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Efficacy analysis of the lipid-lowering and renoprotective effects of rosuvastatin in patients with chronic kidney disease

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Abstract. We aimed to assess the effects of rosuvastatin treatment on lipid levels, albuminuria, and kidney function in patients with chronic kidney disease (CKD). We conducted a prospective, open-label, study of 91 patients with CKD, low-density lipoprotein cholesterol (LDL-C) levels > 120 mg/dL, and well-controlled blood pressure who were undergoing treatment with renin–angiotensin system inhibitors. Subjects were treated with 2.5 mg/day rosuvastatin, which was increased to 10 mg/day for the 24-week study period. Rosuvastatin effectively reduced total cholesterol, LDL-C, triglycerides, non-high density lipoprotein cholesterol (non-HDL-C) levels, and the LDL-C/HDL–C ratio. Although there was no significant change in the estimated glomerular filtration rate (eGFR), serum cystatin C levels and urinary albumin/creatinine ratio were significantly decreased. Subjects were divided into 2 groups: with and without diabetes mellitus (DM). Percent changes of HDL-C, C-reactive protein (CRP), and malondialdehyde-modified (MDA)-LDL were significantly higher in the DM group than in the non-DM group. Furthermore, when the subjects were divided into 2 groups based on eGFR levels (60 mL/min/1.73 m^2 or more, normal-GFR group; less than 60 mL/min/1.73 m^2, decreased-GFR group), the percent reduction of non-HDL-C, CRP, MDA-LDL levels, and albuminuria of DM subjects in the decreased-GFR group were significantly higher than those in the non-DM subjects. Multivariate analysis identified a change in cystatin C to be associated with decreased albuminuria during rosuvastatin treatment. Rosuvastatin administration reduced albuminuria, serum cystatin C levels, and inflammation, and improved lipid profiles, regardless of the presence or absence of DM, and the degree of the eGFR.

Key words: Albuminuria, Chronic kidney disease, Cystatin C, Malondialdehyde-modified LDL (MDA-LDL), Rosuvastatin

IN ADDITION to lipid-lowering effects, statins, a type of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, exert numerous cardioprotective effects by increasing the bioavailability of vascular nitric oxide (NO) and reducing oxidative stress and inflammatory cytokines in the population with high risk of cardiovascular events [1-3]. Among the statins available as medication, rosuvastatin is considered to have robust effects, including highly effective lowering of low-density lipoprotein cholesterol (LDL-C), significant increase in high-density lipoprotein cholesterol (HDL-C), lowering of high-sensitivity C-reactive protein (hs-CRP), and stabilization of risk factors and biomarkers of atherosclerosis both clinically and in experimental animal models [4, 5]. Although it has been reported that rosuvastatin may preserve the glomerular filtration rate (GFR) in subjects who are at a high risk of cardiovascular disease (CVD) [6], little is known about the renoprotective effects of rosuvastatin with regard to the regulation of albuminuria in patients with chronic kidney disease (CKD). Furthermore, no studies have reported additional therapy for further reduction of albuminuria and serum cystatin C levels, which is a more sensitive marker of GFR, and malondialdehyde-modified (MDA)-LDL, which is a major component of oxidized LDLs and a potent risk factor for atherosclerosis, if the blood pressure has been well

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controlled by renin–angiotensin system (RAS) inhibitors. It remains unknown, therefore, whether a ceiling of renoprotection, provided by RAS inhibitors, exists. Thus, we investigated whether rosuvastatin was effective for improving the lipid profiles as well as for reducing albuminuria when given to CKD patients with well-controlled hypertension, who were already treated with RAS inhibitors. Furthermore, diabetes mellitus (DM) is well known to be associated with the progressive impairment of kidney function. The rate of kidney function deterioration in CKD patients is higher in those with than without DM [7]. Therefore, we performed stratified analyses whether the efficacy of rosuvastatin was different between patients with or without DM and between patients with an estimated GFR (eGFR) of more or less than 60 mL/min/1.73 m^2.

Subjects and Methods

Design

This study was conducted as a prospective and open-labeled clinical trial over 24 weeks. Enrollment criteria for the patients entailed: (1) stage 1–3 CKD, as indicated by an eGFR of ≥30 mL/min/1.73 m^2 with no statin treatment within 6 months before the start of the trial; (2) LDL-C levels of ≥120 mg/dL; (3) albuminuria, i.e., urinary albumin/creatinine (Cr) ratio of ≥30 mg/g (average of 2 consecutive measurements taken during a 4-week period before the study); and (4) blood pressure (BP) of <140/90 mmHg with RAS inhibitor treatment for at least 8 weeks before the study.

Exclusion criteria were as follows: (1) age of <20 years or >80 years; (2) stage 4/5 CKD, as indicated by an eGFR of <29 mL/min/1.73 m^2; (3) BP of ≥140/90 mmHg; (4) history of severe heart failure, angina, myocardial infarction, or stroke within 6 months before the start of the trial; (5) previous treatment with steroids or immunosuppressants; or (6) severe DM that led to hospitalization because of extremely high plasma glucose levels or which was associated with complications such as diabetic ketoacidosis.

We designed this study to assess the effect of rosuvastatin in patients with CKD. After initial evaluation, all subjects were treated with 2.5 mg rosuvastatin once daily. This dose was increased to 10 mg daily if the target LDL-C levels (<100 mg/dL) were not reached after 4 weeks. These subjects were already being administered RAS inhibitor and were controlled to ensure a BP of <140/90 mmHg. We analyzed the effects of rosuvastatin in all subjects. Subjects were divided into 2 groups, DM or non-DM groups, and further divided into groups based on the eGFR values at enrollment (≥60 mL/min/1.73 m^2, normal-GFR group; <60 mL/min/1.73 m^2, decreased-GFR group). Individuals with diabetes were diagnosed using criteria from the American Diabetes Association [8]. Diabetic nephropathy was diagnosed on the basis of clinical symptoms and history, including chronic diabetes; increased urinary albumin excretion and retinopathy; laboratory data; or histopathological findings. We obtained written informed consent from all patients participating in the trial, and the protocol of the trial was approved by the ethics committee of our institution. In addition, the study was conducted in accordance with the Declaration of Helsinki. This prospective study was conducted between December 2009 and December 2010, and the subjects were followed up for 24 weeks. Doses of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) were not altered during the study period.

Laboratory analysis

The GFR was estimated using the final recommended modified equation for Japanese patients of the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives because the eGFR obtained by this method is more accurate for application in Japanese patients with CKD than values obtained using other equations [9]. The eGFR was calculated according to the following formula: eGFR (mL/min/1.73 m^2) = 194 × $sCr^{-1.094}$ × $age^{-0.287}$ (0.739 × in the case of women) (sCr: serum creatinine).

Glycated hemoglobin (HbA1c) was measured as a criterion for glycemic control in patients with DM. Levels of hemoglobin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transpeptidase, creatine phosphokinase (CK), total cholesterol (TC), HDL-C, and triglycerides (TG) were routinely measured following clinical chemistry procedures using commercial kits. The serum concentration of LDL-C was estimated using the Friedewald formula (LDL-C = TC − HDL-C − TG × 0.2) in patients with serum TG concentrations of <400 mg/dL [10]. The percent changes of serum TC, LDL-C, TG, HDL-C, non-HDL-C, and LDL-C/HDL-C ratio were calculated in all patients. Serum MDA-LDL was assayed by using an enzyme-linked immunosorbent assay (ELISA) as described previously [11]. Serum cysta-

tin C was measured by using the fully automated sol-particle-immunoassay method as described previously [12]. The hs-CRP level was measured by latex agglutination. Urinary albumin excretion was assessed by measuring urinary concentrations of albumin and creatinine (albumin/Cr ratio) in the first morning urine sample. Urinary albumin levels were measured using the immunoturbidimetry method.

Safety variables

At each visit, patients were asked about compliance (diet and medication), concomitant medication, and adverse events. Safety assessments were performed repeatedly throughout the study period. Adverse events were graded on the basis of intensity (mild, moderate, or severe). Serious adverse events were defined as significant and untoward medical events that resulted in death, hospitalization, or significant disability or incapacity. Patient withdrawal from the study was considered if allergy or intolerance to rosuvastatin appeared during the study; a hypertensive emergency developed; either the serum CK or transaminase concentration increased >2-fold the upper limit of the normal range and the patient concomitantly exhibited symptoms such as muscular pain, loss of appetite, or general fatigue; or the patient was subjected to any other condition or therapy that, in the opinion of the investigators, might have posed a risk to the patient or confounded the results of the study.

Statistical analysis

Results are expressed as the mean ± the standard error of the mean (SEM). We assessed differences between baseline and 24 week values using the *t*-test for paired data. The unpaired *t*-test was used to compare the means of baseline data between the DM and non-DM groups, and normal-GFR and decreased-GFR groups. The Mann–Whitney *U*-test was used to compare the median changes of the monitored parameters between the groups. Relationships between the changes were studied by use of Spearman correlation and multiple linear regression analysis. JMP ver. 9 was used for all statistical analyses. Statistical significance was established at a level of $p < 0.05$.

Results

Baseline Characteristics and the efficacy of rosuvastatin in all subjects

We enrolled 91 subjects in this study and treated them with rosuvastatin. The baseline characteristics and medications administered to all subjects are shown in Table 1. Although the baseline BP was well controlled, adequate LDL-C control had not been achieved in any of the enrolled patients. During treatment, two subjects were excluded from the study because of adverse reactions. Therefore, 89 patients completed the trial and their data were analyzed. The final mean dose of rosuvastatin was 3.4 ± 0.1 mg/day.

The levels of TC, LDL-C, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, and TG at baseline and after 6 months are shown in Table 2. TC, LDL-C, non-HDL-C, LDL-C/HDL-C ratio, and TG levels after administration of rosuvastatin were significantly decreased (Table 2). HDL-C levels after administration of rosuvastatin were increased from 49 ± 1 mg/dL to 52 ± 1 mg/dL ($p = 0.0003$). The hs-CRP levels after administration of rosuvastatin were decreased from 1.7 ± 0.2 mg/L to 0.7 ± 0.1 mg/L ($p < 0.0001$), and the MDA-LDL levels were decreased from 150 ± 6 U/L to 90 ± 3 U/L ($p < 0.0001$).

There was no significant change in sCr levels during the treatment period (from 1.07 ± 0.04 mg/dL to 1.07 ± 0.05 mg/dL). In addition, there was no significant change in the eGFR levels during the treatment period (from 55.1 ± 2.1 to 55.1 ± 2.1 mL/min/1.73 m^2). In contrast, serum cystatin C levels were significantly

Table 1 Baseline characteristics and medications of the study subjects

Characteristics	
Number of patients (male/female)	91 (52/39)
Age (years)	65.3 ± 1.2
Smoking (%)	20
Body mass index (kg/m^2)	22.7 ± 0.3
Causes of chronic kidney disease (%)	
Diabetic nephropathy	50.5
Glomerulonephritis	25.3
Nephrosclerosis	16.5
Interstitial nephritis	4.3
ADPKD	3.4
Systolic blood pressure (mmHg)	123 ± 1
Diastolic blood pressure (mmHg)	71 ± 1
Heart rate (beats per minute)	74 ± 1
Antihypertensive agents (% (n))	
Angiotensin receptor blockers	90 (82)
Angiotensin converting enzyme inhibitors	27 (25)
Calcium channel blockers	82 (69)
Diuretics	30 (25)
α-blockers	20 (17)
β-blockers	26 (18)

ADPKD, Autosomal dominant polycystic kidney disease

Table 2 Monitored parameters at baseline and after 24 weeks of therapy

Variables	Baseline	End	*p* value
TC (mg/dL)	224 ± 3	167 ± 3	< 0.0001
LDL-C (mg/dL)	138 ± 3	83 ± 2	< 0.0001
HDL-C (mg/dL)	49 ± 1	52 ± 1	0.0003
non-HDL-C (mg/dL)	173 ± 3	114 ± 3	< 0.0001
LDL-C/HDL-C ratio	2.9 ± 0.1	1.6 ± 0.1	< 0.0001
TG (mg/dL)	170 ± 9	135 ± 8	< 0.0001
hs-CRP (mg/L)	1.7 ± 0.2	0.7 ± 0.1	< 0.0001
MDA-LDL (U/L)	150 ± 6	90 ± 3	< 0.0001
Serum Cr (mg/dL)	1.07 ± 0.04	1.07 ± 0.05	0.74
eGFR (mL/min/1.73m^2)	55.1 ± 2.1	55.1 ± 2.1	0.92
Cystatin C (mg/L)	1.08 ± 0.04	1.03 ± 0.04	< 0.0001
Urinary albumin/Cr ratio (mg/gCr)	308 ± 38	195 ± 25	< 0.0001

Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde-modified; TC, total cholesterol; TG, triglyceride.

decreased (from 1.08 ± 0.04 to 1.03 ± 0.04 mg/L; $p < 0.0001$). Urinary albumin/Cr ratios were significantly decreased (from 308 ± 38 mg/gCr to 195 ± 25 mg/gCr; $p < 0.0001$).

Characteristics and analysis of the DM and non-DM groups

As shown in Table 3 and Table 4, no significant differences were observed between the DM and non-DM groups with regard to baseline hemodynamics and kidney function. The DM group had a significantly higher BMI (23.6 ± 0.3 kg/m^2) than the non-DM group (21.6 ± 0.3 kg/m^2). As shown in Table 4, the urinary albumin/Cr ratio was significantly higher in the DM group than in the non-DM group ($p < 0.05$). Although there were no significant differences in TC, HDL-C, and LDL-C levels and LDL-C/HDL-C ratio between the 2 groups, DM subjects with CKD had higher non-HDL-C, TG, hs-CRP, and MDA-LDL levels compared to non-DM subjects with CKD.

Final mean doses of rosuvastatin were 3.5 ± 0.2 and 3.2 ± 0.2 mg/day in the DM group, and non-DM group, respectively. No significant difference was observed between the DM and non-DM groups ($p = 0.61$). As listed in Table 4, lipid profiles, including TC, LDL-C, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, and TG, were significantly improved by rosuvastatin treatment in both the DM and non-DM groups. As shown in Fig. 1, although there were no significant differences in the percent reduction of TC, LDL-C, non-HDL-C, LDL-C/HDL-C ratio, and TG between the DM and non-DM subjects, the percentage of increase in HDL-C was significantly higher in the DM group than in the non-DM group (8.2 ± 1.0% and 4.7 ± 1.2%, respectively; $p < 0.05$).

The hs-CRP levels in the DM group and the non-DM group were significantly decreased from 2.01 ± 0.30 to 0.81 ± 0.14 ($p < 0.0001$) and 1.31 ± 0.14 to 0.65 ± 0.09 mg/L ($p < 0.0001$), respectively. MDA-LDL levels in the DM group and the non-DM group were significantly decreased from 162 ± 8 to 92 ± 4 ($p < 0.0001$) and 137 ± 9 to 87 ± 5 U/L ($p < 0.0001$), respectively (Table 4). As shown in Fig. 2, the percent reduction of hs-CRP and MDA-LDL was significantly higher in the DM group than in the non-DM-group.

There was no significant change in sCr levels during the treatment period in the DM group (from 1.04 ± 0.06 to 1.04 ± 0.06 mg/dL), and the non-DM group (from 1.10 ± 0.06 to 1.08 ± 0.06 mg/dL) (Table 4). Additionally, there was no significant change in eGFR levels during the treatment period in the DM group (from 55.8 ± 2.9 to 56.0 ± 3.0 mL/min/1.73 m^2) or the non-DM group (from 54.1 ± 2.9 to 54.1 ± 2.9 mL/min/1.73 m^2). In contrast, serum cystatin C levels were significantly decreased in the DM group (from 1.10 ± 0.06 to 1.04 ± 0.06 mg/L; $p < 0.0001$) and the non-DM group (from 1.05 ± 0.05 to 1.00 ± 0.05 mg/L; $p < 0.0001$).

As shown in Fig. 3, urinary albumin/Cr ratios significantly decreased in the DM group (from 394 ± 57 to 240 ± 36 mg/gCr; $p < 0.0001$) and the non-DM group (from 211 ± 49 to 149 ± 36 mg/g Cr; $p = 0.0001$). Percent changes from baseline values of the urinary albumin/Cr ratio were significantly reduced following rosuvastatin treatment (−41 ± 3%, and −37 ± 4% in the DM group, and the non-DM group, respectively; not significant).

Table 3 Baseline characteristics and medications of the DM and non-DM group

Characteristics	DM group	non-DM group	*p* value
Number of patients (male/female)	46 (26/20)	45 (26/19)	0.39
Age (years)	66.3 ± 1.2	64.2 ± 2.1	0.38
Smoking (%)	22	15	0.55
Diabetic retinopathy (%, for diabetes)	70	-	-
Body mass index (kg/m^2)	23.6 ± 0.3	21.6 ± 0.3	0.001
Systolic blood pressure (mmHg)	124 ± 1	123 ± 1	0.37
Diastolic blood pressure (mmHg)	71 ± 1	70 ± 1	0.27
Heart rate (beats per minute)	74 ± 1	74 ± 1	0.63
Hemoglobin A1c (%, for diabetes)	6.7 ± 0.5	-	-
Medications			
Fibrates (n)	0	0	-
Ezetimibe (n)	0	0	-
Niceritrol (n)	0	0	-
Probucol (n)	0	0	-
Ethyl icosapentate (n)	2	2	0.98
Antihypertensive agents [% (n)]			
Angiotensin receptor blockers	93 (43)	87 (39)	0.28
Angiotensin converting enzyme inhibitor	33 (15)	22 (10)	0.27
Calcium channel blockers	78 (36)	73 (33)	0.29
Diuretics	33 (15)	22 (10)	0.27
α-blockers	24 (11)	13 (6)	0.19
β-blockers	24 (11)	16 (7)	0.32
Antidiabetic agents (n)			
Insulin	14	0	-
DPP-4 inhibitors	9	0	-
Sulphonylureas	9	0	-
Meglitinides	8	0	-
Biguanides	3	0	-
Pioglitazone	5	0	-
α-glucosidase inhibitors	7	0	-

DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4.

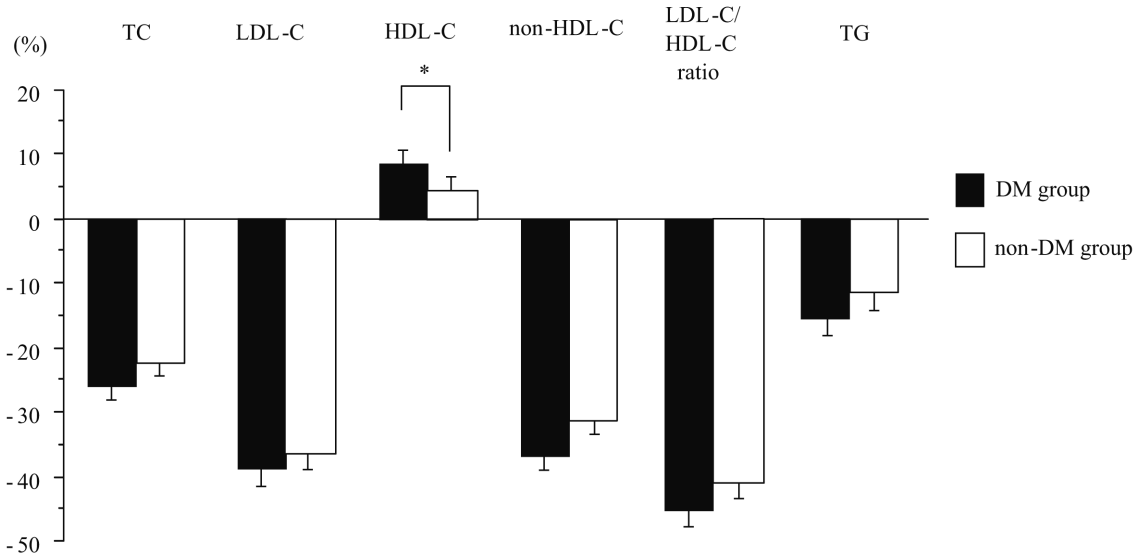

Fig. 1 Percent change of lipid profiles in the DM group and the non-DM group.
* $p < 0.05$ *vs*. non-DM group; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 4 Changes in monitored parameters in the DM and non-DM group

Variables	Period	DM group	*p* value	non-DM group	*p* value
TC (mg/dL)	Baseline	228 ± 4	< 0.0001	221 ± 4	< 0.0001
	24 weeks	165 ± 4		168 ± 4	
LDL-C (mg/dL)	Baseline	138 ± 3	< 0.0001	138 ± 4	< 0.0001
	24 weeks	80 ± 3		83 ± 2	
HDL-C (mg/dL)	Baseline	47 ± 2	0.0032	50 ± 1	0.04
	24 weeks	51 ± 2		53 ± 1	
non-HDL-C (mg/dL)	Baseline	180 ± 4*	< 0.0001	170 ± 4	< 0.0001
	24 weeks	114 ± 4		114 ± 3	
LDL-C/HDL-C ratio	Baseline	2.9 ± 0.1	< 0.0001	2.8 ± 0.1	< 0.0001
	24 weeks	1.6 ± 0.1		1.6 ± 0.1	
TG (mg/dL)	Baseline	177 ± 14*	< 0.0001	148 ± 11	< 0.0001
	24 weeks	147 ± 12		130 ± 10	
hs-CRP (mg/L)	Baseline	2.01 ± 0.30*	< 0.0001	1.31 ± 0.14	< 0.0001
	24 weeks	0.81 ± 0.14		0.65 ± 0.09	
MDA-LDL (U/L)	Baseline	162 ± 8*	< 0.0001	137 ± 9	< 0.0001
	24 weeks	92 ± 4		87 ± 5	
Serum Cr (mg/dL)	Baseline	1.04 ± 0.06	0.96	1.10 ± 0.06	0.72
	24 weeks	1.04 ± 0.06		1.08 ± 0.06	
eGFR (mL/min/1.73m^2)	Baseline	55.8 ± 2.9	0.82	54.1 ± 2.9	0.64
	24 weeks	56.0 ± 3.0		54.1 ± 2.9	
Cystatin C (mg/L)	Baseline	1.10 ± 0.06	0.01	1.05 ± 0.05	< 0.0001
	24 weeks	1.04 ± 0.06		1.00 ± 0.05	
Urinary albumin/Cr ratio (mg/gCr)	Baseline	394 ± 57*	< 0.0001	211 ± 49	0.0001
	24 weeks	240 ± 36*		149 ± 36	

* $p < 0.05$ vs. non-DM group; Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde-modified; TC, total cholesterol; TG, triglyceride.

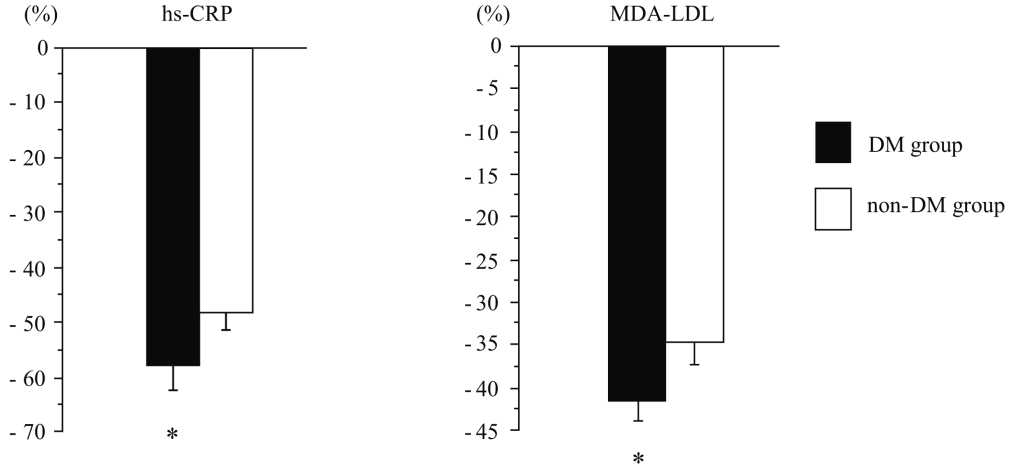

Fig. 2 Percent change of hs-CRP and MDA-LDL levels in the DM group and the non-DM group
* $p < 0.05$ *vs.* non-DM group; hs-CRP, high-sensitivity C-reactive protein; MDA-LDL, malondialdehyde-modified low density lipoprotein.

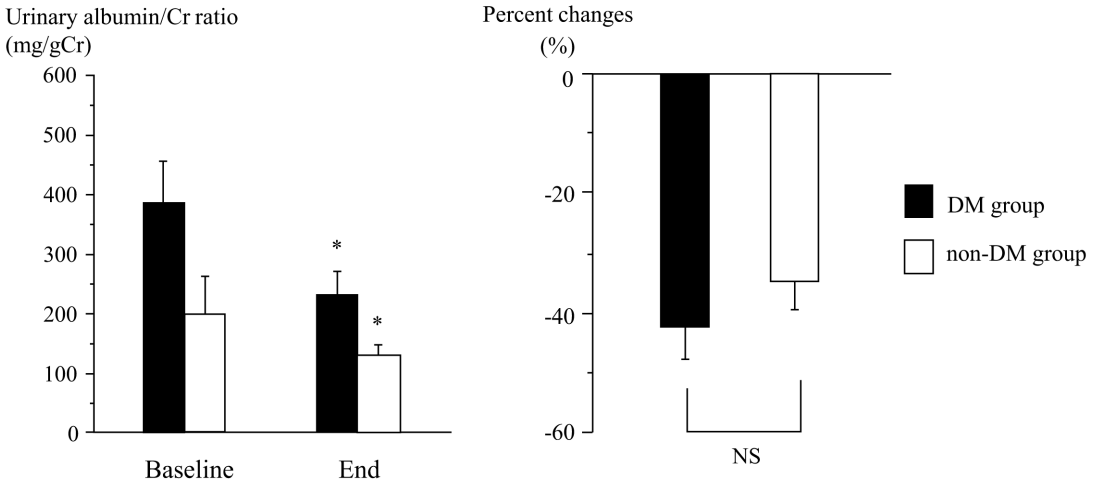

Fig. 3 Changes of urinary albumin/creatinine ratio and percent changes from baseline.
* $p < 0.001$ *vs*. baseline; Cr, creatinine; NS, not significant.

Sub-analysis; Subset of the normal-GFR and decreased-GFR group with or without DM

Subjects were subdivided into a normal-GFR group (eGFR, ≥ 60 mL/min/1.73 m^2) and decreased-GFR group (eGFR, <60 mL/min/1.73 m^2) for each subject (DM and non-DM subjects), and subgroup analyses were performed. In both normal- and decreased-GFR groups of both DM and non-DM subjects, although there were no significant changes in eGFR levels, cystatin C levels and urinary albumin/Cr ratios significantly decreased. Furthermore, lipid profiles, including TC, LDL-C, non-HDL-C, LDL-C/HDL-C ratio, and TG levels, significantly decreased and the HDL-C level significantly increased in both the groups (Table 5).

Percent changes of all monitored parameters were not significantly different between the DM and non-DM groups in the normal-GFR group (Table 6). However, in the decreased-GFR group, there was a significant reduction in TC, non-HDL-C, hs-CRP, and MDA-LDL levels and an increase in HDL-C levels in the DM group compared to in the non-DM group. Furthermore, the percent reduction of non-HDL-C was higher in the DM group of the decreased-GFR group than in that of the normal-GFR group. Percent reduction of the urinary albumin/Cr ratio was significantly greater in the DM group than in the non-DM group in the decreased-GFR group (-40 ± 3 *vs*. -24 ± 3%, DM and non-DM group, respectively; $p = 0.043$).

Multivariable analysis

To identify factors that decrease urinary albumin excretion, multivariate analysis was performed (Table 7). Multivariate regression analysis with percent changes in albuminuria as the dependent variable and age, sex, the presence or absence of diabetes, and changes in lipid profiles as independent variables was performed to investigate the effect of rosuvastatin on albuminuria. Changes in cystatin C levels was the only factor that was significantly related to albuminuria regression ($p = 0.0009$, $r = 0.27$).

Changes in BP and glycemic control

There were no significant changes in BP or heart rate between the groups at baseline and throughout the study period. There were no significant changes in systolic BP (from 124 ± 1 to 123 ± 1 mmHg; $p = 0.40$ and from 123 ± 1 to 122 ± 2 mmHg; $p = 0.51$ in the DM and non-DM group, respectively; $p = 0.15$), in diastolic BP (from 71 ± 1 to 71 ± 1 mmHg; $p = 0.13$ and from 70 ± 1 to 70 ± 1 mmHg; $p = 0.44$ in the DM and non-DM group, respectively; $p = 0.27$), and in heart rate (from 74 ± 1 to 74 ± 1 beats per minute; $p = 0.83$ and from 74 ± 1 to 74 ± 1 beats per minute; $p = 0.54$ in the DM and non-DM group, respectively; $p = 0.79$). Furthermore, although there was no significant change in the HbA1c levels in the DM group (from 6.7 ± 0.5% to 6.6 ± 0.6%; $p = 0.08$), 1 patient was subjected to additional treatment with anti-diabetic agents (dipeptidyl peptidase-4 (DPP-4) inhibitor) due to an increase in the HbA1c level during the study period. On the other hand, there was no new onset of DM in the non-DM group.

Table 5 Changes of monitored parameters in the normal-GFR and decreased-GFR groups

Variables	Period	eGFR ≥ 60 mL/min/1.73m^2				eGFR < 60 mL/min/1.73m^2			
		DM group (n = 19)	*p* value	non-DM group (n = 18)	*p* value	DM group (n = 26)	*p* value	non-DM group (n = 26)	*p* value
TC (mg/dL)	Baseline	229 ± 8	< 0.0001	226 ± 5	< 0.0001	226 ± 5	< 0.0001	217 ± 5	< 0.0001
	24 weeks	176 ± 7		170 ± 7		158 ± 5		167 ± 5	
LDL-C (mg/dL)	Baseline	139 ± 5	< 0.0001	137 ± 5	< 0.0001	137 ± 2	< 0.0001	141 ± 7	< 0.0001
	24 weeks	88 ± 7		90 ± 6		75 ± 4		84 ± 3	
HDL-C (mg/dL)	Baseline	48 ± 2	0.024	50 ± 2	0.029	46 ± 2*	0.001	50 ± 2	0.017
	24 weeks	51 ± 2		53 ± 2		50 ± 2		52 ± 2	
non-HDL-C (mg/dL)	Baseline	182 ± 6	< 0.0001	175 ± 5	0.0008	181 ± 4	< 0.0001	168 ± 5	< 0.0001
	24 weeks	125 ± 7		117 ± 7		108 ± 5		114 ± 4	
LDL-C/HDL-C ratio	Baseline	3.0 ± 0.1	< 0.0001	2.7 ± 0.3	< 0.0001	3.0 ± 0.1	< 0.0001	2.8 ± 0.2	< 0.0001
	24 weeks	1.7 ± 0.2		1.7 ± 0.1		1.5 ± 0.1		1.6 ± 0.1	
TG (mg/dL)	Baseline	209 ± 26	0.014	151 ± 19	< 0.0001	161 ± 13	0.018	142 ± 17	0.018
	24 weeks	180 ± 24		140 ± 17		134 ± 11		122 ± 13	
hs-CRP (mg/L)	Baseline	2.3 ± 0.4*	0.0007	1.1 ± 0.2	< 0.0001	1.8 ± 0.3	0.0004	1.4 ± 0.2	0.0014
	24 weeks	1.0 ± 0.2		0.4 ± 0.1		0.6 ± 0.1		0.8 ± 0.1	
MDA-LDL (U/L)	Baseline	176 ± 14	< 0.0001	146 ± 13	0.001	152 ± 11	< 0.0001	133 ± 10	< 0.0001
	24 weeks	105 ± 8		90 ± 8		83 ± 3		86 ± 6	
eGFR (mL/min/1.73m^2)	Baseline	76.5 ± 2.3	0.63	74.8 ± 3.8	0.66	41.6 ± 1.7	0.28	43.8 ± 1.8	0.69
	24 weeks	75.8 ± 3.0		74.1 ± 2.8		42.3 ± 2.1		44.1 ± 2.3	
Cystatin C (mg/L)	Baseline	0.76 ± 0.03	0.004	0.80 ± 0.03	0.0047	1.34 ± 0.07	0.0047	1.17 ± 0.06	0.0001
	24 weeks	0.71 ± 0.03		0.76 ± 0.03		1.27 ± 0.08		1.12 ± 0.06	
Urinary albumin/ Cr ratio (mg/gCr)	Baseline	235 ± 53*	0.0004	101 ± 22	0.001	512 ± 83*	< 0.0001	286 ± 78	0.0048
	24 weeks	147 ± 41*		59 ± 20		307 ± 51		217 ± 56	

* $p < 0.05$ *vs*. non-DM group; Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde-modified; TC, total cholesterol; TG, triglyceride.

Table 6 Percent changes of parameters between normal-GFR and decreased-GFR in the 2 groups

Variables	eGFR ≥ 60 mL/min/1.73m^2			eGFR < 60 mL/min/1.73m^2		
	DM group (n = 19)	non-DM group (n = 18)	*p* value	DM group (n = 26)	non-DM group (n = 26)	*p* value
TC (%)	-23 ± 1	-24 ± 3	0.46	-30 ± 2	-23 ± 2	0.025
LDL-C (%)	-37 ± 4	-33 ± 4	0.73	-45 ± 3	-40 ± 3	0.38
HDL-C (%)	8 ± 2	4 ± 1	0.09	8 ± 1	5 ± 2	0.015
non-HDL-C (%)	-31 ± 3	-33 ± 3	0.28	-40 ± 3*	-31 ± 3	0.018
LDL-C/HDL-C ratio (%)	-43 ± 5	-37 ± 4	0.73	-50 ± 3	-42 ± 3	0.08
TG (%)	-13 ± 4	-7 ± 3	0.46	-16 ± 6	-13 ± 3	0.45
hs-CRP (%)	-56 ± 5	-63 ± 5	0.73	-66 ± 4	-42 ± 6	0.01
MDA-LDL (%)	-40 ± 3	-38 ± 3	0.69	-45 ± 3	-35 ± 3	0.04
eGFR (%)	-0.9 ± 1.3	-0.9 ± 1.1	0.64	1.6 ± 1.3	0.6 ± 1.5	0.67
Cystatin C (%)	-6.5 ± 1.3	-4.8 ± 1.3	0.80	-5.2 ± 2.0	-4.2 ± 0.7	0.13
Urinary albumin/Cr ratio (%)	-37 ± 6	-41 ± 6	0.74	-40 ± 3	-24 ± 3	0.043

* $p < 0.05$ *vs*. DM group of the eGFR ≥ 60 mL/min/1.73m^2; Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde-modified; TC, total cholesterol; TG, triglyceride.

Table 7 Analysis to identify the clinical factors affecting the albuminuria (multivariable analysis)

Variable	Standerdized β coefficient	*p* value	95%CI
DM (presence or absence)	0.03	0.75	-4.5 to 6.2
Gender (male or female)	0.09	0.41	-6.2 to 14.8
Age	-0.10	0.36	-0.7 to 0.2
LDL-C	-0.12	0.29	-0.48 to 0.15
HDL-C	-0.13	0.26	-0.50 to 0.14
TG	0.05	0.62	-0.11 to 0.14
hs-CRP	-0.09	0.41	-0.24 to 0.10
MDA-LDL	0.10	0.38	-0.19 to 0.50
Cystatin C	0.29	0.0009	0.18 to 1.33

Adjused albuminuria baseline DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive prot; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde-modified.

Safety

During the treatment, adverse reactions were observed in 2 subjects and administration of rosuvastatin was discontinued. Those 2 patients had muscular pain, which was considered to be related to the study drugs, and this symptom was relieved by discontinuation of rosuvastatin treatment. However, elevated CK levels were not observed in these 2 subjects.

Discussion

In the present study, the CKD patients with DM were characterized by higher albuminuria, non-HDL-C, MDA-LDL, and hs-CRP levels, and lower HDL-C levels compared with non-DM patients. Furthermore, rosuvastatin treatment significantly improved TC, LDL-C, HDL-C, non-HDL-C, and TG levels and the LDL-C/HDL-C ratio in patients with CKD, regardless of the presence or absence of DM. When divided into normal- and decreased-GFR groups, although there were no significant differences in the percent changes of any parameters between the DM and non-DM subjects of the normal-GFR group, there were significant differences in the percent changes of TC, non-HDL-C, hs-CRP, MDA-LDL, and albuminuria in DM subjects in the decreased-GFR group compared to in the non-DM subjects in the same group. These findings suggest that rosuvastatin treatment may maintain GFR levels as well as contribute to a reduced risk of CVD in subjects with decreased e-GFR and those with diabetic nephropathy. Rosuvastatin reduced both albuminuria and the rate of progression of kidney disease in patients with CKD, and the benefits appear to supplement those derived from treatment of patients with hypertension.

While the LDL-C level remains the cornerstone of decision making for the initiation of lipid-modifying therapy, it has been proposed that non-HDL-C levels should also be considered, particularly in patients with hypertriglyceridemia or CKD [12]. The rationale behind this proposal is that non-HDL-C includes the cholesterol component of all atherogenic lipoproteins, and is, therefore, a better atherogenic index than LDL-C [14]. The non-HDL-C is highly correlated with apolipoprotein (apoB), the level of which indicates a measure of the total number of atherogenic particles, as there is 1 apoB molecule per particle [14]. Therefore, non-HDL-C is more closely related to vascular risk and is a better guide for the assessment of atherosclerosis in patients with CKD. In addition, because it has been reported that decreasing ratios of LDL-C/HDL-C were correlated with plaque regression, a LDL-C/HDL-C ratio of <1.5 has recently been considered the target level for diabetic patients or secondary prevention after lowering the LDL-C concentration to its target level [15]. In the present study, the percent reduction of non-HDL-C levels was significantly higher in the decreased-GFR group with DM than in that without DM. These findings suggested that DM subjects were characterized by higher levels of non-HDL-C and lower levels of HDL-C at baseline. Therefore, rosuvastatin might more likely increase HDL-C levels in subjects with lower HDL-C levels and reduce non-HDL-C levels in subjects with higher non-HDL-C levels. The present study revealed that even at moderate-stage CKD (dia-

betic nephropathy), lipid-lowering therapy by rosuvastatin is effective in the improvement of lipid profiles while maintaining the kidney function.

Oxidative modification of LDL has been demonstrated to play a central role in the initiation and acceleration of atherosclerosis. Oxidized LDLs exert a variety of effects, such as direct cytotoxicity to endothelial cells, promotion of increased synthesis and secretion of adhesion molecules, and enhanced foam cell formation in atherosclerotic lesions [16]. Furthermore, oxidized LDL may attract monocytes directly or indirectly via activation of monocyte chemoattractant protein-1 (MCP-1) and alteration of its native properties. Such an event will allow scavenger receptors to incorporate LDL into macrophages where it will negatively affect their various functions in the vascular wall, such as inhibition of endothelial NO production, endothelial apoptosis, and proliferation of smooth muscle cells, which might reduce the NO level in the glomeruli contributing to vasoconstriction [17]. MDA-LDL has been isolated from the sera of patients with coronary artery disease (CAD), and levels of MDA-LDL are elevated in patients with CAD, DM, and hyperlipidemia [18]. Circulating levels of MDA-LDL correlate with the intima-media thickness of carotid arteries and are distributed in serum fractions containing small-dense LDL. Therefore, elevated circulating MDA-LDL levels are considered a potent risk factor for atherosclerosis [19]. In the present study, MDA-LDL levels were significantly decreased by rosuvastatin treatment, particularly in the decreased-GFR group with DM. A reduction in the serum concentration of MDA-LDL, which is a major component of oxidized LDLs, may reduce the likelihood of future atherosclerotic disease and cardiovascular events as well as progression of kidney disease.

In a sub-analysis of the Treating to New Targets (TNT) study, treatment with 10 mg and 80 mg atorvastatin was found to increase the eGFR by 3.5 mL/min/1.73 m^2 and 5.2 mL/min/1.73 m^2, respectively [20]. In contrast, in the Prevention of Renal and Vascular End-stage Disease Intervention trial (PREVEND-IT), treatment with 40 mg pravastatin did not result in any changes in the eGFR [21]. Thus, the beneficial effect of statins on the eGFR remains controversial. On the other hand, comparing the levels of sCr with conventional estimates, on the basis of serum cystatin C measurements for detecting a very early reduction in the kidney function, can be useful for measuring the kidney function and will optimize early detection, prevention, and treatment strategies for patients with diabetic nephropathy [22, 23]. Furthermore, compared to classical factors, cystatin C is a potent predictor of cardiovascular mortality in patients with CAD and normal or mildly reduced kidney function [24]. In the present study, there was no significant difference in the sCr and eGFR values. This finding was expected because the duration of the present study was relatively short. However, our results revealed that the cystatin C level, which is a more sensitive marker of changes in the GFR, was significantly reduced by rosuvastatin treatment. Therefore, a long-term study would be needed to clarify the renoprotective effects of rosuvastatin.

Albuminuria is one of the clinical parameters for diagnosing renal damage, particularly in cases of glomerular hypertension, and it has been reported to be a risk factor and predictor of cardiovascular events [25, 26]. Therefore, the reduction of albuminuria is a major goal in the treatment of hypertensive patients with CKD. The renoprotective effects of RAS inhibitors have been indicated previously [27–29]. Blockade of the RAS with ACEIs or ARBs is currently the most effective pharmacological tool for renoprotection. Regarding hemodynamics, systolic and diastolic BPs were similar in the 2 groups at baseline and during follow up, and this provided evidence that rosuvastatin slows the decline in urinary albumin excretion through a renoprotective effect, independent of changes in the BP. Statins are thought to increase renal blood flow and suppress monocyte recruitment, mesangial cell proliferation, and inflammation [30]. Pitavastatin, another type of statin, has been reported to reduce urinary albumin and liver-type fatty acid-binding protein (L-FABP) in patients with diabetic nephropathy, which may be attributable to the antioxidant effects of pitavastatin [31]. Changes in the urinary albumin excretion rate were significantly related with those of serum cystatin C in this analysis, although the correlation coefficient was small. Additionally, the amount of cystatin C change significantly influences changes in albuminuria during rosuvastatin treatment; therefore, decreased cystatin C may decrease albuminuria independently of its lipid lowering and anti-inflammatory effects. However, further analysis is required to clarify the mechanism underlying the decreased albuminuria and cystatin C levels induced by rosuvastatin.

Our study is limited by the relatively small sample size, the short period of treatment, and the lack of a control group. Moreover, further longitudinal, double-

blind, comparative multicenter clinical trials should be conducted in a larger number of patients in order to further clarify the effect and safety of rosuvastatin in the CKD population. Furthermore, although treatment with other statins, such as atorvastatin and pitavastatin, has been shown to result in an increase in the eGFR in the CKD population, this finding was not confirmed in the present study. This can be explained because our subjects were already treated with RAS inhibitors and more than half of our subjects were diagnosed with diabetic nephropathy. Therefore, the background of our subjects differed from that of subjects in previous reports. However, in our study, we noted that rosuvastatin significantly improved the lipid profiles, albuminuria, and cystatin C levels, even when administered only for a short period of time. Therefore, we believe that rosuvastatin may be beneficial for patients with CKD.

In conclusion, we found that rosuvastatin treatment was effective in improving lipid profiles as well as albuminuria and oxidative stress of patients with CKD, regardless of the presence or absence of DM, and the degree of the eGFR. Administration of rosuvastatin may be considered if the target LDL-C level (<120 mg/dL) cannot be achieved. Furthermore, rosuvastatin treatment resulted in a significant decrease in the cystatin C level after 24 weeks, suggesting that rosuvastatin might maintain the GFR as well as contribute to a reduction in the risk of CVD in patients with CKD, including diabetic nephropathy. Further prospective long-term clinical trials are needed for a more precise evaluation of the effects of rosuvastatin on renal function.

Conflict of Interest

The authors declare no conflict of interest.

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