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Comparison between Atorvastatin and Rosuvastatin in Renal Function Decline among Patients with Diabetes

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Background: Although the beneficial effects of statin treatment in dyslipidemia and atherosclerosis have been well studied, there is limited information regarding the renal effects of statins in diabetic nephropathy. We aimed to investigate whether, and which, statins affected renal function in Asian patients with diabetes.

Methods: We enrolled 484 patients with diabetes who received statin treatment for more than 12 months. We included patients treated with moderate-intensity dose statin treatment (atorvastatin 10 to 20 mg/day or rosuvastatin 5 to 10 mg/day). The primary outcome was a change in estimated glomerular filtration rate (eGFR) during the 12-month statin treatment, and rapid renal decline was defined as a >3% reduction in eGFR in a 1-year period.

Results: In both statin treatment groups, patients showed improved serum lipid levels and significantly reduced eGFRs (from 80.3 to 78.8 mL/min/1.73 m^2 for atorvastatin [P=0.012], from 79.1 to 76.1 mL/min/1.73 m^2 for rosuvastatin [P=0.001]). A more rapid eGFR decline was observed in the rosuvastatin group than in the atorvastatin group (48.7% vs. 38.6%, P=0.029). Multiple logistic regression analyses demonstrated more rapid renal function loss in the rosuvastatin group than in the atorvastatin group after adjustment for other confounding factors (odds ratio, 1.60; 95% confidence interval, 1.06 to 2.42).

Conclusion: These results suggest that a moderate-intensity dose of atorvastatin has fewer detrimental effects on renal function than that of rosuvastatin.

Keywords: Atorvastatin calcium; Rosuvastatin calcium; Diabetes mellitus; Renal insufficiency, chronic

INTRODUCTION

The prevalence and incidence of chronic kidney disease (CKD) have been increasing, and CKD is recognized as an epidemic disease [1]. The leading cause of CKD is diabetes mellitus (DM) [2,3]; it starts as diabetic nephropathy and progresses to CKD [4]. In addition to hyperglycemia, dyslipidemia is an important risk factor for renal function loss [5,6]. When DM and dyslipidemia co-occur, the risk of CKD is synergistically increased [2,7]. Conversely, CKD itself can accelerate lipid concentrations, ag-

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gravating dyslipidemia [8] and leading to the need for more treatment [9].

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, referred to as statins, are the fundamental treatment for dyslipidemia, and they decrease the risk of cardiovascular morbidity and mortality [10]. Basic research studies have shown that statins also have the potential to protect the kidney via anti-inflammatory and anti-proliferative pathways [11]. However, the effect of statins on kidney function in the clinic is controversial. The Collaborative Atorvastatin Diabetes Study provided evidence that atorvastatin treatment has beneficial effects on the kidney compared with those of placebo treatment [12]. In contrast, another study showed that more subjects in a high-intensity dose rosuvastatin (40 mg/day) treatment group experienced new-onset proteinuria than in a placebo group; although, rosuvastatin treatment attenuated atherosclerosis progression [13]. A meta-analysis study reported similar renoprotective effects between atorvastatin and rosuvastatin treatment groups [14]. However, recently, a randomized clinical trial using high-intensity dose rosuvastatin (40 mg/day) and atorvastatin (80 mg/day) treatments showed that atorvastatin has more beneficial effects on the kidney than those of rosuvastatin [5].

Previous studies on statins were based largely on Caucasian populations and conducted using high-intensity doses [5,13]. However, interestingly, one study showed a comparable lipid lowering efficacy using lower statin doses in Asians with that observed using higher doses in Caucasians [15]. Therefore, the aim of this study was to investigate and compare the renal effects of moderate-intensity doses of statins in Asian patients with diabetes.

METHODS

Study design and population

In this study, subjects were identified by reviewing patient case notes using the electronic medical records at Severance Hospital, a tertiary university hospital in Korea. We initially selected those aged ≥20 years who were naïve, and started moderate-intensity statin treatment. DM was defined according to the International Classification of Diseases 10th revision (ICD-10). Subjects were excluded if they had any one of the following criteria: (1) missing data for laboratory tests; (2) <12 months of statin treatment; (3) prior kidney transplantation or ongoing dialysis; (4) kidney disease other than diabetic nephropathy (nephritis or nephrotic syndrome); (5) acute renal failure due to septic shock, contrast agents, or drugs; (6) DM developed after statin use; or (7) post-transplant DM with immunosuppressant medication treatment. The study protocol was approved by the Institutional Review Board of the Yonsei University College of Medicine (4-2016-0741).

Clinical and laboratory parameters

Clinical parameters, including age, sex, height, weight, duration of DM, history of hypertension and cardiac disease, and statin treatment information, were collected by carefully reviewing electronic medical records. Fasting blood glucose levels, glycated hemoglobin (HbA1c) levels, lipid profiles (total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], and triglyceride levels), and estimated glomerular filtration rates (eGFR) were measured at baseline and 12 months after statin administration. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the CKD stages were categorized according to previously described guidelines [16]. In addition, the proportion of subjects with rapid renal function decline was analyzed by statin types and was defined as those exhibiting a >3% loss in annual eGFR [17]. Body mass index (BMI) was evaluated using a weight-to-height (kg/m^2) ratio, and obesity was defined as a BMI ≥25 kg/m^2 based on the criteria for Asians.

Statistical analysis

Data are presented as the mean±standard deviation for continuous variables and as a number or percentage for categorical variables. Simple comparisons of continuous variables between statin types were analyzed using Student *t* tests. Paired data measured at baseline and after statin treatment were analyzed using paired *t* tests. Because total cholesterol, triglyceride, HDL-C, LDL-C, aspartate aminotransferase, and alanine transaminase values were not normally distributed, analyses were performed using log-transformed data. Chi-square tests were used to examine the relationships between multiple categorical variables. The relative factor for rapid renal function decline was obtained using multivariable logistic regression models, and the risk is reported in the form of odds ratios (ORs) and 95% confidence intervals (CIs). In multivariable logistic regression analysis, age, sex, diabetes duration, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, systolic blood pressure, hypertension status, baseline eGFR, LDL-C, triglyceride, and HbA1c concentration changes during follow-up periods were adjusted as covariates. Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline Characteristics of Study Population by Categories of Statin Types

Characteristic	Atorvastatin (n=295)	Rosuvastatin (n=189)	P value
Age, yr	61.3±11.3	59.7±11.8	0.141
Male sex	152 (51.5)	114 (60.3)	0.058[a]
Diabetes duration, yr	9.3±9.6	8.6±9.0	0.365
BMI, kg/m^2	25.0±3.9	25.3±3.7	0.373
Obesity	125 (45.1)	76 (50.0)	0.333[a]
SBP, mm Hg	127.8±15.6	129.3±16.7	0.337
DBP, mm Hg	75.4±11.9	76.9±10.9	0.177
FBS, mg/dL	148.5±54.5	150.2±56.3	0.742
PPBS, mg/dL	240.1±88.7	255.2±86.7	0.150
HbA1c, %	7.8±1.6	8.1±1.9	0.053
TC, mg/dL[b]	191.4±47.6	194.2±49.6	0.826
HDL-C, mg/dL[b]	46.0±11.6	44.0±9.8	0.058
TG, mg/dL[b]	151.9±96.3	172.6±114.2	0.002
LDL-C, mg/dL[b]	115.3±39.4	116.0±44.4	0.684
BUN, mg/dL	18.8±10.5	18.7±8.8	0.882
Cr, mg/dL	1.0±0.7	1.0±0.5	0.999
eGFR, mL/min/1.73 m^2[c]	80.3±26.4	79.1±25.6	0.633
CKD stage			0.671[a]
Stage 1	143 (48.5)	84 (44.4)	
Stage 2	86 (29.2)	58 (30.7)	
Stage 3–5	66 (22.4)	47 (24.9)	
WBC, 10^3/μL	7.0±1.9	7.3±2.1	0.227
Hemoglobin, mg/dL	13.4±1.9	13.4±2.0	0.943
Albumin, mg/dL	4.5±2.6	4.4±1.9	0.595
AST, U/L[b]	23.1±13.2	24.2±20.7	0.455
ALT, U/L[b]	25.0±15.7	26.8±20.1	0.319
Comorbidities			
Cardiac disorders	73 (24.7)	49 (25.9)	0.770[a]
Hypertension	137 (46.4)	101 (53.4)	0.133[a]
Antihypertensive medications			
ACE inhibitor or ARB	151 (51.2)	108 (57.1)	0.200[a]
Diuretics	55 (18.6)	36 (19.1)	0.890[a]
CCB	86 (29.2)	65 (34.4)	0.225[a]
β-Blocker	46 (15.6)	37 (19.6)	0.257[a]
Glucose lowering medications			
Metformin	238 (80.7)	153 (81.0)	0.940[a]
Sulfonylurea	124 (42.0)	71 (37.6)	0.328[a]
DPP-4 inhibitor	129 (43.7)	75 (39.7)	0.379[a]
TZD	35 (11.9)	17 (9.0)	0.320[a]
Insulin	63 (21.4)	40 (21.2)	0.960[a]

Values are expressed as mean±SD or number (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; PPBS, postprandial blood sugar; HbA1c, glycated hemoglobin; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine transaminase; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione.
[a]Analyzed by chi-square test; [b]Log-transformed; [c]eGFR was calculated from Chronic Kidney Disease Epidemiology Collaboration.

For all tests, a $P<0.05$ was considered to be statistically significant.

RESULTS

In this study, we analyzed 484 individuals undergoing moderate-intensity statin treatment. The mean age of the study population was 60.7 years, and the mean duration of DM was 9.0 years. Of the 484 patients, 266 (55.0%) were men, 238 (49.2%) had hypertension, and 259 (53.5%) were prescribed an ACE inhibitor or an ARB. The mean daily dosage was 11.2±3.2 mg for atorvastatin (88.1% had 10 mg/day, 11.9% had 20 mg/day) and 9.7±1.3 mg for rosuvastatin (6.9% had 5 mg/day, 93.1% had 10 mg/day). There were no significant differences between the statin groups in age, DM duration, BMI, blood pressure, blood glucose levels, or liver and kidney function (Table 1). In addition, the prevalence of cardiac disorders and hypertension, the class of antihypertensive drug, and the use of hypoglycemic medication, were comparable between the two groups.

Among all patients, the eGFR was slightly, but significantly, decreased from 79.8 to 77.7 mL/min/1.73 m^2 ($P<0.001$). The mean eGFR change was similar as previously reported in diabetes population [18,19]. Although this renal function decline was observed in both statin treatment groups, there was a greater eGFR reduction in the rosuvastatin-treated group (Δ-1.6 mL/min/1.73 m^2 for atorvastatin [$P=0.012$], Δ-3.0 mL/min/1.73 m^2 for rosuvastatin [$P=0.001$]) (Table 2). In addition, more individuals receiving rosuvastatin treatment experienced rapid renal function decline than those receiving atorvastatin treatment (48.7% vs. 38.6%, $P=0.029$).

Serum lipid profiles and blood glucose levels were significantly improved in both study groups (Table 2). The mean reductions in total cholesterol, LDL-C, and triglyceride levels were 19.9%, 27.1%, and 5.4%, respectively, after 1 year of statin treatment (all $P<0.001$), whereas HDL-C levels were slightly increased by 2.7% ($P=0.527$). The proportion of individuals who achieved an LDL-C response (>30% reduction) was similar between the statin groups (52.2% and 59.6% for atorvastatin and rosuvastatin, respectively, $P=0.115$). Total cholesterol and triglyceride levels were also improved regardless of statin treatment; however, neither statin treatment significantly increased or decreased HDL-C levels.

Next, we assessed rapid renal function decline according to statin type after adjusting for confounding factors, including age, sex, and other clinical and laboratory parameters. As the atorvastatin-treated group showed a better response in terms of kidney function maintenance, we set this group as the reference. Multivariable logistic regression analysis showed that rosuvastatin treatment was independently associated with rapid renal function decline (Table 3). Compared with atorvastatin treatment, rosuvastatin treatment increased the risk for rapid renal function loss by approximately 60% (OR, 1.60; 95% CI, 1.06 to 2.42).

Table 2. Changes in Metabolic Parameters after Statin Use

Parameter	Atorvastatin			Rosuvastatin		
	Baseline	1 Year	*P* value	Baseline	1 Year	*P* value
Kidney						
eGFR, mL/min/1.73 m^2	80.3±26.4	78.7±27.5	0.012	79.1±25.6	76.1±26.8	0.001
Lipid						
TC, mg/dL[a]	191.4±47.6	149.7±33.5	<0.001	194.2±49.6	142.1±33.0	<0.001
HDL-C, mg/dL[a]	46.0±11.6	45.5±11.8	0.068	44.0±9.8	45.7±12.7	0.060
TG, mg/dL[a]	151.9±96.3	130.9±79.3	0.001	172.6±114.2	131.2±68.8	<0.001
LDL-C, mg/dL[a]	115.3±39.4	78.1±24.1	<0.001	116.0±44.4	70.4±28.6	<0.001
Glucose						
FBS, mg/dL	148.5±54.5	128.7±36.0	<0.001	150.2±56.3	131.4±40.3	<0.001
PPBS, mg/dL	240.1±88.7	220.6±77.0	<0.001	255.2±86.7	213.9±67.6	<0.001
HbA1c, %	7.8±1.6	7.2±1.1	<0.001	8.1±1.9	7.4±1.5	<0.001

Values are expressed as mean±SD.
GFR, glomerular filtration rate; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; FBS, fasting blood sugar; PPBS, postprandial blood sugar; HbA1c, glycated hemoglobin.
[a]Log-transformed.

Table 3. Odds Ratio and 95% Confidence Interval of Rapid Renal Function Decline (>3% per Year) According to Statin Types

Variable	Atorvastatin	Rosuvastatin	*P* value
Crude	1 (reference)	1.51 (1.04–2.18)	0.030
Model 1[a]	1 (reference)	1.48 (1.01–2.15)	0.042
Model 2[b]	1 (reference)	1.48 (1.00–2.20)	0.052
Model 3[c]	1 (reference)	1.60 (1.06–2.42)	0.026

[a]Model 1: adjusted for age and sex; [b]Model 2: adjusted for age, sex, diabetes duration, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, systolic blood pressure, and hypertension; [c]Model 3: adjusted for age, sex, diabetes duration, ACE inhibitor/ARB use, systolic blood pressure, hypertension, baseline glomerular filtration rate, low density lipoprotein cholesterol change, triglyceride change, and glycated hemoglobin change.

DISCUSSION

Because of the suggested similarity in pathophysiology between atherosclerosis and glomerulosclerosis [20], the association between hyperlipidemia and kidney disease progression has been explored in experimental studies. High-fat diet induces aggravation in glomerulosclerosis, accumulation of mesangial matrix, and podocyte injury [21,22]. Conversely, statin treatment decreases macrophage recruitment and reduces the levels of inflammatory cytokines, including monocyte chemoattractant protein-1, transforming growth factor β, and interleukin 6; thereby, attenuating renal fibrosis [23-25]. Although there is some debate regarding the effect of statin treatment on kidney function in humans, there is increasing evidence that statins have a renoprotective effect [25-27]. A large, population-based retrospective cohort study reported that preoperative statin use is associated with a lower incidence of acute kidney injury and acute dialysis after major elective surgery [26]. Additionally, statin use is associated with an early recovery of kidney injury and a reduced risk of all-cause mortality after vascular surgery [27]. A meta-analysis study also reported favorable changes in GFR, albuminuria, and proteinuria in patients treated with statins [28].

However, renal outcome according to statin potency is more controversial. A Canadian group reported a dose-dependent favorable effect of statin treatment, with 37% of the patients undergoing a high-potency statin treatment [26]. Similarly, another study showed that high-dose atorvastatin (80 mg/day) improves renal outcome compared with that of the low-dose group (10 mg/day) [29]. In contrast, a recent large epidemiology study showed an increased risk of hospitalization for acute kidney injury in patients receiving high-potency statin treatment compared with those receiving low-potency statin treatment [30]. Moreover, a meta-analysis study also reported that high-dose rosuvastatin (40 mg/day) causes a higher new-onset proteinuria incidence than low-dose rosuvastatin [13].

Regarding statin types and renal function, atorvastatin seems to be more beneficial than rosuvastatin [5,13]. In a previous randomized control trial, the rosuvastatin group showed greater reductions in lipid profiles, and concomitantly showed significant reductions in the GFRs and more acute renal failure events, compared with those in the atorvastatin group [5]. In another study, the GFR reduction was less in the atorvastatin-treated group than in the rosuvastatin-treated group [13]. These data are consistent with our results and support the notion that a more rapid GFR loss is associated with rosuvastatin use than with atorvastatin use. However, previous studies were mainly conducted in Caucasians and did not include Asian populations [5,12,13]. Our study supports the notion that the beneficial effects of atorvastatin treatment in Asians are not different from those previously observed in Caucasians [5,13], and that these effects are maintained using moderate-intensity doses.

Although the differences between the mechanisms of atorvastatin and rosuvastatin in kidney function remains unknown, the following observations regarding these drugs may contribute to their unique renal effects. One retrospective study demonstrated a greater decrease in serum uric acid levels with atorvastatin treatment than with rosuvastatin treatment, which could lead to increased endothelial function and renal blood flow [31]. Even though we did not observe a significant difference between the serum uric acid levels in the two statin treatment groups in the current study, both statin treatments did reduce patient serum uric acid levels. In addition, X-ray diffraction analyses have shown various distributions of each statin class in the cellular membrane, which are associated with the metabolites of each statin, and this altered distribution could affect the pharmacologic and pleiotropic properties of the statins [32]. For instance, this altered distribution might influence intracellular signaling in the kidney, which could explain the observed decrease in urinary podocyte excretion in patients that were switched to atorvastatin treatment from rosuvastatin treatment for a 6-month period [33]. We analyzed the correlation between changes in eGFR and LDL-C reduction, found no statistical significance in the current study (Pearson coefficient=0.08, P=0.08). This might be due to the difference effect of atorvastatin and rosuvastatin. Further studies are necessary to elucidate the downstream mediators of the distinct renal effects of these two statins.

Our study has some limitations. First, this was a retrospective

investigation, and thus, causal relationships cannot be clearly deducted. Second, although there were no differences in medication use, including ACE inhibitors and ARB, among the statin groups, and we accounted for the differences in glucose and lipid levels at baseline and 12 months after statin treatment, the changes in blood glucose and blood pressure during the treatment period could not be determined. Third, we did not include a control group in the present study; therefore, no definitive conclusions can be drawn regarding which statin is more harmful, neutral, or protective. Fourth, as shown in Table 1, more individuals with impaired baseline metabolic parameters were included in the rosuvastatin group. Although we adjusted for changes in glucose and lipid levels in the multivariable model, this discrepancy could be a confounding factor. Finally, we applied GFR-EPI equation as renal function in the current study, which is indirect renal function.

Despite these limitations, the present study has several strengths. To the best of our knowledge, this study is the first to show that moderate-intensity statin treatment in Asians, who are known to respond well to lower statin doses, exerted beneficial effects to maintain kidney function. Although this study was retrospective, which is not suitable to precisely determine patient compliance, we limited enrollment to patients whose prescriptions consistently included the same statins by careful reviewing their medical records. In addition, patients with other kidney disease, such as nephritis or nephrotic syndrome, were excluded to specifically evaluate the effects of statins on urinary kidney disease and diabetic nephropathy.

In conclusion, moderate-intensity dose statin treatment for 12 months significantly improved LDL-C and triglyceride levels in patients with diabetes. We found that moderate-intensity dose rosuvastatin treatment was associated with more rapid GFR loss than that of atorvastatin treatment. Our findings suggest that atorvastatin treatment in diabetic patients is more beneficial in preserving the GFR than rosuvastatin treatment. However, further prospective and randomized trials are needed to verify this effect compared with placebo and other statin treatments. If the class effects of statins on diabetic nephropathy are clearly demonstrated, the options for treating diabetic patients with statins will be vastly improved.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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