subgroup treated with niacin and without statin. Therefore, the renoprotective effect of niacin was not related with statin co-administration although the combination of niacin and statin showed cardioprotective effect in another study [23]. Recently, niacin administration was reported to improve GFR and kidney function in 5/6 nephrectomized rat model [24]. This study may explain the improved renal function because niacin improves renal tissue lipid metabolism, oxidative stress, and inflammation. However, further prospective studies are necessary to confirm the effect of niacin on the GFR in patients with CKD.

An increase of serum uric acid levels could be regularly seen during treatment with niacin [3]. However, decreased serum uric acid levels were found in the niacin group of our study. We partially explain this result based on the slightly increased prescription rate for allopurinol and increased GFR in the niacin group.

Interpretation of the current study in patients with CKD is limited, because the data were derived from a small sample

size and the study employed a retrospective design. Despite these limitations, this study is the first report showing that administration of niacin at a dose of 500 mg/day improves several clinical findings in patients with CKD.

In conclusion, low-dose niacin (500 mg/day) produced a low frequency of adverse effects and also improved dyslipidemia, lowered serum phosphorus levels, and increased GFR in patients with CKD. Further studies are necessary to evaluate the long-term effects of low-dose niacin for renal progression of CKD.

Conflict of interest

No conflict of interest has been declared.

Acknowledgments

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