INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

# Renal and Vascular Protective Effects of Ezetimibe in Chronic Kidney Disease

Tatsuyori Morita[1], Satoshi Morimoto[1,2], Chikara Nakano[1], Rika Kubo[1], Yoshiki Okuno[1], Maiko Seo[1], Kazunori Someya[1], Mitsutaka Nakahigashi[1], Hiroko Ueda[1], Nagaoki Toyoda[1], Makiko Kusabe[1], Fusakazu Jo[1], Nobuyuki Takahashi[1], Toshiji Iwasaka[1] and Ichiro Shiojima[1]

## Abstract

**Objective** Dyslipidemia is a risk factor for not only cardiovascular diseases (CVD), but also chronic kidney disease (CKD). Ezetimibe, a cholesterol absorption inhibitor, lowers cholesterol levels by inhibiting both extrinsic and intrinsic cholesterol absorption via the gastrointestinal duct. However, very few studies have examined its efficacy and safety for patients with dyslipidemia complicated with CKD.

**Methods** Thirty-seven dyslipidemic patients (low density lipoprotein cholesterol (LDL-C) levels ≥120 mg/dL) complicated with CKD were given ezetimibe (10 mg/day) for twenty-four weeks. The efficacy and safety of the therapy, including the anti-atherosclerotic and renal protective effects, were then examined.

**Results** Significant decreases were observed in the levels of LDL-C (158.9±26.9 mg/dL→123.0±31.8 mg/dL; $p<0.0001$), remnant-like lipoprotein cholesterol (9.3±5.3 mg/dL→7.3±3.8 mg/dL; $p<0.05$) and lipoprotein (a) (22.0±16.1 mg/dL→16.4±11.0 mg/dL; $p<0.01$). The estimated glomerular filtration rate did not change, but the urine protein to creatinine ratio decreased significantly (1,107.3±1,454.2 mg/gCre→732.1±1,237.8 mg/gCre; $p<0.05$). No changes were observed in the carotid intima media thickness, but the brachial-ankle pulse wave velocity decreased significantly (1,770.4±590.3 cm/sec→1,702.5±519.9 cm/sec; $p<0.05$). No adverse events were observed.

**Conclusion** Ezetimibe can be safely administered even to patients with CKD. The results of this study indicate that ezetimibe may provide some renal protection and suppress the complications of CVD in CKD patients.

**Key words:** chronic kidney disease, cardiovascular disease, ezetimibe, brachial-ankle pulse wave velocity, intima-media thickness

**(Intern Med 53: 307-314, 2014)**
**(DOI: 10.2169/internalmedicine.53.0649)**

## Introduction

In 2004, Keith et al. reported the results of a three-year prospective follow-up observation of 27,998 subjects with chronic kidney disease (CKD), noting that the number of subjects who died from cardiovascular disease (CVD) was far greater than the number of subjects who had shifted to renal replacement therapy due to impaired renal function (1). They pointed out that the issue for these CKD subjects was not a shift to end-stage renal dysfunction, but cardiovascular death. The risk of death from myocardial infarction in patients undergoing dialysis is reportedly ten to thirty times higher than that in the general population (2). An analysis of the onset of CVD categorized by renal function in one million twelve thousand residents twenty years of age or older around San Francisco, California, during the three-year follow-up, revealed that the risk of death from CVD increased step-wise with a decrease in glomerular filtration rate (GFR) before dialysis was started (3). CKD itself is

[1]The Second Department of Internal Medicine, Kansai Medical University, Japan and [2]Department of Medicine II, Endocrinology and Hypertension, Tokyo Women's Medical University, Japan
Received for publication March 29, 2013; Accepted for publication August 18, 2013
Correspondence to Dr. Satoshi Morimoto, smorimoto@endm.twmu.ac.jp

now recognized world-wide as a risk factor for the development of cardiovascular disease (4).

CKD is often complicated with dyslipidemia (3). Moreover, dyslipidemia is not only a major risk factor for CVD, but also for CKD, so lipid-lowering drugs are considered to be effective for suppressing the onset or development of CKD. Recently, large-scale clinical studies have successively shown the usefulness of 3-hydroxy-3-methy-glutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors (statins) (5, 6). The statins lower low-density lipoprotein cholesterol (LDL-C) levels by selectively and competitively inhibiting HMG-CoA reductase, which is a rate-limiting enzyme of the cholesterol biosynthesis pathway in the liver, and by suppressing cholesterol biosynthesis from acetate. This decreases the intrahepatic cholesterol level, and to compensate for the decrease, induces the expression of the LDL receptors. Through these LDL receptors, the liver uptakes more LDL containing a high level of cholesterol, and the serum cholesterol level is decreased (7). However, some patients with impaired renal function who had been administered a statin have experienced the onset of rhabdmyolysis, so caution is required when administering statins to patients with renal dysfunction.

Ezetimibe, which is a cholesterol absorption inhibitor, induces the expression of the LDL receptors and lowers the serum cholesterol levels by inhibiting the absorption of both extrinsic dietary cholesterol (from food intake) and intrinsic cholesterol (biologically synthesized in the liver and then ectopically excreted into the duodenum) via the digestive duct (8, 9). However, very few studies have examined its efficacy and safety for patients with dyslipidemia complicated with CKD. Whether or not ezetimibe has a positive effect on the onset of CVD events or suppresses the development of CVD is an issue that requires further study.

In this study, we examined ezetimibe's lipid lowering action, its impact on renal function and atherosclerosis, and its safety for dyslipidemic patients complicated with CKD.

## Materials and Methods

### Study subjects

From July 2007 to July 2009, CKD patients being treated in the Division of Nephrology, Department of Internal Medicine of the Kansai Medical University Hirakata Hospital who had LDL-C levels of 120 mg/dL or higher were enrolled. CKD was defined according to the guidelines of the Kidney Disease Outcome Quality Initiative (10), as patients with confirmed urinary abnormalities, the presence of renal dysfunction (confirmed by diagnostic imaging, or hematological or pathological examinations), or a persistent GFR <60 mL/min/1.73 $m^2$ for three months or longer. The GFR was calculated using the estimated glomerular filtration rate: eGFR (mL/min/1.73 $m^2$)=194×$age^{-0.287}$×$Cr^{-1.094}$ (×0.739 if female), as described in the project "Equations for estimating GFR from serum creatinine in Japan" by the Committee to Develop Measures Against CKD of the Japanese Society of Nephrology (11). The exclusion criteria are shown in Table 1.

**Table 1. Patients' Selection and Exclusion Criteria**

| |
|---|
| Selection criteria |
| Chronic kidney disease |
| Low-density lipoprotein cholesterol levels of 120 mg/dL or higher |
| Exclusion criteria |
| Undergoing dialysis |
| Triglyceride levels of 500 mg/dL or higher |
| Moderate or severe hepatic disease |
| Onset of myocardial infarction within the previous twelve weeks |
| Onset of heart failure within the previous twelve weeks |
| Onset of cerebrovascular diseases within the previous twelve weeks |
| Being treated with steroid or immunosuppressive medications |
| Being treated with antidyslipidemic agents |

### Study protocol

Study subjects were given ezetimibe (10 mg) once daily for twenty-four weeks, and no other dyslipidemic agents were added. Moreover, the anti-hypertensive, hypoglycemic and anti-platelet aggregation agents were not changed or added.

The height, weight, waist circumference, blood pressure and pulse rate were measured before and after the study, and compared. The LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels were quantified before the study began and at four, eight, 12, 16, 20 and 24 weeks after the start of ezetimibe administration, and the groups were compared at the individual time points. The aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine phosphokinase (CPK) levels were quantified before the study began and at four, eight, 12, 16, 20 and 24 weeks after the start of ezetimibe administration, and the presence or absence of side effects were observed.

Remnant-like lipoprotein cholesterol (RLP-C), lipoprotein a (Lp(a)), Hemoglobin A1c (HbA1c), high sensitivity C-reactive protein, lathosterol (as a cholesterol synthesis marker) and sitosterol and campesterol (as cholesterol absorption markers) were measured before the study began and at twenty-four weeks after the start of ezetimibe administration, and the measurements were compared. In addition, the urine protein to creatinine ratio, blood urea nitrogen (BUN), serum creatinine level, eGFR, brachial-ankle pulse wave velocity (baPWV) and carotid intima-media thickness of the carotid artery (IMT) (as markers for arterial stiffness) were also quantified before the study began and twenty-four weeks after the start of ezetimibe administration, and the results were compared.

The study was approved by the Ethics Committee of Kansai Medical University. Written informed consent was obtained from all individuals before their participation in the trial. The authors had full access to the data and take responsibility for their integrity. All of the authors have read the paper and agreed with the contents.

The waist circumference was measured at the height of the naval while the patient was standing and after exhaling. The clinical blood pressure and pulse rate were measured using an automated oscillometric sphygmomanometer (MPV 3301, Nihon Kohden, Tokyo, Japan) between 11 AM and noon while the patient was seated and after at least five minutes of rest. Three measurements were taken at two-minute intervals. The average of the second and third readings was used for all analyses.

The total protein and creatinine concentrations in the urine from spot urine samples were quantified by the standardized assessment methods at our clinical laboratory center.

Blood samples were obtained by noon after the subjects had fasted for at least twelve hours. The LDL-C, HDL-C, TG, AST, ALT, CPK, HbA1c, high-sensitivity CRP, BUN and creatinine levels were quantified using the standardized assessment methods at our clinical laboratory center. An external laboratory (SRL, Inc., Tokyo, Japan) quantified the RLP-C and Lp(a) using an enzyme-linked immune sorbent assay and latex agglutination-turbidimetric immunoassay, respectively, and also quantified the lathosterol, sitosterol and campesterol using gas chromatography.

The ABI and baPWV values were measured using a volume-plethysmographic apparatus PWV/ABI (Omron Healthcare Co., Ltd, Kyoto, Japan) in accordance with the methodology described previously (12, 13). The lower and higher values were accepted as the ABI and baPWV values, respectively

Carotid ultrasound examinations of the common carotid artery, bulb and internal carotid artery were performed bilaterally using the Prosound α10 ultrasound system (ALOKA, Tokyo, Japan). The examinations were conducted while the subjects were in a supine position with the head turned 45° from the site being scanned. Both carotid arteries were scanned longitudinally in order to visualize the IMT in the far wall of the artery, and the maximum IMT was assessed.

### Safety

Adverse events consisted of the presence or absence of abnormalities of associated symptoms, such as muscle pain, or overt abnormalities of the clinical laboratory examination results, which were defined as levels three times higher than the upper threshold of the standardized levels for CPK, AST and ALT.

### Statistical analyses

Paired Student's *t*-tests were used to determine the significance of differences between values before the study began and 24 weeks after ezetimibe treatment. The LDL-C, HDL-C and TG levels before the study began and at four, eight, 12, 16, 20 and 24 weeks after the start of ezetimibe administration were examined using a one-way repeated measures analysis of variance (ANOVA), and the degree of change in the urinary protein excretion was compared among the CKD stages using a one-way factorial ANOVA. The correlation between two variables was examined using a linear regression analysis. The data are shown as the mean values ± SD, and differences were considered to be statistically significant at values of $p<0.05$.

## Results

### Patients

The characteristics of the study subjects are shown in Table 2. Thirty-seven patients were enrolled in the study (15 men/22 women). The average age was 62.3±11.3 years. The number of patients in each stage of CKD is also listed in the Table 2.

### Clinical and laboratory data

### Lipid profiles

The levels of both HDL-C (57.9±19.2→57.3±16.1 mg/dL) and TG (168.1±92.6→150.6±87.6 mg/dL) showed no significant changes during the study (Table 2, Fig. 1A, B). The LDL-C levels showed a significant decrease four weeks after ezetimibe administration started, and the significant suppressive effect was maintained until the end of the twenty-four week study (158.9±26.9→123.0±31.8 mg/dL) (Table 2, Fig. 1A).

The levels of both RLP-C (9.3±5.3 mg/dL→7.3±3.8 mg/dL, $p<0.05$) and Lp(a) (22.0±16.1 mg/dL→16.4±11.0 mg/dL, $p<0.01$) were significantly lower after twenty-four weeks of ezetimibe administration (Fig. 2).

No changes were observed in the serum concentration of lathosterol, a marker for cholesterol biosynthesis, after twenty-four weeks of ezetimibe administration (2.2±2.1 mg/dL→2.1±1.6 mg/dL, *N.S.*). However, the serum concentrations of sitosterol and campesterol (markers for cholesterol absorption), were significantly lower twenty-four weeks after ezetimibe administration (sitosterol: 2.3±1.1 mg/dL→1.4±0.6 mg/dL, $p<0.005$) (campesterol: 3.9.±2.0 mg/dL→1.5±0.7 mg/dL, $p<0.001$) (Fig. 3).

### Renal function

Ezetimibe administration produced no significant changes in the markers for renal function, such as the HbA1c (5.6±0.9→5.5±0.4%), BUN (25.9±14.2→27.8±19.9 mg/dL), creatinine (1.5±0.9→1.6±1.0 mg/dL) and eGFR (43.9±23.8→42.5±23.1 mL/min. 1.73 $m^2$)(Table 2), but did lead to a significant decrease in the urine protein to creatinine ratio (1,073±1,454.2 mg/gCr→732.1±1,237.8 mg/gCr; $p<0.05$) (Fig. 4). The degree of change in the urine protein/creatinine ratio showed no significant correlation with the degree of change in the RLP-C levels ($r=0.043$, $p=0.8105$), but did correlate significantly and positively with the degrees of change in the LDL-C ($r=0.35$, $p=0.0419$) and LP(a) ($r=0.35$, $p=0.0420$) levels. There were no significant correlations between the changes in the urine protein to creatinine ratio and CKD stages ($p=0.6928$).

**Table 2. Patients' Characteristics**

| | Before treatment | Twenty four weeks after treatment |
|---|---|---|
| n | 37 | |
| Age (years old) | 62.3± 11.3 | |
| Gender (male/female) | 15/22 | |
| CKD stage n (male/female) | | |
| G1 | 2(1/1) | 2(1/1) |
| G2 | 3(1/2) | 5(2/3) |
| G3 | 17(7/10) | 15(6/9) |
| G4 | 12(5/7) | 11(4/7) |
| G5 | 3(1/2) | 4(2/2) |
| Diabetes mellitus (+/-) | 7/30 | 7/30 |
| Body mass index (kg/m$^2$) | 23.4± 3.6 | 23.1± 3.3 |
| Waist circumference (cm) | 83.0± 9.4 | 82.9± 9.5 |
| Systolic blood pressure (mmHg) | 122.9± 18.4 | 119.3± 12.6 |
| Diastolic blood pressure (mmHg) | 71.6± 12.1 | 69.2± 9.9 |
| Pulse rate (beats/min) | 77.9± 12.8 | 76.2± 12.4 |
| Low-density lipoprotein cholesterol (mg/dL) | 158.9± 26.9 | 123.0± 31.8 |
| High-density lipoprotein cholesterol (mg/dL) | 57.9± 19.2 | 57.3± 16.1 |
| Triglyceride (mg/dL) | 168.1± 92.6 | 150.6± 87.6 |
| Hemoglobin A1C (%) | 5.6± 0.9 | 5.5± 0.4 |
| C-reactive protein (mg/dL) | 0.32± 0.93 | 0.20± 0.40 |
| Asparatate aminotransferase (IU/L) | 21.4± 7.0 | 23.1± 6.7 |
| Alanine aminotransferase (IU/L) | 18.2± 11.0 | 21.0± 15.0 |
| Creatine phosphopkinase (IU/L) | 130.3± 67.6 | 145.7± 86.4 |
| Urine protein to creatinine ratio (mg/gCre) | 1,107± 1,454 | 732.1± 1,237.8 |
| Blood urea nitrogen (mg/dL) | 25.9± 14.2 | 27.8± 19.9 |
| Creatinine (mg/dL) | 1.5± 0.9 | 1.6± 1.0 |
| Estimated glomerular filtration rate (mL/min/1.73m$^2$) | 43.9± 23.8 | 42.5± 23.1 |

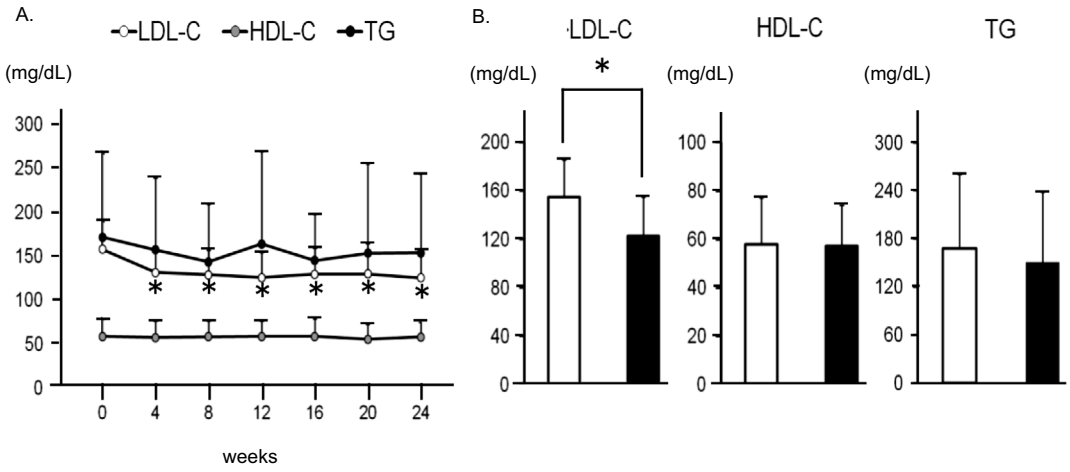


**Figure 1. The changes in the low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels. A: The changes during the time course; B: A comparison of the levels before and after twenty-four weeks of ezetimibe administration. *p<0.0001 before ezetimibe administration. Abbreviations: LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides**

### *Atherosclerosis*

With regard to the IMT assessed by carotid ultrasonography, no significant changes were observed during ezetimibe administration (0.82±0.38 mm→0.89±0.42 mm, *N.S.*). However, a significant decrease was seen in the baPWV after ezetimibe administration (1,770.4±590.3 cm/sec→1,702.5± 519.9 cm/sec, p<0.05) (Fig. 5). The degree of change in the baPWV (ΔbaPWV) did not correlate significantly with the degrees of change in the levels of LDL-C (ΔLDL-C; r=0.35,

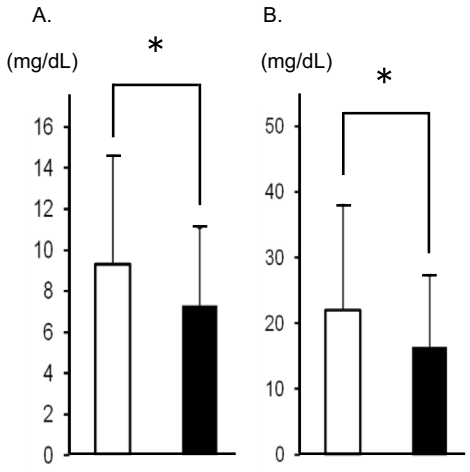


**Figure 2.** **The changes in remnant-like particle cholesterol (A) and lipoprotein a (B). Open columns: Before ezetimibe administration; Closed columns: After twenty-four weeks of ezetimibe administration. *p<0.05 compared with the levels before ezetimibe administration.**

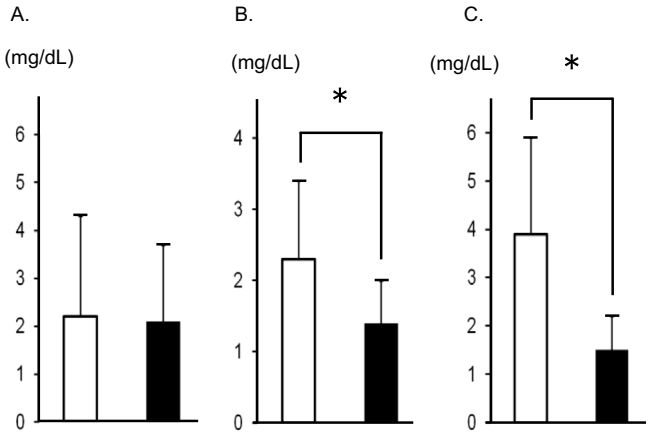


**Figure 3.** **The changes in cholesterol synthesis and absorption markers. A: Lathosterol, B: Sitosterol, C: Campesterol. Open columns: Before ezetimibe administration; Closed columns: After twenty-four weeks of ezetimibe administration. *p<0.005 compared with the levels before ezetimibe administration.**

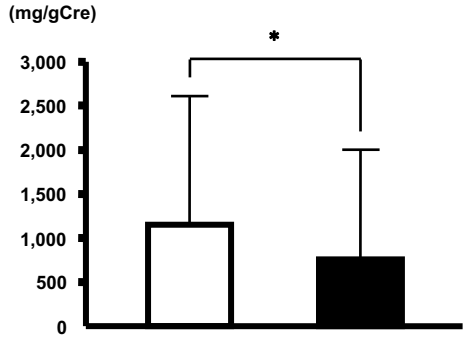


**Figure 4.** **The changes in the urinary protein/creatinine ratio. Open columns: Before ezetimibe administration; Closed columns: After twenty-four weeks of ezetimibe administration. *p<0.05 compared with the ratio before ezetimibe administration.**

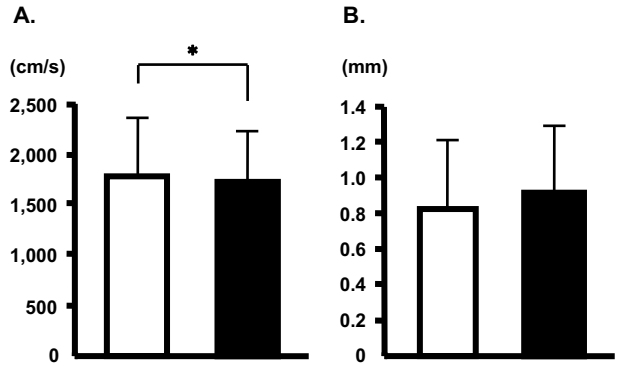


**Figure 5.** **The changes in the brachial-ankle pulse wave velocity (A) and intima-media thickness of the carotid artery (B). Open columns: Before ezetimibe administration; Closed columns: After twenty-four weeks of ezetimibe administration. *p<0.05 compared with the levels before ezetimibe administration.**

p=0.0419), RLP-C (ΔRLP-C; r=0.043, p=0.8105) or Lp(a) (ΔLp(a); r=0.35, p=0.0420), while the ΔbaPWV showed significant positive correlations with the degrees of change in the levels of sitosterol (r=0.689, p=0.0112) and campesterol (r=0.759, p=0.0028) (data not shown).

### *Adverse events*

During the study period, neither adverse events nor apparent associated symptoms were observed. No significant changes were observed in the levels of AST (post; 23.1±6.7 IU/L), ALT (post; 21.0±15.0 IU/L) or CPK (post; 145.7±86.4 IU/L), and no patient showed elevated levels of those markers that were three times or greater than the pre-study levels during the study period.

## Discussion

In this study, ezetimibe (10 mg/day) alone was given for twenty-four weeks to CKD subjects who had not undergone dialysis and were diagnosed with untreated dyslipidemia. As a result, the levels of LDL-C, RLP-C and LP(a), as well as sitosterol and campesterol (as markers for cholesterol absorption) were significantly decreased. Moreover, the urine protein to creatinine ratio and the baPWV were also significantly decreased, and no adverse events worthy of comment were observed. Therefore, ezetimibe may be safely administered to CKD patients, and may improve their lipid profiles and decrease their urinary protein levels and arterial stiffness.

Ezetimibe is known to suppress the re-absorption of both extrinsic dietary and intrinsic biosynthesized cholesterol ectopically excreted into the duodenum via the gastrointestinal tract and thereby, to lower the serum cholesterol levels (14). In patients with hypercholesterolemia, ezetimibe (10 mg/

day) administration reportedly lowers the LDL-C levels by approximately 20%, which is equivalent to the effects produced by the administration of a statin, pravastatin (10 mg/day) (15). In our study, ezetimibe (10 mg/day) administration lowered the LDL-C levels by approximately 23% in CKD patients, and led to reductions in the RLP-C and LP(a) levels. Its mode of action suggests that inhibiting chylomicron production inhibits the inflow of cholesterol into the liver, and this may upregulate remnant receptors (16-18). Ezetimibe has also been reported to significantly lower LP (a) concentrations (18).

CKD is often complicated with dyslipidemia. Modification of the lipid profile in CKD patients may help prevent not only the risk of CVD onset, but also the risk of developing worsening of the CKD (19). Statin therapy is commonly used for modifying the lipids profile in CKD patients. Other than their ability to lower lipids, statins reportedly have various pleiotropic effects, although statin monotherapy often fails to achieve the recommended LDL-cholesterol goal. A previous study demonstrated the beneficial effects of ezetimibe combined with a statin on the cardiovascular disease in patients with chronic heart diseases. In the SHARP (Study of Heart And Renal Protection) study, ezetimibe therapy combined with simvastatin reduced the incidence of major atherosclerotic events, but not the urinary albumin excretion in CKD patients (20). On the other hand, Nakamura et al. described the renal protective effects of ezetimibe in CKD patients with dyslipidemia. They reported that ezetimibe administration reduced the lipid levels and the volume of urinary protein excretion due to a decrease in asymmetric dimethylarginine, an intrinsic nitric oxide synthase enzyme inhibitor, and the suppression of oxidative stress (21). They also showed that ezetimibe, combined with pitavastatin, reduced the proteinuria levels in non-diabetic CKD patients (22). Kinouchi et al. reported that ezetimibe therapy, combined with fluvastatin, yielded an elevation of the eGFR in CKD patients (23). In keeping with these findings, our data showed that ezetimibe monotherapy lowered the LDL-C, RLP-C and Lp(a) levels, as well as the volume of urinary protein excretion in CKD patients with dyslipidemia.

The mode of action by which ezetimibe reduces the volume of urinary protein excretion must be discussed. Ezetimibe only circulates in the enterohepatic circulation, without entering the circulating blood. Therefore, it is not considered to directly act on the kidneys via the blood flow. Notably, in our study, the degrees of reductions in the LDL-C or Lp(a) levels and the degree of reduction in the urine protein to creatinine ratio showed significant positive correlations. Therefore, ezetimibe may suppress the urinary protein excretion via its lipid lowering action, but the actual mechanism is a topic for future studies.

Atherosclerosis is an independent prognostic factor for CVD-related death, and at the same time, is a useful marker for evaluating therapies used for risk modification (12, 24, 25). The aortic pulse wave velocity has also been considered a predictor of the cardiovascular outcome (26, 27). The baPWV measurements include not only the aortic component, but also the muscular arterial component (28). Moreover, the baPWV has been shown to be associated with asymptomatic cerebral ischemic lesions (29), cerebral arteriosclerosis (29), carotid atherosclerosis (13), coronary artery disease (30), occlusive atherosclerosis (30), and to be useful for determining a patient's prognosis (31, 32). Antihypertensive therapy (33, 34), hypoglycemic therapy (35) and the administration of statins (36) have all been reported to reduce the baPWV values. In this study, the administration of ezetimibe (10 mg/day) affected neither the blood pressure nor HbA1c levels, but significantly decreased the baPWV values. Ezetimibe may reduce the baPWV values independently from the reductions in blood pressure or glucose levels. This may be similar to the phenomenon reported by Miyashita et al. (17), in which ezetimibe administration decreased the arterial stiffness, as assessed by the cardio-ankle vascular index, in patients with type 2 diabetes mellitus.

A sub-analysis of this study showed that the statins secondary prevention effect was diminished in the quartile of patients with higher cholesterol absorption (37). Strandberg et al. (38) also examined the association between cholesterol absorption and cardiovascular events in patients with a history of coronary artery disease. They reported that the lowest cholesterol absorption quartile showed a higher cardiovascular event-free rate than the other quartiles combined. The acceleration of cholesterol absorption in the small intestine may be a sign of a higher risk for cardiovascular events. In the current study, ezetimibe administration reduced the cholesterol absorption even in CKD patients, and the reduction in the baPWV values showed significant positive correlations with the degrees of reductions in the sitosterol and campesterol levels (as markers for cholesterol absorption). Therefore, ezetimibe's suppression of cholesterol absorption may be associated with a lower value of the baPWV. However, the mechanism(s) by which ezetimibe affects atherosclerosis through the suppression of cholesterol absorption is unknown and awaits further study.

The carotid IMT has been shown to be associated with various atherosclerotic diseases (39-42), and is used as a prognostic indicator (43). Statins have been reported to lower the IMT values (44-46). However, our study unexpectedly showed no reductions in the IMT values. The cause of this finding is unknown, but possible reasons may include the fact that the mean IMT value for the subjects in this study was relatively low, at 0.82 mm, which left little room for improvement. A second possibility may be that the significance of IMT measurement is itself an issue. The IMT is considered to be an important marker for CVD risk, but in patient subgroups in which the specific risks for ischemic events were sufficiently controlled, decreased or increased risks of an event could not clearly be associated with a variation in the IMT values, and so the IMT cannot be a predictor of risk. Supporting this, the U.S. Food and Drug Ad-

ministration has not yet approved the carotid IMT as a surrogate endpoint for CVD events (47). In Europe, a consensus has been reached that there is no need to treat IMT values or to monitor IMT values in individual patients (47). The third possibility is that, in CKD patients, atherosclerotic diseases result from a variety of mechanisms (48), and lipid-lowering therapy alone may be insufficient to improve the IMT values. In any event, these explanations remain a matter of conjecture, and further studies are needed.

When a statin therapy has failed to lower a high cholesterol level to the targeted level, the dose is often increased. However, doubling the statin dose result in only an approximately 6% additional reduction in cholesterol (the "6% rule of statins") (49). Long-term statin administration does not diminish its ability to inhibit cholesterol synthase. Rather, it has been shown to accelerate cholesterol absorption (50). Practically, when ezetimibe (10 mg/day) is combined with a statin, the reduction rate is reported to be as high as approximately 23-27% (51, 52), however, the efficacy for CKD patients treated with a combination of a statin and ezetimibe has not been clarified. We are currently investigating the usefulness of such combination therapy from the viewpoints of the lipid lowering effects, renal protection and vascular protection.

This study has several limitations. First, there was no control group in this study. Although some factors which may affect the urinary protein excretion, such as the diabetic status, BMI, waist circumference and blood pressure were unchanged during the study period, the possibility that some factors other than ezetimibe therapy reduced the urinary protein excretion cannot be ruled out. Second, the follow-up period was short. Third, the number of subjects was small. A larger-scale prospective examination with a control group is needed to determine whether or not ezetimibe provides long-term lipid control in CKD patients, without damaging their renal function, as this study seemed to show.

In conclusion, in this study, we investigated the usefulness of ezetimibe, a cholesterol lowering drug, for patients with CKD. The study confirmed that ezetimibe can be safely administered to patients with CKD and has a cholesterol lowering effect. The therapy also decreased the urinary protein excretion and atherosclerosis, suggesting that ezetimibe may provide renal protection and suppress CVD complications in CKD patients.

**The authors state that they have no Conflict of Interest (COI).**

## *References*


1. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med **164**: 659-663, 2004.
2. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis **32**: 853-906, 1998.
3. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med **351**: 1296-1305, 2004.
4. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation **108**: 2154-2169, 2003.
5. Strippoli GF, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ **336**: 645-651, 2008.
6. Holme I, Fayyad R, Faergeman O, et al. Cardiovascular outcomes and their relationships to lipoprotein components in patients with and without chronic kidney disease: results from the IDEAL trial. J Intern Med **267**: 567-575, 2010.
7. Repa JJ, Turley SD, Quan G, et al. Delineation of molecular changes in intrahepatic cholesterol metabolism resulting from diminished cholesterol absorption. J Lipid Res **46**: 779-789, 2005.
8. Altmann SW, Davis HR Jr, Zhu LJ, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science **303**: 1201-1204, 2004.
9. Davis HR Jr, Hoos LM, Tetzloff G, et al. Deficiency of Niemann-Pick C1 Like 1 prevents atherosclerosis in ApoE-/- mice. Arterioscler Thromb Vasc Biol **27**: 841-849, 2007.
10. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis **49**: S12-S154, 2007.
11. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.
12. Diehm C, Darius H, Burghaus I, et al. Ankle brachial index vs metabolic syndrome for risk prediction. Lancet **372**: 1221; author reply 1221-1222, 2008.
13. Munakata M, Sakuraba J, Tayama J, et al. Higher brachial-ankle pulse wave velocity is associated with more advanced carotid atherosclerosis in end-stage renal disease. Hypertens Res **28**: 9-14, 2005.
14. Davis HR Jr, Compton DS, Hoos L, et al. Ezetimibe, a potent cholesterol absorption inhibitor, inhibits the development of atherosclerosis in ApoE knockout mice. Arterioscler Thromb Vasc Biol **21**: 2032-2038, 2001.
15. Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J **24**: 717-728, 2003.
16. Masuda D, Nakagawa-Toyama Y, Nakatani K, et al. Ezetimibe improves postprandial hyperlipidaemia in patients with type IIb hyperlipidaemia. Eur J Clin Invest **39**: 689-698, 2009.
17. Miyashita Y, Endo K, Saiki A, et al. Effect of ezetimibe monotherapy on lipid metabolism and arterial stiffness assessed by cardio-ankle vascular index in type 2 diabetic patients. J Atheroscler Thromb **17**: 1070-1076, 2010.
18. Nozue T, Michishita I, Mizuguchi I. Effects of ezetimibe on remnant-like particle cholesterol, lipoprotein (a), and oxidized low-density lipoprotein in patients with dyslipidemia. J Atheroscler Thromb **17**: 37-44, 2010.
19. Sandhu S, Wiebe N, Fried LF, et al. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol **17**: 2006-2016, 2006.
20. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet **377**: 2181-2192, 2011.

**21.** Nakamura T, Sato E, Fujiwara N, et al. Ezetimibe decreases serum levels of asymmetric dimethylarginine (ADMA) and ameliorates renal injury in non-diabetic chronic kidney disease patients in a cholesterol-independent manner. Pharmacol Res **60**: 525-528, 2009.

**22.** Nakamura T, Sato E, Fujiwara N, et al. Co-administration of ezetimibe enhances proteinuria-lowering effects of pitavastatin in chronic kidney disease patients partly via a cholesterol-independent manner. Pharmacol Res **61**: 58-61, 2010.

**23.** Kinouchi K, Ichihara A, Bokuda K, Morimoto S, Itoh H. Effectc of adding ezetimibe to fluvastatin on kidney function in patients with hypercholesterolemia: a randomized control trial. J Atheroscler Thromb **20**: 245-256, 2013.

**24.** Nicholls SJ, Sipahi I, Schoenhagen P, et al. Application of intravascular ultrasound in anti-atherosclerotic drug development. Nat Rev Drug Discov **5**: 485-492, 2006.

**25.** Nicholls SJ, Uno K, Tuzcu EM, et al. Lessons from coronary intravascular ultrasound on the importance of raising high-density lipoprotein cholesterol. Curr Atheroscler Rep **12**: 301-307, 2010.

**26.** Blacher J, Guerin AP, Pannier B, et al. Impact of aortic stiffness on survival in end-stage renal disease. Circulation **99**: 2434-2439, 1999.

**27.** Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension **37**: 1236-1241, 2001.

**28.** Munakata M, Ito N, Nunokawa T, et al. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. Am J Hypertens **16**: 653-657, 2003.

**29.** Matsumoto M, Inoue K, Moriki A. Associations of brachial-ankle pulse wave velocity and carotid atherosclerotic lesions with silent cerebral lesions. Hypertens Res **30**: 767-773, 2007.

**30.** Xu Y, Wu Y, Li J, et al. The predictive value of brachial-ankle pulse wave velocity in coronary atherosclerosis and peripheral artery diseases in urban Chinese patients. Hypertens Res **31**: 1079-1085, 2008.

**31.** Morimoto S, Yurugi T, Aota Y, et al. Prognostic significance of ankle-brachial index, brachial-ankle pulse wave velocity, flow-mediated dilation, and nitroglycerin-mediated dilation in end-stage renal disease. Am J Nephrol **30**: 55-63, 2009.

**32.** Kitahara T, Ono K, Tsuchida A, et al. Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. Am J Kidney Dis **46**: 688-696, 2005.

**33.** Morimoto S, Yano Y, Maki K, et al. Renal and vascular protective effects of telmisartan in patients with essential hypertension. Hypertens Res **29**: 567-572, 2006.

**34.** Morimoto S, Yano Y, Maki K, et al. Renal and vascular protective effects of cilnidipine in patients with essential hypertension. J Hypertens **25**: 2178-2183, 2007.

**35.** Koshiba K, Nomura M, Nakaya Y, et al. Efficacy of glimepiride on insulin resistance, adipocytokines, and atherosclerosis. J Med Invest **53**: 87-94, 2006.

**36.** Rizos EC, Agouridis AP, Elisaf MS. The effect of statin therapy on arterial stiffness by measuring pulse wave velocity: a systematic review. Curr Vasc Pharmacol **8**: 638-644, 2010.

**37.** Miettinen TA, Gylling H, Strandberg T, et al. Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study. Finnish 4S Investigators. Bmj **316**: 1127-1130, 1998.

**38.** Strandberg TE, Tilvis RS, Pitkala KH, et al. Cholesterol and glucose metabolism and recurrent cardiovascular events among the elderly: a prospective study. J Am Coll Cardiol **48**: 708-714, 2006.

**39.** O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med **340**: 14-22, 1999.

**40.** Fan AZ. Metabolic syndrome and progression of atherosclerosis among middle-aged US adults. J Atheroscler Thromb **13**: 46-54, 2006.

**41.** Okimoto H, Ishigaki Y, Koiwa Y, et al. A novel method for evaluating human carotid artery elasticity: possible detection of early stage atherosclerosis in subjects with type 2 diabetes. Atherosclerosis **196**: 391-397, 2008.

**42.** Shah AS, Dolan LM, Kimball TR, et al. Influence of duration of diabetes, glycemic control, and traditional cardiovascular risk factors on early atherosclerotic vascular changes in adolescents and young adults with type 2 diabetes mellitus. J Clin Endocrinol Metab **94**: 3740-3745, 2009.

**43.** Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation **115**: 459-467, 2007.

**44.** Watanabe K, Sugiyama S, Kugiyama K, et al. Stabilization of carotid atheroma assessed by quantitative ultrasound analysis in non-hypercholesterolemic patients with coronary artery disease. J Am Coll Cardiol **46**: 2022-2030, 2005.

**45.** Crouse JR 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. Jama **297**: 1344-1353, 2007.

**46.** Meaney A, Ceballos G, Asbun J, et al. The VYtorin on Carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. J Clin Pharmacol **49**: 838-847, 2009.

**47.** Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis **23**: 75-80, 2007.

**48.** van Kuijk JP, Flu WJ, Chonchol M, et al. The prevalence and prognostic implications of polyvascular atherosclerotic disease in patients with chronic kidney disease. Nephrol Dial Transplant **25**: 1882-1888, 2010.

**49.** McKenney JM. Optimizing LDL-C lowering with statins. Am J Ther **11**: 54-59, 2004.

**50.** Miettinen TA, Gylling H, Lindbohm N, et al. Serum noncholesterol sterols during inhibition of cholesterol synthesis by statins. J Lab Clin Med **141**: 131-137, 2003.

**51.** Pearson TA, Denke MA, McBride PE, et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc **80**: 587-595, 2005.

**52.** Simons L, Tonkon M, Masana L, et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. Curr Med Res Opin **20**: 1437-1445, 2004.