Original Article

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Comparative Effects of Statins on the Kidney Function in Patients with Type 2 Diabetes

Ko Hanai[1], Tetsuya Babazono[1], Shunsuke Takemura[1], Aiko Toyonaga[1], Noriko Yoshida[1] and Yasuko Uchigata[2]

[1]Division of Nephrology and Hypertension, Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan
[2]Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

Aim: Whether there are differences among statins in their effect on the kidney function in diabetic patients remains controversial. In this report, we aimed to examine the comparative effects of statins on the kidney function in a long-term follow-up study.

Methods: This was a single-center longitudinal observational historical cohort study. We enrolled 326 Japanese adult ambulatory patients with type 2 diabetes who were newly prescribed one of four statins (pravastatin, rosuvastatin, atorvastatin and pitavastatin) and who had an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2. The outcome measurement was the annual rate of change in eGFR. We used the standardized inverse probability of treatment weighted (IPTW) method based on the propensity score to adjust for the effects of confounding factors. Furthermore, in order to take into account the variety in the number and spacing of eGFR measurements and the duration of the follow-up period for each individual, we conducted a linear mixed-effects model regression analysis.

Results: The median follow-up period was 4.3 years (range, 3.0-7.1 years). In an analysis using the IPTW method, the mean (±standard error) annual rate of change in eGFR among the patients treated with pravastatin (−0.86±0.28 mL/min/1.73 m^2/year) was significantly lower than that observed among the patients treated with rosuvastatin (−1.80±0.27, $p=0.02$), atorvastatin (−1.99±0.28, $p=0.004$) and pitavastatin (−2.23±0.49, $p=0.02$). Similar results were obtained in the linear mixed-effects model regression analysis.

Conclusions: Pravastatin may be superior to rosuvastatin, atorvastatin and pitavastatin in preserving the kidney function in patients with type 2 diabetes.

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Key words: Statin, Diabetic kidney disease, Propensity score, Inverse probability of treatment weighted method, Linear mixed-effects model regression analysis

Introduction

Diabetic kidney disease (DKD) is a major public health problem worldwide[1, 2]; therefore, the establishment of new management strategies is urgently needed. Currently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first choice and essential agents for the treatment of dyslipidemia. Numerous studies have shown that decreasing the low-density lipoprotein (LDL) cholesterol level using statins significantly reduces the risk of cardiovascular disease in diabetic patients[3]. Furthermore, accumulating evidence indicates the renoprotective effects of statins[4-7], although whether the beneficial effects are independent of the lipid-lowering actions of these drugs remains unknown.

Many types of statins are clinically available; however, there is currently no clear selection criteria for the different types of drugs. Interestingly, several

Address for correspondence: Tetsuya Babazono, Division of Nephrology and Hypertension, Diabetes Center, Tokyo Women's Medical University School of Medicine. 8-1 Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan
E-mail: babazono@dmc.twmu.ac.jp
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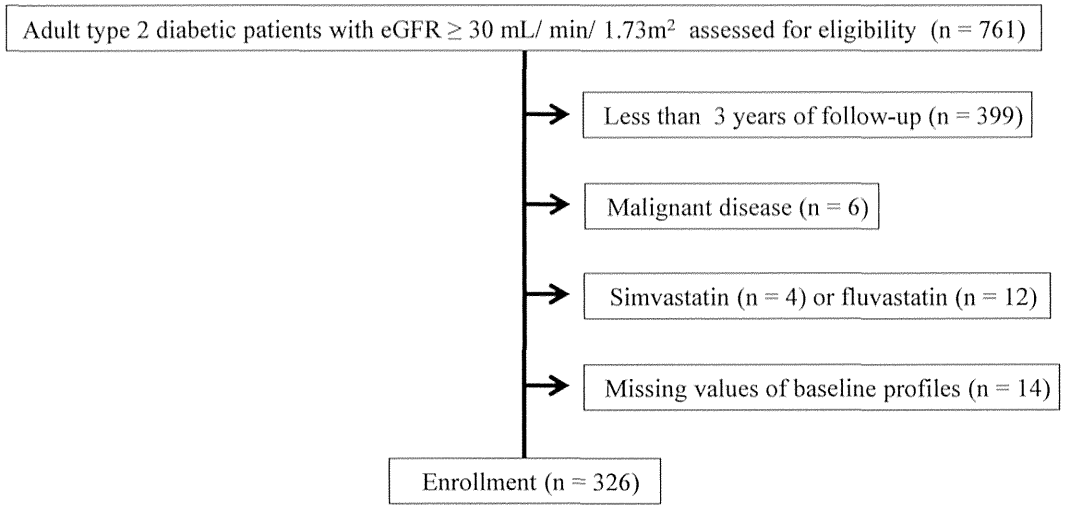

Fig. 1. Flow diagram of the study population.

previous reports have shown differences among statins in their effect in the progression of DKD[8, 9], and such differences are thought to have a significant influence on the selection of statins for diabetic patients. In the PLANET 1 trial of diabetic patients, atorvastatin significantly reduced the urinary protein levels without decreasing the glomerular filtration rate (GFR). In contrast, the patients treated with rosuvastatin exhibited a significant decline in GFR without any effect on the urinary protein levels[8]. However, other studies have reported no differences in the changes in GFR or urinary albumin levels among statins in type 2 diabetic patients[10, 11]. Hence, whether there is a distinction between statins against the progression of DKD remains controversial. Furthermore, the duration of follow-up in the above-mentioned studies was relatively short (all within one year).

Aim

In this study, we aimed to longitudinally examine the comparative effects of statins on the kidney function in patients with type 2 diabetes over a 3-year follow-up period.

Methods

Study Design and Participants

This study was a hospital-based single-center observational longitudinal cohort study using a historical cohort of adult Japanese patients with type 2 diabetes. The study protocol was designed in adherence to the Declaration of Helsinki and approved by the Ethics Committee of Tokyo Women's Medical University Hospital. The present study used data obtained from clinical information systems (electronic medical records). We initially recruited 761 ambulatory patients newly prescribed statins who exhibited an estimated GFR (eGFR) of ≥ 30 mL/min/1.73 m^2 at the Diabetes Center, Tokyo Women's Medical University Hospital, Tokyo, Japan, during the period between April 2006 and June 2010. Follow-up data were collected until June 2013. Type 2 diabetes was diagnosed according to the Japan Diabetes Society (JDS) criteria[12].

At their regular ambulatory visit, the subjects underwent baseline anthropometric and physical examinations. Laboratory data for random spot samples were used. If statin therapy was discontinued or switched to another statin, follow-up was terminated. A flow diagram of the study population is presented in **Fig. 1**. Patients with less than three years of follow-up (n=399) were excluded to assure a valid assessment of the change in GFR[13]. Patients with malignant disease (n=6) at baseline were also excluded, as were those prescribed simvastatin (n=4) or fluvastatin (n=12) because the number of these patients was too small to conduct an adequate analysis. Patients with missing values for baseline data (n=14) were also excluded. Therefore, a total of 326 patients were included in the final analysis.

Measurements

High-density lipoprotein (HDL) cholesterol levels were determined using polyethylene glycol-pretreated enzymes, triglyceride levels based on enzymatic methods and LDL cholesterol levels according to enzymatic methods or Friedewald's equation (for a triglyceride level of <400 mg/dL). Serum creatinine levels

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were determined using enzymatic methods. Hemoglobin A1c (HbA1c) levels were measured with high-performance liquid chromatography (HPLC) using a set of calibrators assigned by the JDS (normal range, 4.3-5.8%). Therefore, in the present study, National Glycohemoglobin Standardization Program (NGSP)-equivalent values were obtained using the following equation: HbA1c (%) = 1.02 × HbA1c (JDS) (%) + 0.25% [14]. Proteinuria was determined according to a urine dipstick test and defined as a finding of protein ± (trace) or more.

GFR was estimated using the following modified three-variable equation, as proposed by the Japanese Society for Nephrology: eGFR (mL/min/1.73 m^2) = 194 × Age (years)$^{-0.287}$ × serum creatinine level (in mg/dL)$^{-1.094}$ × (0.739 if female) [15].

Outcome Measurements

The first outcome measurement was the annual rate of change in eGFR (mL/min/1.73 m^2/year). For each individual, the rate of change in eGFR per year was determined using a simple linear regression analysis, with eGFR as a function of time in years, applied to eGFR values obtained during the follow-up period. In addition, we assessed this outcome measurement using a linear mixed-effects model regression analysis.

The second outcome measurement was as follows: (1) a reduction in eGFR of > 30 mL/min/ 1.73 m^2 for individuals with a baseline eGFR of ≥ 60 mL/min/1.73 m^2 or (2) a reduction in eGFR of > 50% for individuals with a baseline eGFR of < 60 mL/min/1.73 m^2. We consider these cutoff values to be clinically significant and similar to those selected in other studies including a similar range of eGFR values [16, 17].

Statistical Analysis

Continuous variables are expressed as the arithmetic mean ± standard deviation (SD), geometric mean with the 95% confidence interval (CI) or least squares mean ± standard error (SE), as appropriate according to the data distribution. Categorical data are expressed as numbers (%). For the statistical analyses, Fisher's exact probability test, chi-square test, analysis of variance (ANOVA), analysis of covariance (ANCOVA), simple linear regression analysis, linear mixed-effects model regression analysis and Cox proportional hazards model analysis were used as appropriate.

Due to the potential impact of bias in the selection of statin in the present observational study, the standardized inverse probability of treatment weight (IPTW) was calculated based on the probability of receiving each statin (propensity score: PS). The PS was estimated using a multinomial logistic regression model that included the following parameters; age, sex, body mass index (BMI), duration of diabetes, smoking status, history of cardiovascular disease, start date of statin therapy, use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, other hypertensive agents or lipid-lowering agents other than statins, systolic blood pressure, diastolic blood pressure, HbA1c, logarithmically transformed triglycerides, HDL cholesterol, LDL cholesterol, eGFR, urinary protein ± or 1 + and urinary protein 2 + or over.

The rate of change in eGFR determined using a simple linear regression analysis does not take into account the variety in the number and spacing of eGFR measurements and the duration of the follow-up period for each individual. Therefore, we also determined the rate of change in eGFR using a linear mixed-effects model regression analysis in order to minimize the effects of this limitation. The intercept and slope were treated as random effects in this analysis. In the adjusted model using a linear mixed-effects model regression analysis, the above-mentioned 20 parameters were used as covariates. A p value of < 0.05 was considered to be significant. All statistical analyses were performed using the SAS version 9.3 software program (SAS Institute, Cary, NC).

Results

Baseline Characteristics

We analyzed a total of 326 patients, including 126 women and 200 men with a mean (± SD) age of 60 ± 11 years (range, 23-84 years). The baseline demographic and laboratory data for each statin group are presented in **Table 1**. The mean daily initial dose of each statin was 7.6 ± 2.5 mg (range, 5-10 mg), 2.6 ± 0.4 mg (range, 2.5-5 mg), 5.9 ± 2.0 mg (range, 2.5-10 mg) and 1.1 ± 0.3 mg (range, 1-2 mg) for pravastatin, rosuvastatin, atorvastatin and pitavastatin, respectively.

Changes in the LDL Cholesterol Levels in Each Statin Group

The mean daily dose of each statin at the final visit was 8.3 ± 3.2 mg (range, 5-20 mg), 2.9 ± 1.0 mg (range, 2.5-7.5 mg), 7.0 ± 3.0 mg (range, 2.5-20 mg) and 1.4 ± 0.8 mg (range, 1-4 mg) for pravastatin, rosuvastatin, atorvastatin and pitavastatin, respectively. The mean (± SD) difference between the LDL cholesterol levels at the start and final measurements during the follow-up period was 41 ± 25, 68 ± 28, 62 ± 29 and 49 ± 25 mg/dL in the patients treated with pravastatin, rosuvastatin, atorvastatin and pitavastatin, respectively. The LDL cholesterol levels at the final measurement were 120 ± 23, 95 ± 30, 103 ± 29 and 100 ± 20 mg/dL

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Table 1. Baseline demographic and laboratory data for each statin group

	Pravastatin (n=98)	Rosuvastatin (n=92)	Atorvastatin (n=72)	Pitavastatin (n=64)	p value
Age, mean (SD), year	62 (12)	59 (10)	60 (11)	60 (11)	0.4
Men, n (%)	50 (51.0)	71 (77.2)	41 (56.9)	38 (59.4)	0.002
Duration of diabetes, mean (SD), year	12 (10)	10 (9)	11 (9)	10 (8)	0.4
Body mass index, mean (SD), kg/m^2	24.3 (3.0)	25.9 (3.9)	25.1 (3.6)	25.8 (4.5)	0.01
Diabetes therapy, n (%)					0.2
None	24 (24.5)	17 (18.5)	12 (16.7)	15 (23.4)	
OHA	54 (55.1)	58 (63.0)	43 (59.7)	28 (43.8)	
Insulin	20 (20.4)	17 (18.5)	17 (23.6)	21 (32.8)	
Systolic blood pressure, mean (SD), mmHg	135 (18)	133 (19)	136 (22)	133 (19)	0.6
Diastolic blood pressure, mean (SD), mmHg	78 (11)	77 (12)	77 (11)	76 (10)	0.8
Use of ACE inhibitor blockers, n (%)	5 (5.1)	11 (12.0)	7 (9.7)	5 (7.8)	0.4
Use of angiotensin receptor blocker blockers, n (%)	36 (36.7)	37 (40.2)	25 (34.7)	27 (42.2)	0.8
Use of other antihypertensive drug, n (%)	30 (30.6)	25 (27.2)	21 (29.2)	22 (34.4)	0.8
Use of lipid lowering agents other than statin, n (%)	5 (5.1)	5 (5.4)	3 (4.2)	5 (7.8)	0.8
History of cardiovascular disease, n (%)	8 (8.2)	17 (18.5)	10 (13.9)	16 (25.0)	0.03
Former or current smokers, n (%)	35 (35.7)	54 (58.7)	36 (50.0)	29 (45.3)	0.02
Date started statin prescription, n (%)					<0.001
April 2006 - December 2008	57 (58.2)	49 (53.3)	52 (72.2)	22 (34.4)	
January 2009 - June 2010	41 (41.8)	43 (46.7)	20 (27.8)	42 (65.6)	
Laboratory data					
HbA1c, mean (SD), %	7.5 (1.2)	8.0 (1.4)	7.8 (1.3)	7.6 (1.4)	0.09
Triglycerides, geometric mean (95% CI), mg/dL	127 (115-140)	159 (145-174)	154 (138-172)	144 (127-164)	0.009
HDL cholesterol, mean (SD), mg/dL	56 (14)	49 (11)	53 (16)	49 (14)	0.001
LDL cholesterol, mean (SD), mg/dL	161 (19)	163 (23)	165 (26)	149 (27)	<0.001
Creatinine, mean (SD), mg/dL	0.75 (0.18)	0.86 (0.25)	0.75 (0.18)	0.79 (0.21)	0.002
Estimated GFR, mean (SD), mL/min/1.73 m^2	74.4 (16.3)	72.5 (19.1)	77.4 (20.0)	73.7 (17.3)	0.4
Urinary protein, n (%)					0.02
none	65 (66.3)	53 (57.6)	39 (54.2)	42 (65.6)	
± (trace) or 1+	31 (31.6)	26 (28.3)	22 (30.5)	20 (31.3)	
2+ or over	2 (2.1)	13 (14.1)	11 (15.3)	2 (3.1)	

Abbreviations: OHA: oral hypoglycemic agents, ACE: angiotensin-converting enzyme, GFR: glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, SD: standard deviation, CI: confidence interval

in the patients treated with pravastatin, rosuvastatin, atorvastatin and pitavastatin, respectively.

Comparison of the Annual Rate of Change in eGFR

The median follow-up period was 4.3 years (range, 3.0-7.1 years). The mean (±SD) number of creatinine measurements used to determine the change in eGFR was 18±12. Of the 326 patients, 18 were lost to follow-up. The mean (±SE) annual rate of change in eGFR among the 326 patients determined using the simple linear regression analysis was −1.71±0.15 mL/min/1.73 m^2/year. In the linear mixed-effects model regression analysis, the mean rate of change in eGFR was −1.71±0.15 mL/min/1.73 m^2/year.

When the changes in eGFR were compared between the four statin groups, the mean (±SE) rate of change in eGFR among the patients treated with pravastatin (−0.86±0.28 mL/min/1.73 m^2/year) was significantly lower than that observed among the patients treated with rosuvastatin (−1.80±0.27, p=0.02), atorvastatin (−1.99±0.28, p=0.004) and pitavastatin (−2.23±0.49, p=0.02) in the analysis using the IPTW method (**Table 2**). Similar results were obtained in the linear mixed-effects model regression analysis (**Table 2**). As expected, the mean rate of change in eGFR among the patients treated with pravastatin was significantly lower than that noted in the non-pravastatin group (**Table 2**). There were no differences in the changes in eGFR between three groups, other than with the pravastatin group, in all models. Further-

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Table 2. Comparison of the change in eGFR in each statin group

	Pravastatin (n=98)	Rosuvastatin (n=92)	Atorvastatin (n=72)	Pitavastatin (n=64)	Pravastatin (n=98)	Non-Pravastatin (n=228)
Model 1						
eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.89 (0.27)	−1.99 (0.28)†	−2.20 (0.32)†	−2.02 (0.33)†	−0.89 (0.27)	−2.06 (0.18)‡
Model 2						
eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.86 (0.28)	−1.80 (0.27)*	−1.99 (0.28)†	−2.23 (0.49)*	−0.81 (0.27)	−1.92 (0.18)‡
Model 3						
eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.89 (0.27)	−2.00 (0.28)†	−2.15 (0.31)†	−2.03 (0.34)†	−0.89 (0.27)	−2.06 (0.18)‡
Model 4						
eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.88 (0.27)	−1.97 (0.28)†	−2.14 (0.31)†	−2.00 (0.34)*	−0.88 (0.27)	−2.04 (0.18)‡

Non-pravastatin refers to rosuvastatin, atorvastatin and pitavastatin. The data are expressed as the mean (SE). Model 1 was analyzed using a simple regression analysis of the eGFR values obtained during the follow-up period for each individual. In model 2, the change in eGFR calculated according to the simple regression analysis was adjusted using the standardized inverse probability of treatment weighted (IPTW) method. Model 3 was analyzed using the linear mixed-effects model. Model 4 was analyzed using the linear mixed-effects model adjusted for the covariates.
Abbreviations: eGFR: estimated glomerular filtration rate, SE: standard error, *$p<0.05$ versus pravastatin, $^{\dagger}p<0.01$ versus pravastatin, $^{\ddagger}p<0.001$ versus pravastatin

more, we obtained similar results when the difference between the LDL cholesterol levels at the first and final measurements during the follow-up period was incorporated into the analysis as an independent variable.

We next conducted sensitivity analyses among the subgroups classified according to the degree of baseline eGFR (≥60 mL/min/1.73 m^2 or less), proteinuria (absence or presence), HbA1c (≥8% or less), blood pressure (≥140/90 mmHg or less), HDL cholesterol (≥40 mg/dL or less), BMI (≥25 kg/m^2 or less) and cardiovascular disease (absence or presence) (**Table 3**). In order to maintain statistical power, we compared the rate of change in eGFR between the pravastatin group and the non-pravastatin group. Among the patients with an eGFR of <60 mL/min/1.73 m^2, those with an HbA1c level of ≥8%, blood pressure of ≥140/90 mmHg, HDL cholesterol level of <40 mg/dL, BMI of <25 kg/m^2 or cardiovascular disease, we were unable to conduct the analyses using the IPTW method because the convergence criterion was not satisfied when the PS was calculated. Among the patients with an eGFR of <60 mL/min/1.73 m^2, those without proteinuria, an HDL cholesterol level of <40 mg/dL or with cardiovascular disease, the pravastatin group showed a slower, although not significantly, change in eGFR compared to the non-pravastatin group. Among the other patients, the rate of change in eGFR in the pravastatin group was significantly lower than that observed in the non-pravastatin group. Furthermore, in order to reduce the influence of renin-angiotensin system blockers (ACE inhibitors and angiotensin receptor blockers) on the rate of change in eGFR, we conducted a sensitivity analysis in a subgroup excluding 53 patients for whom renin-angiotensin system blockers were newly prescribed or discontinued during the follow-up period. In this sensitivity analysis, the pravastatin group (n=91) also demonstrated a significantly slower rate of change in eGFR than the non-pravastatin group (n=182). Finally, we conducted a sensitivity analysis in 183 patients in whom the urinary albumin levels were measured at baseline. We conducted the analyses using the logarithmically urinary albumin levels in place of the urinary protein levels obtained with the urine dipstick test. In this analysis, the mean rate of change in eGFR among the patients treated with pravastatin (n=49) was also significantly lower than that seen in the patients treated without pravastatin (n=134).

Comparison of Risk Factors for the Incidence of the Secondary Outcomes in Each Statin Group

During the median follow-up period of 4.2 years (range, 1.0-7.1 years), one of the 98 patients treated with pravastatin, five of the 92 patients treated with rosuvastatin, five of the 72 patients treated with atorvastatin and four of the 64 patients treated with pitavastatin progressed to the second outcome. The hazard ratios for the incidence of the second outcome in each

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Table 3. Comparison of the changes in eGFR based on the sensitivity analysis

Patients with eGFR ≥ 60 mL/min/ 1.73 m^2	Pravastatin (n = 81)	Non-pravastatin (n = 176)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.84 (0.31)	− 2.06 (0.21)	0.001
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.88 (0.26)	− 1.90 (0.21)	0.002
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.85 (0.31)	− 2.07 (0.21)	0.001
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.82 (0.31)	− 2.02 (0.21)	0.001
Patients with eGFR < 60 mL/ min/ 1.73 m^2	Pravastatin (n = 17)	Non-pravastatin (n = 52)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.14 (0.53)	− 2.09 (0.30)	0.1
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.14 (0.53)	− 2.08 (0.30)	0.1
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.13 (0.53)	− 2.08 (0.30)	0.1
Patients without proteinuria	Pravastatin (n = 65)	Non-pravastatin (n = 134)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.88 (0.25)	− 1.26 (0.17)	0.2
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.03 (0.31)	− 1.21 (0.18)	0.6
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.82 (0.25)	− 1.27 (0.17)	0.1
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.79 (0.25)	− 1.24 (0.17)	0.1
Patients with proteinuria	Pravastatin (n = 33)	Non-pravastatin (n = 94)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.91 (0.57)	− 3.20 (0.33)	< 0.001
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.73 (0.38)	− 3.00 (0.33)	< 0.001
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.97 (0.57)	− 3.19 (0.33)	< 0.001
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.99 (0.57)	− 3.16 (0.33)	0.001
Patients with HbA1c < 8%	Pravastatin (n = 75)	Non-pravastatin (n = 146)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.69 (0.24)	− 1.41 (0.17)	0.02
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.60 (0.27)	− 1.39 (0.19)	0.02
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.72 (0.24)	− 1.37 (0.17)	0.03
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.70 (0.24)	− 1.38 (0.17)	0.02
Patients with HbA1c ≥ 8%	Pravastatin (n = 23)	Non-pravastatin (n = 82)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.53 (0.70)	− 3.23 (0.37)	0.03
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.51 (0.72)	− 3.28 (0.37)	0.03
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.49 (0.71)	− 3.25 (0.37)	0.03
Patients with blood pressure < 140/90 mmHg	Pravastatin (n = 52)	Non-pravastatin (n = 138)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.03 (0.33)	− 1.83 (0.20)	0.04
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.96 (0.47)	− 1.75 (− 0.22)	0.1
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.98 (0.33)	− 1.85 (0.20)	0.02
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 1.00 (0.33)	− 1.83 (0.20)	0.03
Patients with blood pressure ≥ 140/90 mmHg	Pravastatin (n = 46)	Non-pravastatin (n = 90)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.72 (0.44)	− 2.42 (0.32)	0.002
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.75 (0.45)	− 2.41 (0.32)	0.003
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.69 (0.45)	− 2.39 (0.32)	0.002
Patients with HDL cholesterol ≥ 40 mg/dL	Pravastatin (n = 91)	Non-pravastatin (n = 184)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.89 (0.27)	− 1.99 (0.19)	0.001
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.93 (0.26)	− 1.83 (0.20)	0.006
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.89 (0.27)	− 1.98 (0.19)	0.001
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.87 (0.27)	− 1.96 (0.19)	0.001
Patients with HDL cholesterol < 40 mg/dL	Pravastatin (n = 7)	Non-pravastatin (n = 44)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.84 (1.17)	− 2.36 (0.47)	0.2
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.85 (1.19)	− 2.37 (0.47)	0.2
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	− 0.91 (1.19)	− 2.35 (0.47)	0.3

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(Cont Table 3)

Patients with body mass index <25 kg/m^2	Pravastatin (n=60)	Non-pravastatin (n=111)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.72 (0.30)	−1.78 (0.22)	0.004
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.71 (0.30)	−1.77 (0.21)	0.004
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.71 (0.30)	−1.77 (0.22)	0.005
Patients with body mass index ≥25 kg/m^2	Pravastatin (n=38)	Non-pravastatin (n=117)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−1.15 (0.49)	−2.33 (0.28)	0.04
Model 2. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.95 (0.40)	−2.17 (0.28)	0.01
Model 3. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−1.15 (0.49)	−2.33 (0.28)	0.04
Model 4. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−1.14 (0.48)	−2.31 (0.28)	0.04
Patients without cardiovascular disease	Pravastatin (n=90)	Non-pravastatin (n=185)	p value
Model 1. eGFR change rate, mean (SE), mL/min/1.73 m^2/year	−0.86 (0.28)	−2.14 (0.20)	<0.001
Model 2. eGFR change rate, mean (SE), mL/ min/1.73 m^2/year	−0.77 (0.27)	−1.99 (0.20)	<0.001
Model 3. eGFR change rate, mean (SE), mL/ min/1.73 m^2/year	−0.88 (0.28)	−2.13 (0.20)	<0.001
Model 4. eGFR change rate, mean (SE), mL/ min/1.73 m^2/year	−0.88 (0.28)	−2.10 (0.19)	<0.001
Patients with cardiovascular disease	Pravastatin (n=8)	Non-pravastatin (n=43)	p value
Model 1. eGFR change rate, mean (SE), mL/ min/1.73 m^2/year	−1.16 (0.94)	−1.72 (0.41)	0.6
Model 3. eGFR change rate, mean (SE), mL/ min/1.73 m^2/year	−1.01 (0.99)	−1.74 (0.42)	0.5
Model 4. eGFR change rate, mean (SE), mL/ min/1.73 m^2/year	−0.96 (0.99)	−1.74 (0.42)	0.5

Non-pravastatin refers to rosuvastatin, atorvastatin and pitavastatin. The data are expressed as the mean (SE). Model 1 was analyzed using a simple regression analysis of the eGFR values obtained during the follow-up period for each individual. In model 2, the change in eGFR calculated using the simple regression analysis was adjusted using the standardized inverse probability of treatment weighted (IPTW) method. Model 3 was analyzed using the linear mixed-effects model. Model 4 was analyzed using the linear mixed-effects model adjusted for the covariates.
Abbreviations: eGFR: estimated glomerular filtration rate, SE: standard error, HDL: high-density lipoprotein

statin group are shown in **Table 4**. The patients treated with pitavastatin had a higher risk of progressing to the second outcome than those treated with pravastatin. The hazard ratios for the patients treated with rosuvastatin or atorvastatin tended to be higher than those for the pravastatin group; however, the difference was not significant.

Discussion

In this single-center longitudinal observational study using a historical cohort observed over at least three years, we found that pravastatin may be superior to rosuvastatin, atorvastatin and pitavastatin in preserving the kidney function in patients with type 2 diabetes. The decline in eGFR observed in the patients treated with pravastatin was significantly slower than that noted in those treated with the other three statins. This finding was confirmed using the IPTW method based on the PS and the linear mixed-effects model regression analysis.

Although we were unable to clarify the mechanisms underlying the differences between statins in the present study, the following explanations can be speculated. First, differences in the lipophilicity of statins may have contributed to the present findings. Pravastatin is considered to be the most hydrophilic statin[18]. Lipophilic statins are able to easily penetrate extrahepatic cellular membranes. Statins inhibit cholesterol synthesis as well as the production of ubiquinone (coenzyme Q10; CoQ10), a lipid-soluble endogenous antioxidant that prevents the oxidation of lipids, proteins and DNA[19, 20]. Therefore, the other three statins are thought to more strongly inhibit the production of CoQ10 in extrahepatic cells than pravastatin. Recent basic studies have clearly shown that CoQ10 treatment prevents the development of DKD by reducing oxidative stress in db/db mice employed as a model of type 2 diabetes[21, 22]. In light of these findings, the superiority of pravastatin demonstrated in the present study may be partly explained by differences in CoQ10 production in extrahepatic cells as a result of differences in lipophilicity. Second, differences in effects on glucose metabolism among statins may partly explain the present findings. An association between statin use and the increasing number of cases of new-onset diabetes was recently suggested[23]. However, pravastatin has been shown to increase insulin sensitivity by enhancing adiponectin secretion in both mice and humans[24]. Indeed, the West of Scotland

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Table 4. Hazard ratios for the incidence of the secondary outcomes in each statin group

	Pravastatin ($n=98$)	Rosuvastatin ($n=92$)	Atorvastatin ($n=72$)	Pitavastatin ($n=64$)	Pravastatin ($n=98$)	Non-Pravastatin ($n=228$)
Crude model						
Hazard ratio (95%CI) for the incidence of the secondary outcome	1.00 (ref.)	5.52 (0.64-47.33) $p=0.1$	6.42 (0.75-54.98) $p=0.09$	6.71 (0.75-60.15) $p=0.09$	1.00 (ref.)	6.14 (0.81-46.70) $p=0.08$
Adjusted model						
Hazard ratio (95%CI) for the incidence of the secondary outcome	1.00 (ref.)	5.50 (0.61-49.68) $p=0.1$	7.26 (0.80-65.82) $p=0.08$	19.38 (2.11-178.28) $p=0.009$	1.00 (ref.)	8.69 (1.13-67.02) $p=0.04$

The second outcome was defined as follows: (1) a reduction in eGFR of >30 mL/min/1.73 m^2 for individuals with a baseline eGFR of ≥60 mL/min/1.73 m^2 or (2) a reduction in eGFR of >50% for individuals with a baseline eGFR of <60 mL/min/1.73 m^2. Non-pravastatin refers to rosuvastatin, atorvastatin and pitavastatin. The adjusted model was analyzed using the standardized inverse probability of treatment weighted (IPTW) method. Abbreviations: eGFR: estimated glomerular filtration rate, CI: confidence interval

Coronary Prevention Study (WOSCOP) suggested that pravastatin reduces the risk of incident diabetes by 30% compared to a placebo[25], and the United States Food and Drug Administration mandated labeling changes for all statins except pravastatin in February 2012[26, 27]. Moreover, previous clinical studies have suggested an independent association between insulin resistance and DKD progression[28, 29].

The present findings may be unique to Asian populations, as lower statin doses have been shown to achieve lipid improvements in Asians comparable to those obtained with higher doses in Caucasians[30]. Indeed, the doses of statins used in the present study were relatively low. Furthermore, the targeted level of LDL cholesterol in Japanese diabetic patients is milder than that for Western populations[31, 32], which may be reflected in the present findings among Japanese diabetic patients.

In the current sensitivity analyses, the superiority of pravastatin in preserving the eGFR was not confirmed in the non-proteinuric patients. The change in eGFR observed in the non-proteinuric patients in the present study was more stable than that seen in the other groups. In such patients, the kidney function may be insusceptible to the additional beneficial effects of statins. In the post hoc sub-analysis of the Collaborative Atorvastatin in Diabetes Study (CARDS), atorvastatin was shown to exert significant beneficial effects on the changes in GFR in albuminuric patients, but not in normoalbuminuric patients with a stable change in GFR[33]. Meanwhile, the follow-up period and/or sample size used in the present study may be simply inadequate to evaluate changes in GFR.

In contrast to the results of the present study, in the PLANET 1 trial, rosuvastatin was found to be inferior to atorvastatin in preserving the kidney function in diabetic patients[8]. However, recent studies using meta-analysis have shown that the effects of rosuvastatin and atorvastatin on the changes in GFR are similar[6, 7]. Furthermore, the dose of statins administered in the PLANET 1 trial was much higher than that observed in the present study[8]. Kimura *et al.* demonstrated the superiority of pitavastatin versus pravastatin in reducing the urinary albumin levels in type 2 diabetic patients with macroalbuminuria[9]. However, the decline in GFR in the patients treated with pitavastatin tended to be steeper than that noted in the patients treated with pravastatin[9]. Finally, several reports have shown improvements in the kidney function with statin therapy in type 2 diabetic patients, unlike the present study[10, 11, 33-35]. However, studies reporting improvements in the GFR with statin therapy involved post hoc sub-analyses of clinical trials designed to assess non-renal outcomes[33-35]. In addition, the follow-up duration in certain studies was inadequate to evaluate changes in the kidney function[10, 11].

The present study has several limitations. First, this was an observational historical cohort study, which comes with inherent bias in the selection of drugs, unlike randomized controlled trials. Recently, analyses using PS have been increasingly used to reduce or minimize the effects of confounding factors when assessing observational or non-randomized data[36]. In the present study, we adopted the IPTW method based on the PS in order to analyze the comparative effects of statins on the changes in eGFR. This method has been shown to be a powerful tool for evaluating observational data[37, 38], although we understand that it is not possible to correct for bias resulting from unknown or unmeasured potential confounding factors. Further-

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more, in order to take into account the variety in the number and spacing of eGFR measurements and the duration of the follow-up period for each individual, we determined the rate of change in eGFR using a linear mixed-effects model regression analysis. Second, the present study was performed using a relatively small cohort. Third, the GFR values were estimated using only the serum creatinine levels. Fourth, the urinary albumin level, a strong risk factor for a decline in GFR, was not measured in all patients, although similar results were obtained when the sensitivity analysis was performed among the patients with urinary albumin measurements. Fifth, the present study did not include a control group not prescribed statin therapy. Sixth, we cannot exclude the possibility that the present cohort included patients with renal diseases other than diabetic nephropathy or nephrosclerosis, such as glomerulonephritis, even though none of the subjects were diagnosed as such at baseline. Finally, the present study was carried out at a single urban university hospital; therefore, the study sample may not be representative of the entire Japanese type 2 diabetic patient population.

Conclusion

The present findings provide evidence of the superiority of pravastatin over rosuvastatin, atorvastatin and pitavastatin in preserving the kidney function in Japanese patients with type 2 diabetes. Despite the understanding that the most important role of statins is cardiovascular protection, the current results may be useful for selecting particular drugs for patients with type 2 diabetes. Nevertheless, the present findings should be confirmed in further studies including larger sample sizes and a multi-center design as well as randomized controlled trials.

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Conflicts of Interest

There are no conflicts of interest to declare for any of the authors.

References

1) Imai E, Yamagata K, Iseki K, Iso H, Horio M, Makino H, Matsuo S: Kidney disease screening program in Japan: History, outcome, and perspectives. Clin J Am Soc Nephrol, 2007; 2: 1360-1366
2) Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N, Mogensen CE, Cooper M, Marre M, Williams B, Hamet P, Mancia G, Woodward M, MacMahon S, Chalmers J on behalf of the ADVANCE Collaborative Group: Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol, 2009; 20: 1813-1821
3) Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C: Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet, 2008; 371: 117-125
4) Sandhu S, Wiebe N, Fried LF, Tonelli M: Statins for improving renal outcomes: A meta-analysis. J Am Soc Nephrol, 2006; 17: 2006-2016
5) Douglas K, O'Malley PG, Jackson JL: Meta-analysis: the effect of statins on albuminuria. Ann Intern Med, 2006; 145: 117-124
6) Wu Y, Wang Y, An C, Dong Z, Liu H, Zhang Y, Zhang M, An F: Effects of rosuvastatin and atorvastatin on renal function. Circ J, 2012; 76: 1259-1266
7) Savarese G, Musella F, Volpe M, Paneni F, Perrone-Filardi P: Effects of atorvastatin and rosuvastatin on renal function: a meta-analysis. Int J Cardiol, 2013; 167: 2482-2489
8) Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease: XLVII European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress, June 25-28, 2010, Munich, Germany
9) Kimura S, Inoguchi T, Yokomizo H, Maeda Y, Sonoda N, Takayanagi R: Randomized comparison of pitavastatin and pravastatin treatment on the reduction of urinary albumin in patients with type 2 diabetic nephropathy. Diabetes Obes Metab, 2012; 14: 666-669
10) Sorof J, Berne C, Siewert-Delle A, Jørgensen L, Sager P on behalf of the URANUS study investigators: Effect of rosuvastatin or atorvastatin on urinary albumin excretion and renal function in type 2 diabetic patients. Diabetes Res Clin Pract, 2006; 72: 81-87
11) Mori H, Okada Y, Tanaka Y: Effects of pravastatin, atorvastatin, and rosuvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia. Diabetol Int, 2013; 4; 117-125
12) Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, Nanjo K, Sasaki A, Seino Y, Ito C, Shima K, Nonaka K, Kadowaki T; Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract, 2002; 55: 65-85
13) Levey AS, Gassman JJ, Hall PM, Walker WG: Assessing the progression of renal disease in clinical studies: effects of duration of follow-up and regression to the mean. Modification of Diet in Renal Disease (MDRD) Study Group. J Am Soc Nephrol, 1991; 1: 1087-1094
14) Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito

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H, Tominaga M, Oikawa S, Noda M, Kawamura T, Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y, Ohashi H, Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest, 2012; 3; 39-40
15) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis, 2009; 53: 982-992
16) Fried LF, Duckworth W, Zhang JH, O'Connor T, Brophy M, Emanuele N, Huang GD, McCullough PA, Palevsky PM, Seliger S, Warren SR, Peduzzi P, for VA NEPHRON-D Investigators: Design of Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D). Clin J Am Soc Nephrol, 2009; 4: 361-368
17) Hurg AM, Roumie CL, Greevy RA, Liu X, Grijalva CG, Murff HJ, Ikizler TA, Griffin MR: Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int, 2012; 81: 698-706
18) Mukhtar RY, Reid J, Reckless JP: Pitavastatin. Int J Clin Pract, 2005; 59: 239-252
19) Marcoff L, Thompson PD: The role of coenzyme Q10 in statin-associated myopathy: a systematic review. J Am Coll Cardiol, 2007; 49: 2231-2237
20) Frei B, Kim MC, Ames BN: Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc Natl Acad Sci USA, 1990; 87: 4879-4883
21) Sourris KC, Harcourt BE, Tang PH, Morley AL, Huynh K, Penfold SA, Coughlan MT, Cooper ME, Nguyen TV, Ritchie RH, Forbes JM: Ubiquinone (coenzyme Q10) prevents renal mitochondrial dysfunction in an experimental model of type 2 diabetes. Free Radic Biol Med, 2012; 52: 716-723
22) Persson MF, Franzén S, Catrina SB, Dallner G, Hansell P, Brismar K, Palm F: Coenzyme Q10 prevents GDP-sensitive mitochondrial uncoupling, glomerular hyperfiltration and proteinuria in kidneys from db/db mice as a model of type 2 diabetes. Diabetologia, 2012; 55: 1535-1543
23) Preiss D, Sattar N: Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol, 2011; 22: 460-466
24) Koh KK, Sakuma I, Quon MJ: Differential metabolic effects of distinct statins. Atherosclerosis, 2011; 215: 1-8
25) Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A: Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation, 2001; 103: 357-362
26) US Food and Drug Administration. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. 2012. www.fda.gov/Drugs/DrugSafety/ ucm293101.htm.
27) Center for Drug Evaluation and Research. Approval package for: application number 019898Orig1s062. 2012. www.accessdata.fda.gov/drugsatfda_docs/nda/2012/019898s062.pdf.
28) Parvanova AI, Trevisan R, Iliev IP, Dimitrov BD, Vedovato M, Tiengo A, Remuzzi G, Ruggenenti P: Insulin resistance and microalbuminuria: a cross-sectional, case-control study of 158 patients with type 2 diabetes and different degree of urinary albumin excretion. Diabetes, 2006; 55: 1456-1462
29) Hsu CC, Chang HY, Huang MC, Hwang SJ, Yang YC, Tai TY, Yang HJ, Chang CT, Chang CJ, Li YS, Shin SJ, Kuo KN: Association between insulin resistance and development of microalbuminuria in type 2 diabetes: a prospective cohort study. Diabetes Care, 2011; 34: 982-987
30) Liao JK: Safety and efficacy of statins in Asians. Am J Cardiol, 2007; 99: 410-414
31) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K; Japan Atherosclerosis Society. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan – 2012 version. J Atheroscler Thromb, 2013; 20: 517-523
32) American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care, 2014; 37 (Suppl. 1): S14-S80
33) Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Charlton-Menys V, DeMicco DA, Fuller JH; CARDS Investigators: Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis, 2009; 54: 810-819
34) Shepherd J, Kastelein JP, Bittner VA, Carmena R, Deedwania PC, Breazna A, Dobson S, Wilson DJ, Zuckerman AL, Wenger NK; Treating to New Targets Steering Committee and Investigators: Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clin Proc, 2008; 83; 870-879
35) Kimura K, Shimano H, Yokote K, Urashima M, Teramoto T: Effects of pitavastatin (LIVALO tablet) on the estimated glomerular filtration rate (eGFR) in hypercholesterolemic patients with chronic kidney disease. Subanalysis of the LIVALO Effectiveness and Safety (LIVES) Study. J Atheroscler Thromb, 2010; 17: 601-609
36) Rosenbaum P, Rubin DB: The central role of the propensity score in observational studies for causal effects. Biometrika, 1983; 70: 41-55
37) Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ: Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. Med Care, 2007; 45 (10 Suppl. 2): S103-S107
38) Austin PC: The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. Med Decis Making, 2009; 29: 661-677

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SPECIAL ARTICLE

A new classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy

Masakazu Haneda · Kazunori Utsunomiya · Daisuke Koya · Tetsuya Babazono · Tatsumi Moriya · Hirofumi Makino · Kenjiro Kimura · Yoshiki Suzuki · Takashi Wada · Susumu Ogawa · Masaaki Inaba · Yoshihiko Kanno · Takashi Shigematsu · Ikuto Masakane · Ken Tsuchiya · Keiko Honda · Kazuko Ichikawa · Kenichiro Shide

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Abstract The Joint Committee on Diabetic Nephropathy has revised its Classification of Diabetic Nephropathy (Classification of Diabetic Nephropathy 2014) in line with the widespread use of key concepts such as the estimated glomerular filtration rate (eGFR) and chronic kidney disease. In revising the Classification, the Committee carefully evaluated, as relevant to current revision, the report of a study conducted by the Research Group of Diabetic Nephropathy, Ministry of Health, Labour and Welfare of Japan. Major revisions to the Classification are summarized as follows: (1) eGFR is substituted for GFR in the Classification; (2) the subdivisions A and B in stage 3 (overt nephropathy) have been reintegrated; (3) stage 4 (kidney failure) has been redefined as a GFR less than 30 mL/min/1.73 m^2, regardless of the extent of albuminuria; and (4) stress has been placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy.

Keywords Diabetic nephropathy · Chronic kidney disease (CKD) · Albuminuria · Proteinuria · Glomerular filtration rate (GFR)

Japan Diabetes Society, Japanese Society of Nephrology, Japanese Society for Dialysis Therapy, and Japan Society of Metabolism and Clinical Nutrition established the Joint Committee on Diabetic Nephropathy, which published the revised Classification of Diabetic Nephropathy 2014 in Japanese [1–4]. This is the English version of that revision.

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The following authors are members of Japan Diabetes Society: Masakazu Haneda, Kazunori Utsunomiya, Daisuke Koya, Tetsuya Babazono, Tatsumi Moriya.
The following authors are members of Japanese Society of Nephrology: Hirofumi Makino, Kenjiro Kimura, Yoshiki Suzuki, Takashi Wada, Susumu Ogawa.
The following authors are members of Japanese Society for Dialysis Therapy: Masaaki Inaba, Yoshihiko Kanno, Takashi Shigematsu, Ikuto Masakane, Ken Tsuchiya.
The following authors are members of Japan Society of Metabolism and Clinical Nutrition: Keiko Honda, Kazuko Ichikawa, Kenichiro Shide.

Introduction

Diabetic nephropathy became the leading cause of chronic dialysis in 1998. Since then, the incidence of this condition has increased with only a recent plateau. However, diabetic nephropathy continues to account for a large proportion of all cases of chronic kidney disease (CKD) and remains by far the most common underlying cause of chronic dialysis among all kidney diseases [5], consequently leading to the escalation of healthcare costs, thus representing a compelling medico-social issue of interest.

The Classification of Diabetic Nephropathy (hereafter "Classification") developed earlier by the Research Group

M. Haneda
Division of Metabolism and Biosystemic Science, Department of Medicine, Asahikawa Medical University, 1-1-1 Higashi-Nijyo, Midorigaoka, Asahikawa, Hokkaido 078-8510, Japan

K. Utsunomiya
Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine, Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan

of Diabetic Nephropathy at the Ministry of Health, Labour and Welfare (MHLW) [6] and later revised by the Joint Committee on Diabetic Nephropathy (hereafter "Committee") [7] is widely used in Japan. However, as the concept of CKD was proposed, followed by the classification of CKD stages [8], it became clear that there exists a subpopulation of patients with discrepant classifications of diabetic nephropathy and CKD. This is thought to be due to the fact that diabetic nephropathy is primarily classified according to the extent of albuminuria in addition to the glomerular filtration rate (GFR) (i.e., creatinine clearance [CCr]), whereas CKD is primarily classified based on the estimated GFR [estimated GFR (eGFR)]. Meanwhile, eGFR has become increasingly used to assess GFR, and a new classification of CKD was developed in 2012 [9]. Against this background, the Committee therefore discussed issues of interest in depth and sought to develop a revision of the Classification.

Development of the 2014 Classification (Revised Classification) (see Table 1)

Prior to revising the Classification, as part of a MHLW-subsidized project on kidney disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan", a "historical cohort study" was conducted by the Research Group of Diabetic Nephropathy, MHLW, involving a total of 4,355 subjects with type 2 diabetes from 10 participating healthcare facilities with the aim of evaluating renal events (i.e., a decrease in eGFR to half the baseline level and/or the need for dialysis), cardiovascular events and all-cause mortality [10, 11]. Summarized below are the major findings of this study (for detailed information, please access the MHLW website http://www.mhlw.go.jp/ or refer to the literature cited above).

1. Renal and cardiovascular events and all-cause mortality were significantly increased in the subjects with micro- or macroalbuminuria compared to that observed in the subjects with normoalbuminuria.
2. In those with renal impairment (defined as a GFR less than 60 mL/min/1.73 m^2):
   a. The risk of renal events increased in association with the onset of microalbuminuria and further increased with the onset of macroalbuminuria in the subjects;
   b. The risk of cardiovascular events was increased in those with micro-/macroalbuminuria; and
   c. All-cause mortality was increased in the subjects with macroalbuminuria as well as those with normoalbuminuria and microalbuminuria who exhibited a GFR of less than 30 mL/min/1.73 m^2.

While that study was not a true prospective study and involved only a limited number of facilities and patients from a population known to be less prone to cardiovascular

D. Koya
Department of Diabetology and Endocrinology, Kanazawa Medical University, 1-1 Uchinadamachi-daigaku, Kahoku-gun, Ishikawa 920-0293, Japan

T. Babazono
Department of Medicine, Diabetes Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-Ku, Tokyo 162-8666, Japan

T. Moriya
Health Care Center, Kitasato University, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan

H. Makino (✉)
Okayama University Hospital, 2-5-1 Shikada-machi, Kita-ku, Okayama, Okayama 700-8558, Japan
e-mail: makino@md.okayama-u.ac.jp

K. Kimura
Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan

Y. Suzuki
Health Administration Center, Niigata University, 2-8085 Igarashi, Nishi-ku, Niigata, Niigata 950-2181, Japan

T. Wada
Division of Nephrology, Department of Laboratory Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

S. Ogawa
Center for the Advancement of Higher Education, Tohoku University, Sendai, Japan

S. Ogawa
Division of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Hospital, 1-1 Seiryou-cho, Aoba-ku, Sendai, Miyagi 980-8574, Japan

M. Inaba
Department of Metabolism, Endocrinology, Molecular Medicine, Faculty of Medicine, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-cho, Abeno-ku, Osaka, Osaka 545-8585, Japan

Y. Kanno
Department of Nephrology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-Ku, Tokyo 160-0023, Japan

T. Shigematsu
Division of Nephrology, Department of Internal Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama, Wakayama 641-8509, Japan

events than those in Western countries, the findings provide important insight into the prognosis of diabetic nephropathy in Japanese patients. Therefore, in seeking to revise the Classification, the Committee gave due consideration to the above findings. At the same time, the following considerations were also taken into account.

1. The bulk of evidence for the classification of diabetic nephropathy comes from randomized controlled studies enrolling patients with diabetic nephropathy as defined based on the extent of albuminuria, and very little evidence is available for diabetic nephropathy as defined based on GFR.
2. The current "Medical Service Fee Schedule for Guidance on Preventing Diabetes-Associated Dialysis" was developed with the Classification in mind.
3. The "Guidelines for Clinical Efficacy Evaluation of Pharmacological Agents for Diabetic Nephropathy (Draft)" currently in use were developed with the Classification in mind.

Therefore, after giving due consideration to all of these issues during the course of several sessions, the Committee decided to leave the Classification essentially unchanged for now (Table 1), while showing how it may be aligned with the widespread CKD classification based on GFR (eGFR) ("see Appendix"). The former is not, however, presented as a heat map, due to the limitations of the study referred to above, which involved a small number of patients with diabetic nephropathy and included no dialysis patients, providing the basis for this revision. Again, as all kidney diseases affecting patients with diabetes are covered in the Classification, the Committee called for attention with notes included which were required, in order to highlight the importance of the differential diagnosis between diabetic nephropathy and non-diabetic kidney disease in all stages. The differential diagnosis calls for collaboration with nephrologists; such collaboration is not limited to cases requiring a renal biopsy. Furthermore, given that the disease may not always progress in some patients, numerous notes were included in the table in order to call attention to these cases. Additionally, in view of the potential need to use multiple anti-diabetic drugs over time, "Key Precautions in View of Drug Use" are included below the table. The major revisions to the Classification are summarized below:

1. eGFR is now substituted for GFR in the Classification.

Table 1 Classification of Diabetic Nephropathy 2014

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/1.73 m^2)
Stage 1 (pre-nephropathy)	Normoalbuminuria (< 30)	≥30[a]
Stage 2 (incipient nephropathy)	Microalbuminuria (30–299)[b]	≥30
Stage 3 (overt nephropathy)	Macroalbuminuria (≥ 300) or Persistent proteinuria (≥ 0.5)	≥30[c]
Stage 4 (kidney failure)	Any albuminuria/proteinuria status[d]	<30
Stage 5 (dialysis therapy)	Any status on continued dialysis therapy	

Diabetic nephropathy does not always progress from one stage to the next. The revised classification takes into account findings on the prognosis of type 2 diabetic patients from a "historical cohort study" conducted as part of the MHLW-subsidized Project on Kidney Disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan" [10, 11]

[a] While a GFR of less than 60 mL/min/1.73 m^2 is consistent with the diagnosis of CKD, underlying causes other than diabetic nephropathy may be involved in patients with a GFR below 60 mL/min/1.73 m^2 thus calling for the differential diagnosis between diabetic nephropathy and any other potential non-diabetic kidney diseases

[b] Patients with microalbuminuria are to be diagnosed as incipient nephropathy after the differential diagnosis based on the criteria for an early diagnosis of diabetic nephropathy

[c] Precautions are required in patients with macroalbuminuria, in whom renal events (e.g., a decrease in eGFR to half its baseline value, the need for dialysis) have been shown to increase as the GFR decreases below 60 mL/min/1.73 m^2

[d] All patients with a GFR of less than 30 mL/min/1.73 m^2 are classified as exhibiting kidney failure, regardless of their urinary albumin/protein values. However, in those with normoalbuminuria and microalbuminuria, the differential diagnosis is required between diabetic nephropathy and any other potential non-diabetic kidney diseases

Key Precautions in View of Drug Use: This table is intended, first and foremost, as a classification of diabetic nephropathy and not as a guide to drug use. All drugs, including anti-diabetic drugs, particularly renally metabolized agents, are to be used in accordance with their prescribing information, with due consideration to relevant factors such as GFR in each patient

I. Masakane
Department of Nephrology, Yabuki Hospital, 4-5-5 Shimakita, Yamagata, Yamagata 990-0885, Japan

K. Tsuchiya
Department of Internal Medicine IV, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-Ku, Tokyo 162-8666, Japan

K. Honda
Division of Medicine/Nutrition, Department of Applied Nutrition, Kagawa Nutrition University, 3-9-21 Chiyoda, Sakado, Saitama 350-0288, Japan

K. Ichikawa
Department of Nutrition, Kawasaki Medical School Hospital, 577 Matsushima, Kurashiki, Hiroshima 701-0192, Japan

K. Shide
Department of Metabolism and Clinical Nutrition, Kyoto University Hospital, 54 Shogoinkawara-cho, Sakyo-ku, Kyoto, Kyoto 606-8507, Japan

2. The stages used in the Classification have been simplified to include normoalbuminuria, microalbuminuria, macroalbuminuria and kidney failure.
3. The division between A and B (early versus late macroalbuminuria) in stage 3 has been abandoned and A and B have been reintegrated, due to the paucity of evidence for proteinuria of 1 g/day as the threshold for dividing the stage.
4. Kidney failure has been redefined in all cases as a GFR less than 30 mL/min/1.73 m^2, which represents the threshold value for kidney failure obtained by quantifying the existing definition of kidney failure in the Classification based on the Classification of the Japanese Society of Nephrology (JSN) [12] with all other pre-kidney failure conditions redefined as a GFR of 30 mL/min/1.73 m^2 or greater.
5. Qualifying or illustrating phases in parentheses, such as "e.g., incipient nephropathy", have been retained throughout the Classification, as they have become common currency in the field, although their removal from the Classification was suggested during the process of revision.
6. Stress is now placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy.

Of note, the American Diabetes Association (ADA) proposed in its Clinical Practice Recommendations 2013 that all cases of albuminuria of 30 μg/mg Cr (=mg/g Cr) be defined as "increased urinary albumin excretion", thus abandoning the division between micro- and macroalbuminuria [13]. Again, while this concept was retained in the Clinical Practice Recommendations 2014, the ADA further proposed that microalbuminuria and macroalbuminuria be redefined as persistent albuminuria of 30–299 mg/24 h and ≥300 mg/24 h, respectively [14]. While this change may result in the terms micro- and macroalbuminuria ceasing to be common currency in the clinical setting in the US, to avoid confusion, the Committee has chosen not to follow suit and rather err on the side of caution, thereby retaining these terms in the Classification, given that they are less likely to no longer be used in scientific publications and are expected to remain common currency in Japan.

Last but not least, with a number of multicenter prospective studies currently underway, including the Japan Diabetes Complication and Prevention prospective (JDCP) study, JSN registries, Japan Diabetes Clinical Data Management (JDDM) studies and Japan Diabetes Optimal Integrated Treatment for 3 Major Risk Factors of Cardiovascular Diseases (J-DOIT3) randomized study, the Committee also plans to further revise the Classification in a timely fashion as required, as relevant evidence becomes available from these and other studies.

Conclusions

In order to resolve the discrepancy between the existing Classification of Diabetic Nephropathy and the current Classification of CKD stages, the Joint Committee on Diabetic Nephropathy revised its Classification of Diabetic Nephropathy. The new classification has already been uploaded onto the website of each member society represented on the Joint Committee as of January 10, 2014. Again, in view of further revisions in the years to come, the Joint Committee has termed the revised classification as the "Classification of Diabetic Nephropathy 2014."

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Conflict of interest Masakazu Haneda has received speaker honoraria from pharmaceutical companies Boehringer Ingelheim GmbH, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Daiichi-Sankyo Co., Ltd., Taisho Pharmaceutical Co., Ltd., Sanofi K.K., Merck Sharp & Dohme, Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd., Kowa Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Novartis Pharma K.K., scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., Merck Sharp & Dohme, Boehringer Ingelheim GmbH, and Eli Lilly and Company; Daisuke Koya has received speaker honoraria from pharmaceutical companies Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, and Eli Lilly and Company, research grants from Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, Japan Tabacco Inc., Eli Lilly and Company, and Ono Pharmaceutical Co., Ltd.; Tetsuya Babazono has received speaker honoraria from pharmaceutical company Merck Sharp & Dohme; Tatsumi Moriya has received travel expenses from pharmaceutical companies Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., and Daiichi-Sankyo Co., Ltd.; Hirofumi Makino has received speaker honoraria from pharmaceutical companies Teijin Pharma Limited, Chugai Pharmaceutical Co., Ltd., AbbVie GK, Astellas Pharma Inc., Boehringer Ingelheim GmbH, Daiichi-Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Merck Sharp & Dohme, Novartis Pharma K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., and Mitsubishi Tanabe Pharma Corporation, research grants from Project for accelerating Practice and Research on Community Medicine in Okayama Prefecture, scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Merck Sharp & Dohme, Takeda Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., and Mitsubishi Tanabe Pharma Corporation; Kenjiro Kimura has received research grants from pharmaceutical companies Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Limited, Boehringer Ingelheim GmbH, Baxter International Inc., and Sekisui Medical Co., Ltd.; Takashi Wada has received speaker honoraria from pharmaceutical company Daiichi-Sankyo Co., Ltd., scholarship grants from Chugai pharmaceutical Co., Ltd.; Susumu Ogawa has received speaker honoraria from pharmaceutical companies Daiichi-Sankyo Co., Ltd., Eli Lilly and Company, and Novo Nordisk

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Human rights statement and Informed consent This article does not contain any studies with human or animal subjects performed by the any of the authors.

Appendix

Relationship between the 2014 categories for diabetic nephropathy stages and the CKD severity categories

	Albuminuria category	A1	A2	A3
	Quantitative urinary albumin estimation Urinary albumin/Cr ratio (mg/g Cr) (quantitative urinary protein estimation) (urinary protein/Cr ratio (g/g Cr)	Normoalbuminuria < 30	Microalbuminuria 30-299	Macroalbuminuria ≥300 (or increased proteinuria) (≥0.50)
GFR category (mL/min/1.73 m^2)	≥90 60-89 45-59 30-44	Stage 1 (pre-nephropathy)	Stage 2 (incipient nephropathy)	Stage 3 (overt nephropathy)
	15-29 < 15	Stage 4 (kidney failure)		
	(dialysis therapy)	Stage 5 (dialysis therapy)		

References

1. Haneda M, Utsunomiya K, et al. On the Development of the Classification of Diabetic Nephropathy 2014 (Revised Classification of Diabetic Nephropathy). J Japan Diab Soc. 2014;57:529–34 (in Japanese).
2. Haneda M, Utsunomiya K, Koya D, et al. On the Development of the Classification of Diabetic Nephropathy 2014 (Revised Classification of Diabetic Nephropathy). Jpn J Nephrol. 2014;56:547–52 (in Japanese).
3. Haneda M, Utsunomiya K, Koya D, et al. On the Development of the Classification of Diabetic Nephropathy 2014 (Revised Classification of Diabetic Nephropathy). J Jpn Soc Dial Ther. 2014;47:415–9 (in Japanese).
4. Haneda M, Utsunomiya K, Koya D, et al. On the Development of the Classification of Diabetic Nephropathy 2014 (Revised Classification of Diabetic Nephropathy). Clin Nutr. 2014;17:325–30 (in Japanese).
5. Committee for Statistical Surveys, Japanese Society for Dialysis Therapy (JSDT): Current state of dialysis therapy in Japan, 2013 illustrated. http://docs.jsdt.or.jp/overview/index.html.
6. Diabetes survey research report. Ministry of Health and Welfare, Japan, 1991. p. 320.
7. Yoshikawa R. (principal investigator) Report of the Joint Committee on Diabetic Nephropathy. 1 On revision of the Ministry of Health, Labour and Welfare Version of the Classification of Diabetic Nephropathy. J Japan Diab Soc. 2001;44:623 (in Japanese).
8. Guide to the management of chronic kidney disease (CKD). Jpn J Nephrol. 2007;49:767. (in Japanese).
9. Guide to the management of chronic kidney disease (CKD). 2012. Jpn J Nephrol. 2012;54:1047. (in Japanese).
10. Systematic research report from the Research Group of Diabetic Nephropathy, 2009–2012, Ministry of Health, Labour and Welfare, Japan, 2012. p. 1–28. http://mhlw-grants.niph.go.jp/.
11. Wada T, Haneda M, Furuichi K, Babazono T, Yokoyama H, Iseki K, Araki SI, Ninomiya T, Hara S, Suzuki Y, Iwano M, Kusano E, Moriya T, Satoh H, Nakamura H, Shimizu M, Toyama T, Hara A, Makino H, The Research Group of Diabetic Nephropathy, Ministry of Health, Labour and Welfare of Japan. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol. 2014;18:613–20.
12. Guidelines for lifestyle modification/diet therapy in patients with kidney disease. Jpn J Nephrol. 1997;39:1–37. (in Japanese).
13. Summary of revisions for the 2013 clinical practice recommendations. Diabetes Care. 2013;36 Suppl 1:S3. doi:10.2337/dc13-S003.
14. Summary of revisions to the 2014 Clinical Practice Recommendations. Diabetes Care 2014;37 Suppl 1:S4. doi:10.2337/dc14-S004.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Effects of Alogliptin in Chronic Kidney Disease Patients with Type 2 Diabetes

Yukinao Sakai[1], Anna Suzuki[1], Koji Mugishima[1], Yuichiro Sumi[1], Yusuke Otsuka[1], Tomoyuki Otsuka[1], Dai Ohno[1], Tsuneo Murasawa[1] and Shuichi Tsuruoka[2]

Abstract

Objective Diabetes is a major risk factor for chronic kidney disease (CKD). In this study, we examined the effects of alogliptin on blood glucose control and the renal function in type 2 diabetes CKD patients.

Methods We recruited 36 CKD patients with type 2 diabetes. The patients were followed up for six months after adding alogliptin. Blood biochemical, urine test and office BP values were obtained six months before and after the start of treatment.

Results The mean HbA1c value was not decreased; however, the 1,5-AG values tended to improve (p= 0.1023). The mean eGFR was unchanged. There were no significant changes in the patients with an eGFR of 60 mL/min/1.73 m^2 or more (25 patients) or in the patients with an eGFR less than 60 mL/min/1.73 m^2 (11 patients). A total of 15 patients were identified to have rapidly declining diabetic nephropathy, with an annual reduction in eGFR of 5 mL/min/1.73 m^2 or more. The slope of the regression line for eGFR (-1.296 before starting treatment with alogliptin) was positive, increasing up to 0.08786. The eGFR values appeared to stop decreasing and positively reversed. The urinary albumin-to-creatinine ratio exhibited a downward trend. The effect on the renal function was independent of the levels of blood sugar, blood pressure and lipids.

Conclusion We examined the ability of alogliptin to maintain the renal function in patients with CKD complicated by type 2 diabetes. Our study suggests that alogliptin can be safely administered in patients with CKD. However, although we expected alogliptin to demonstrate renal protective effects, were unable to detect statistically significant differences. One reason for this finding is that there are few registered cases.

Key words: alogliptin, dipeptidyl deptidase-4 (DPP-4) inhibitor, chronic kidney disease (CKD), diabetic nephropathy, rapid progress diabetic nephropathy

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Introduction

Diabetes is a risk factor for a reduced renal function (1). Deterioration of the renal function is known to be an important risk factor for cardiovascular events and diabetes (2). In order to reduce these risk factors, it is important to control the blood glucose levels while avoiding possible hypoglycemia in patients with diabetes in the early stages of the disease (3-6). Elderly patients with diabetes and those who have suffered from the disease for a long time, however, often experience deterioration of the renal function (7). Indeed, patients with diabetes whose renal function is deteriorated have more hypoglycemic episodes (8-10). Therefore, diabetes treatment must address the possible effects of a reduced renal function in patients with diabetes (11, 12).

Among the recently launched diabetes drugs that have achieved marked progress in treatment, oral dipeptidyl peptidase-4 (DPP-4) inhibitors ("DPP-4 inhibitors") carry a lower risk of hypoglycemia and body weight gain (13-17). Their benefits in protecting the kidneys have been also reported in recent studies (18-24). These drugs have attracted extensive interest as promising new alternatives to existing diabetes drugs in patients with diabetes and a reduced renal

[1]Department of Nephrology, Nippon Medical School Musashikosugi Hospital, Japan and [2]Division of Nephrology, Department of Internal Medicine, Graduate School of Medicine, Nippon Medical School, Japan
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Correspondence to Dr. Yukinao Sakai, y-sakai@nms.ac.jp

Table 1. **Patient Baseline Characteristics (n=36)**

	ALL (n=36)			
Parameter	*Statistics*			
Age	63.0 ± 13.1			
Male, *n* (%)	24 (66.7)			
BMI (kg/m^2)	23.6 ± 5.6			
Dulation (y)	16.3 ± 9.1			
ARB, *n* (%)	17 (47.2)			
Statin, *n* (%)	15 (41.7)			
	-6M	0M	6M	
Blood pressure (mmHg)				
Systolic	119.6 ± 23.4	114.0 ± 23.9	120.4 ± 17.5	ns
Diastolic	65.3 ± 17.6	61.4 ± 16.4	66.1 ± 14.2	ns
HbA1c (%)	7.31 ± 1.18	7.07 ± 1.17	7.23 ± 1.07	ns
1,5-AG (μg/mL)	7.32 ± 4.82	5.95 ± 3.63	9.40 ± 7.63	ns
eGFR (mL/min/1.73m^2)	72.3 ± 25.0	71.0 ± 28.9	68.5 ± 29.2	ns
eGFR <60mL/min/1.73m^2, n (%)		11 (30.6)		
Albuminuria (mg/gCr)	76.6 ± 85.5	111.5 ± 111.1	61.9 ± 57.2	ns
TC (mg/dL)	212.1 ± 57.4	201.7 ± 33.6	200.9 ± 33.6	ns
HDL-C (mg/dL)	49.6 ± 8.8	51.7 ± 10.0	52.4 ± 10.0	ns
LDL-C (mg/dL)	135.5 ± 28.3	131.4 ± 26.2	134.5 ± 26.4	ns
TG (mg/dL)	177.7 ± 135.4	167.3 ± 96.8	160.9 ± 98.2	ns

function.

To obtain further insight into the efficacy of DPP-4 inhibitors, we examined the effects of alogliptin on blood glucose control and the renal function in patients with chronic kidney disease (CKD) complicated by type 2 diabetes.

Materials and Methods

This was a retrospective observational exploratory study performed in type 2 diabetes patients who had attended the Nippon Medical School Musashikosugi Hospital between November 2011 and August 2012. The study population involved all patients with CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or micro albuminuria >30 mg/gCr) (25) who had been treated for diabetes for six months or longer.

The initial daily dose of alogliptin was set at 6.25 mg. The dose was increased up to 25 mg in patients whose HbA1c (National Glycohemoglobin Standardization Program [NGSP] value) (26) level did not favorably change after treatment. The patients were followed up for six months after the commencement of treatment. During the treatment and follow-up periods, no other diabetes drugs were added and no antihyperlipidemic drugs were replaced. Data regarding the HbA1c, 1,5-AG and serum creatinine levels, other blood biochemical parameters, urinalysis results and systolic and diastolic blood pressure within the six-month periods before and after the start of alogliptin treatment were extracted from the patients' medical records. The usual laboratory methods employed by the hospital were used throughout the study. The estimated GFR was calculated using a formula based on the serum creatinine level developed by the Japanese Society of Nephrology for the Japanese population (27).

The measurement values are shown as the mean±standard deviation (mean±SD). A one-way ANOVA of the longitudinal data was performed to address multiplicity. Tukey's multiple comparison test was then used to perform the post hoc test. p values less than 0.05 were regarded to be statistically significant. Regression lines were separately determined for the data collected during the six-month period before the start of treatment and the six-month period after the start of treatment for comparison. For the various intergroup comparisons, Fisher's exact test was used. The correlations between parameters were examined using a Pearson product-moment correlation analysis. The patients were divided into two groups based on an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 or more or an eGFR less than 60 mL/min/1.73 m^2. In addition, regression lines were determined for the two groups for comparison.

Results

The patients' background characteristics are shown in Table 1. The subjects consisted of 24 men and 12 women. The mean (±SD; the data are hereinafter presented in this format) age was 63.0±13.1 years and the mean duration of disease was 16.3±9.1 years. The mean HbA1c level was 7.1±

1.2%, the mean 1,5-AG value was 6.0±3.6 μg/mL, the mean eGFR was 71.0±28.9 mL/min/1.73 mm^2 and the mean level of albuminuria (urinary albumin-to-creatinine ratio, UACR) was 111.5±111.1 mg/gCr. The last dose of alogliptin was 6.25 mg in five subjects and 25 mg in 31 subjects. The existing therapeutic agents included sulfonylureas in 14 subjects, a combination of sulfonylureas and thiazolidines in four subjects, insulin in seven subjects and glinides in three subjects. Eight subjects were treated with diet only. The mean BMI was 23.6±5.6 kg/m^2, the mean systolic blood pressure was 114.0±23.9 mmHg and the mean diastolic blood pressure was 61.4±16.4 mmHg. The mean total cholesterol level was 201.7±33.6 mg/dL, the mean HDL cholesterol level was 51.7±10.0 mg/dL, the mean LDL cholesterol level was 131.4±26.2 mg/dL and the mean triglyceride level was 167.3±96.8 mg/dL. No parameters showed any significant changes during the examined period. Angiotensin receptor blockers (ARBs) and statins were used in 17 and 15 subjects, respectively. The dose of ARBs was increased in four subjects and decreased in three subjects. The dose of statins was not changed.

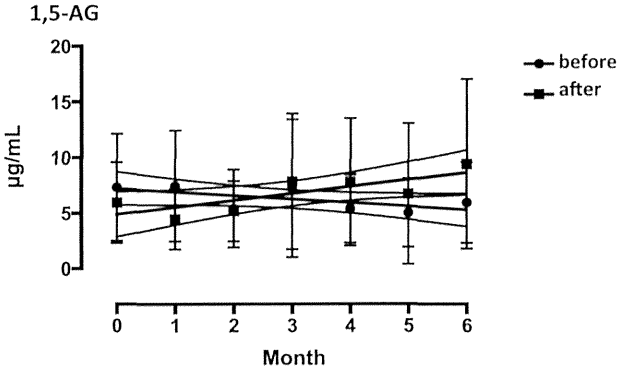

Figure 1. Comparison of the slopes of the regression lines of the 1,5-AG values before and after treatment.
Before: Y=-0.3212*X+7.213, After: Y=0.6255*X+4.886, p=0.0059

The mean HbA1c level was 7.2±1.1% after six months of alogliptin therapy and did not show any significant changes for 13 months (p=0.9031) (Table 1). However, the mean 1,5-AG improved to 9.4±7.6 μg/mL after six months of treatment, although the change was not significant (p=0.1023). The slope of the regression line was negative (-0.3212) for the six months before treatment and positive (0.6255) after the start of treatment. The difference between the slopes of the regression lines was significant (p=0.0059) (Fig. 1).

We divided the subjects into two groups: those whose HbA1c level improved (improved group) and those whose HbA1c level was exacerbated (exacerbated group). The background characteristics of these two groups are shown in

Table 2. Baseline Characteristics of the Improved Group (n=14) and the Exacerbation group (n=22)

	Improvement group (n=14)				Exacerbation group (n=22)			
Parameter	*Statistics*				*Statistics*			
Age	62.8 ± 13.7				63.1 ± 13.1			ns
Male, n (%)	11 (78.6)				13 (59.1)			ns
BMI (kg/m^2)	24.0 ± 5.6				23.4 ± 6.2			ns
Dulation (y)	16.1 ± 9.3				16.5 ± 9.2			ns
ARB, n (%)	6 (42.9)				11 (50.0)			ns
Statin, n (%)	5 (35.7)				10 (45.5)			ns
	-6M	0M	6M		-6M	0M	6M	
Blood pressure (mmHg)								
Systolic	113.7 ± 22.5	106.1 ± 20.0	115.9 ± 13.7	ns	123.3 ± 23.8	119.2 ± 25.3	123.4 ± 19.2	ns
Diastolic	60.6 ± 9.7	58.7 ± 10.9	63.0 ± 9.3	ns	68.3 ± 20.8	63.1 ± 19.2	68.1 ± 16.5	ns
HbA1c (%)	7.78 ± 1.65	7.41 ± 1.38	6.73 ± 1.09	ns	7.05 ± 0.76	6.84 ± 0.96	7.60 ± 0.92	p=0.0332 (0M vs. 6M)
1,5-AG (μg/mL)	5.64 ± 4.69	6.32 ± 4.44	11.59 ± 9.13	ns	8.22 ± 4.86	5.67 ± 3.07	7.55 ± 5.83	ns
eGFR ($mL/min/1.73m^2$)	77.5 ± 29.4	75.3 ± 26.4	73.1 ± 28.0	ns	68.8 ± 21.9	69.5 ± 32.2	64.8 ± 30.3	ns
eGFR <60$mL/min/1.73m^2$, n (%)		4 (28.6)				7 (31.8)		
Albuminuria (mg/gCr)	79.7 ± 94.3	124.7 ± 127.1	67.4 ± 54.5	ns	72.1 ± 84.0	85.1 ± 78.8	52.0 ± 67.1	ns
TC (mg/dL)	217.8 ± 86.9	186.3 ± 33.5	188.9 ± 37.5	ns	208.3 ± 26.1	212.0 ± 30.2	209.0 ± 29.6	ns
HDL-C (mg/dL)	49.0 ± 10.7	52.7 ± 11.4	53.5 ± 10.4	ns	50.0 ± 7.7	51.1 ± 9.4	51.6 ± 9.9	ns
LDL-C (mg/dL)	123.4 ± 23.7	123.3 ± 21.0	124.0 ± 30.1	ns	143.6 ± 29.0	136.3 ± 28.3	141.6 ± 21.7	ns
TG (mg/dL)	218.7 ± 199.9	170.1 ± 128.2	159.3 ± 109.6	ns	150.3 ± 58.5	165.4 ± 72.4	162.0 ± 92.7	ns

TC: p=0.0242 (Improvement group 0M vs. Exacerbation group 0M)
BMI: body mass index, ARB: angiotensin receptor blockers, ns: not significant

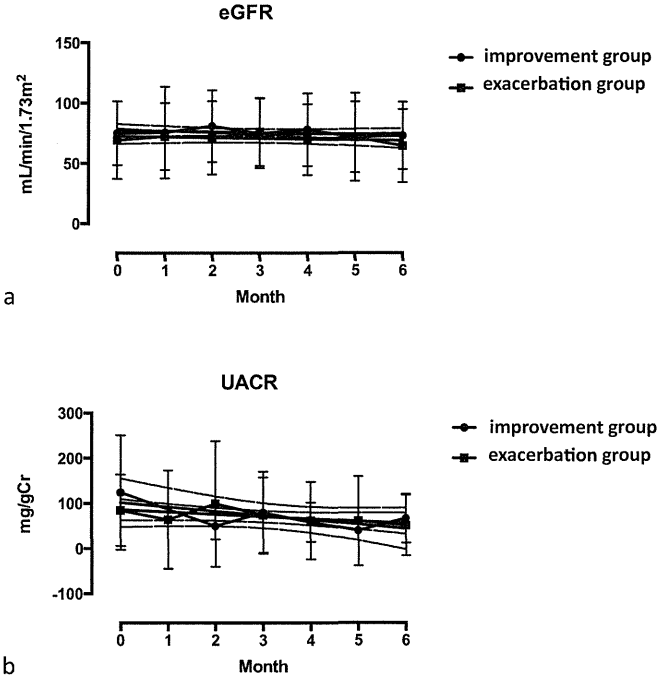

Figure 2. Comparison of the slopes of the regression lines of the eGFR (a) and UACR (b) values in the improved group and the exacerbation group.
a. Improved group: Y=-0.6182*X+77.68, Exacerbation group: Y=-0.5982*X+72.76, p=0.9825
b. Improved group: Y=-9.561*X+102.2, Exacerbation group: Y=-5.097*X+86.65, p=0.4211

Table 2. Only the TC levels demonstrated a significant difference between the improved group and the exacerbated group at baseline (p=0.0242), and only the HbA1c levels in the exacerbated group showed significant changes during the examined period (p=0.0332). In the analysis of variance of the eGFR and UACR, no significant differences were noted in any parameter in either the improved or exacerbated group (the eGFR was 0.9992 in both the improved and exacerbated groups, while the UACR was 0.8201 in the improved group and 0.8080 in the exacerbated group). No significant differences were observed in the slopes of the regression lines for eGFR and UACR between the improved group and the exacerbated group (eGFR: p=0.9825, UACR: p=0.4211) (Fig. 2).

The Pearson product-moment correlation analysis performed to identify parameters correlated with the HbA1c levels after the administration of alogliptin revealed a significant correlation with the eGFR values (Y=0.01349*X+6.237, r=0.3989, p=0.0160), indicating higher HbA1c levels in the subjects with a better renal function (Fig. 3).

No major changes were observed in the eGFR values after six months; the mean eGFR was 68.5±29.2 mL/min/1.73 mm^2. No significant differences were noted in the analysis of variance (p=0.9996) (Table 1). The slope of the regression line was -0.3318 for the six months before treatment and -0.5829 for the six months after the start of treatment, with no significant differences (p=0.6439) (Fig. 4).

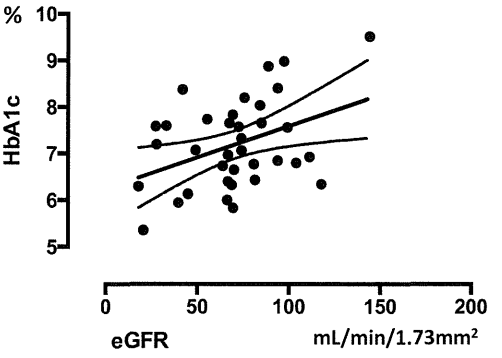

Figure 3. Correlation between the mean value of HbA1c and the mean value of eGFR after treatment.
Y=0.01349*X+6.237, r=0.3989, p=0.0160

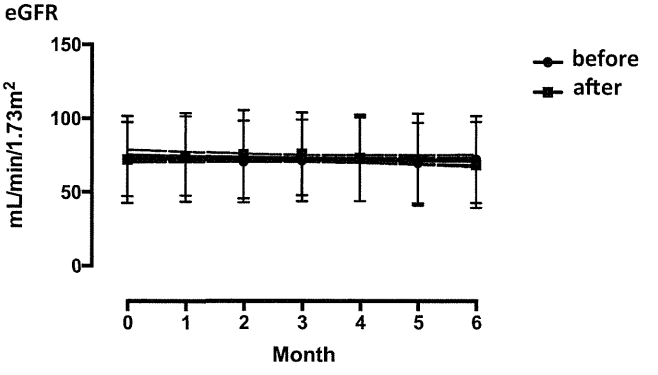

Figure 4. Comparison of the slopes of the regression lines of the eGFR values in all subjects before and after treatment.
Before: Y=-0.3318*X+72.77, After: Y=-0.5829*X+74.65, p=0.6439

The analysis of the two groups determined based on the eGFR [eGFR of 60 mL/min/1.73 m^2 or higher (25 subjects); eGFR below 60 mL/min/1.73 m^2 (11 subjects)] revealed no significant changes in either group (p=0.9982 in the former group and p=0.9149 in the latter group). The slopes of the regression lines before treatment and after the start of treatment were -0.2389 and -0.3571 in the former group and 0.1089 and -0.4257 in the latter group, respectively, without any significant differences (p=0.8419, p=0.6328) (Fig. 5).

We considered the subjects whose eGFR decreased by 5 mL/min/1.73 m^2 per year or faster as having rapidly progressive diabetic nephropathy (rapid decliner group). A total of 15 such patients were identified based on changes in the eGFR during the six months before treatment with alogliptin (Table 3 shows the background characteristics of the rapid decliner group and the remaining subjects). In the subjects with rapid progression of renal dysfunction, the mean eGFR was 70.1±28.4 mL/min/1.73 m^2 six months before treatment with alogliptin, decreased to 64.2±25.6 mL/min/1.73 m^2 at the start of treatment and was 64.7±28.3 mL/min/1.73 m^2 six months after the start of treatment. Although the analysis of variance did not reveal any significant differences (p=0.9992) (Table 3), the slope of the regression line was

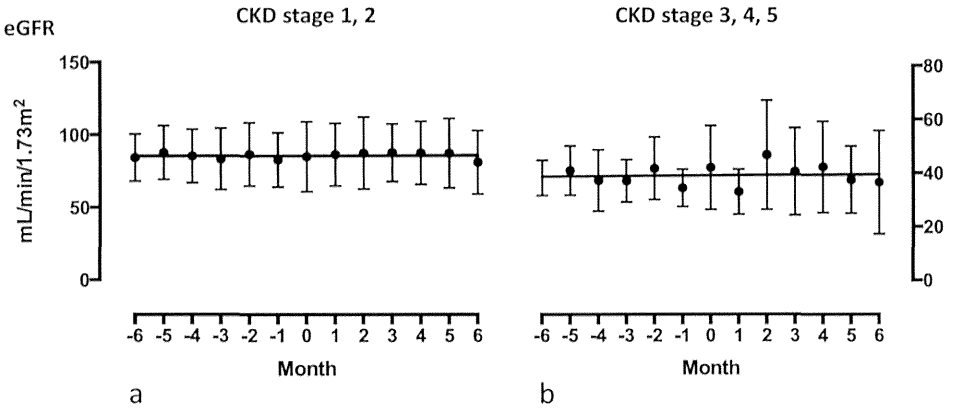

Figure 5. Changes in the eGFR values in the patients with CKD stage 1 and 2 (a) and those with CKD stage 3, 4 and 5 (b).
a. n=25, Y=0.02681*X+85.43, p=0.9982
b. n=11, Y=0.06698*X+39.12, p=0.9149

Table 3. Baseline Characteristics of the Rapid Decliner Group (n=15) and the Other Subjects (n=21)

	Rapid decliner group (n=15)				Other subjects (n=21)			
Parameter	*Statistics*				*Statistics*			
Age	63.8 ± 14.1				62.4 ± 12.7			ns
Male, n (%)	9 (60.0)				15 (71.4)			ns
BMI (kg/m^2)	24.5 ± 5.9				23.0 ± 5.9			ns
Dulation (y)	18.3 ± 9.1				14.9 ± 9.0			ns
ARB, n (%)	8 (53.3)				9 (42.9)			ns
Statin, n (%)	4 (26.7)				11 (52.4)			ns
	-6M	0M	6M		-6M	0M	6M	
Blood pressure (mmHg)								
Systolic	111.9 ± 20.7	105.2 ± 17.5	113.7 ± 14.7	ns	125.0 ± 24.2	120.5 ± 26.2	125.2 ± 18.0	ns
Diastolic	58.3 ± 9.0	52.8 ± 6.5	60.3 ± 8.6	p=0.0426 (0M vs. 6M)	70.3 ± 20.5	67.5 ± 18.7	70.3 ± 16.0	ns
HbA1c (%)	7.03 ± 0.87	6.95 ± 0.87	7.09 ± 0.94	ns	7.59 ± 1.41	7.16 ± 1.34	7.34 ± 1.17	ns
1,5-AG (μg/mL)	6.93 ± 4.32	5.56 ± 4.48	8.18 ± 5.33	ns	7.58 ± 5.29	6.14 ± 3.30	10.14 ± 8.82	ns
eGFR (mL/min/1.73m^2)	70.1 ± 28.4	64.2 ± 25.6	64.7 ± 28.3	ns	74.4 ± 22.4	77.2 ± 31.4	71.3 ± 30.3	ns
eGFR <60mL/min/1.73m^2, n (%)		5 (33.3)				6 (28.6)		
Albuminuria (mg/gCr)	66.1 ± 54.4	122.6 ± 134.4	50.0 ± 39.9	ns	83.7 ± 106.0	106.0 ± 107.5	68.6 ± 66.1	ns
TC (mg/dL)	213.9 ± 26.0	205.6 ± 36.4	207.5 ± 39.9	ns	210.9 ± 71.9	198.8 ± 32.0	196.1± 28.8	ns
HDL-C (mg/dL)	49.6 ± 8.9	50.5 ± 8.6	52.7 ± 9.3	ns	49.6 ± 9.1	52.6 ± 11.1	52.1 ± 10.7	ns
LDL-C (mg/dL)	139.9 ± 23.3	139.2 ± 24.3	137.8 ± 28.8	ns	132.1 ± 32.2	125.9 ± 26.8	132.1 ± 25.0	ns
TG (mg/dL)	177.0 ± 122.6	167.4 ± 85.0	153.7 ± 106.6	ns	178.1 ± 146.8	167.2 ± 107.0	166.3 ± 93.2	ns

BP diastolic: p=0.0061 (Rapid decliner group 0M vs. Other subjects 0M)
BMI: body mass index, ARB: angiotensin receptor blockers, ns: not significant

-1.296 before treatment with alogliptin and became positive at 0.08786 after the start of treatment, indicating that the eGFR values stopped declining and instead showed a tendency to increase (p=0.1105) (Fig. 6).

Regarding the background factors, a significant difference was observed in diastolic blood pressure (p=0.0061); i.e., the diastolic blood pressure values were significantly lower in the rapid decliner group. During the examined period, the diastolic blood pressure values in the rapid decliner group were significantly increased (p=0.0426). No other background factors demonstrated significant differences, and no other significant changes were noted during the examined period (Table 3).

We defined the subjects whose eGFR was decreased (<60) without overt proteinuria as early decliners, identifying eight such subjects. Among these subjects, the eGFR