

Effects of switching to low-dose rosuvastatin (5 mg/day) on glucose metabolism and lipid profiles in Japanese patients with type 2 diabetes and dyslipidemia: a single-arm, prospective, interventional trial

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Abstract

Aims We investigated the effects of switching from other statins, such as pravastatin (5 or 10 mg/day), rosuvastatin (2.5 mg/day), or pitavastatin (1 or 2 mg/day), to low-dose rosuvastatin (5 mg/day) on glucose metabolism and lipid profiles in Japanese patients with type 2 diabetes and dyslipidemia.

Methods This was a prospective, two-center, open-label, single-arm, interventional trial. Several clinical parameters were analyzed at baseline and 24 weeks after switching from other statins to rosuvastatin at 5 mg/day. The primary endpoints were changes in hemoglobin (Hb) A1c level and lipid profile.

Results Forty-five patients were enrolled in the trial. The mean HbA1c level increased significantly from 7.1 ± 0.7 to $7.5 \pm 0.9\%$ ($P < 0.001$), whereas the mean low-density lipoprotein cholesterol (LDL-C) level decreased significantly from 108.9 ± 16.5 to 91.6 ± 24.5 mg/dL ($P < 0.001$). Multiple linear regression analysis showed that changes in HbA1c levels were significantly and positively correlated with fasting plasma glucose (FPG) levels

at baseline. Receiver operating characteristic (ROC) curve analysis examining the relationship between HbA1c and FPG showed that FPG was a significant predictor of changes in HbA1c levels (area under the curve, 0.72). The cutoff FPG value of 168 mg/dL had a sensitivity of 47% and a specificity of 93%.

Conclusions Switching to a low dose of rosuvastatin impaired glucose metabolism in Japanese patients with type 2 diabetes and dyslipidemia. Patients with high FPG levels were particularly prone to an exacerbation of glucose metabolism.

Keywords Dyslipidemia · Type 2 diabetes · Rosuvastatin · Glucose metabolism · LDL cholesterol

Introduction

The beneficial effects of statins in reducing cardiovascular events are well established, as demonstrated by several studies including the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study conducted [1] in Japan and a meta-analysis reported by the Cholesterol Treatment Trialists' Collaborators [2]. In the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, 20 mg/day rosuvastatin was given to patients with normal glucose tolerance and a reduction in cardiovascular disease risk was confirmed, although rosuvastatin therapy was found to increase the incidence of new-onset diabetes [3, 4]. Park et al. reported that treatment with 10 mg/day rosuvastatin reduced total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels in patients with no diabetes; however, the mean hemoglobin (Hb)A1c level increased significantly from 5.88 ± 0.04 to $5.93 \pm 0.03\%$

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in those patients [5]. A meta-analysis also showed that intensive-dose statin therapy increased the risk of new-onset diabetes compared with moderate-dose statin therapy [6]. Given that the statin doses evaluated in these reports were 2–4 times higher than the standard dose used in Japan, it remains unclear whether the results of these studies are applicable to Japanese patients whose conditions are managed with low-dose statins.

Kurabayashi et al. [7] compared the efficacy and safety of rosuvastatin (5 mg/day) and atorvastatin (10 mg/day) given once daily to Japanese diabetic patients with hypercholesterolemia who had previously received atorvastatin (10 mg/day) and found that rosuvastatin improved not only LDL-C but also fasting plasma glucose (FPG) levels. However, whether low-dose rosuvastatin given at 5 mg/day could improve the lipid profile as well as the glucose metabolism in Japanese patients with dyslipidemia and preexisting type 2 diabetes at the start of statin therapy remains unclear. In the present study, we investigated the effect of switching from other statins to rosuvastatin (5 mg/day) on the lipid profile and glucose metabolism of Japanese patients with type 2 diabetes and dyslipidemia.

Methods

Patients

This was a 24-week, two-center, open-label, single-arm trial. Japanese patients with type 2 diabetes and dyslipidemia who visited the outpatient clinics of the Yokohama City University Hospital or Fujisawa Shounandai Hospital were recruited between July 2012 and January 2014.

Type 2 diabetes was diagnosed in accordance with the criteria proposed by the Japan Diabetes Society (JDS) [8]. The inclusion criteria were age ≥ 20 and ≤ 80 years, HbA1c (National Glycohemoglobin Standardization [NGSP]) level of $< 9.4\%$, oral intake of any type of statin for ≥ 2 months, and LDL-C level ≥ 100 mg/dL. The exclusion criteria were type 1 diabetes, oral intake of fibrates, pregnancy, possible pregnancy, and lactation. Patients with a history of severe hepatic or renal dysfunction were also excluded.

Trial protocol

This was a prospective, interventional trial. Treatment in subjects was switched from other statins to rosuvastatin (5 mg/day), and several clinical parameters were analyzed at baseline and at 24 weeks after the switch. The primary endpoints were changes in HbA1c levels and components of the lipid profile—including LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C)

levels—between baseline and 24 weeks after switching. The secondary endpoints were changes in fasting C-peptide immunoreactivity (CPR), oxidized LDL, small dense low-density lipoprotein (sd-LDL), apolipoprotein B (apoB), apolipoprotein A-1 (apoA-1), high-molecular-weight adiponectin, and tumor necrosis factor alpha (TNF- α) levels between baseline and 24 weeks after switching. Blood tests were performed in the morning after overnight fasting. Furthermore, as a rule, no lifestyle guidance was provided, and no additions or changes to oral antidiabetic drugs or insulin therapy were made during the observation period.

This trial was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yokohama City University Hospital (reference number: B110512011, B120112025, and B130110051) and the Ethics Committee of Fujisawa Shounandai Hospital (reference number: 25042201). All patients provided written informed consent to participate.

This trial was registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN 000009156. The name of the registered trial is “Study for effects of rosuvastatin on glucose and lipid metabolism in patients with type 2 diabetic patients.”

Measurements

HbA1c was measured by high-pressure liquid chromatography (HPLC) at Yokohama City University Hospital, and by the latex coagulating method (LA) at Fujisawa Shounandai Hospital. HPLC (x) and LA (y) were reported to be highly homologous for HbA1c, with the following relationship: $y = 0.971x + 0.87\%$ [9]. Therefore, HbA1c values obtained by both HPLC and LA were included in this study. Plasma glucose was measured by the glucose oxidase method (GOD) at Yokohama City University Hospital and by the glucose dehydrogenase method (GDH) at Fujisawa Shounandai Hospital.

TC, HDL-C, and triglyceride (TG) levels were measured directly at both hospitals. Serum LDL-C was calculated according to the Friedewald formula from fasting blood samples obtained at baseline and at 24 weeks following the switch [10]. Data from homogeneous assays were used for the direct determination of LDL-C levels from blood samples obtained as needed at 8 and 16 weeks.

CPR was determined using electrochemiluminescence immunoassay (ECLIA) at Yokohama City University Hospital and using a chemiluminescence enzyme immunoassay method (CLEIA) at Fujisawa Shounandai Hospital. Oxidized LDL was measured with an enzyme-linked immunosorbent assay (ELISA) using AP-X (Japan Electron Optics Laboratory, Tokyo, Japan) at both hospitals (reference range 61.0–105.0 U/L). Sd-LDL was

measured directly using a Hitachi 7170 chemistry analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan) at both hospitals (reference range 10.7–48.7 mg/dL). ApoB and apoA-1 were measured using a turbidimetric immunoassay at both hospitals. High-molecular-weight adiponectin was measured using ECLIA at both hospitals. TNF- α was measured with ELISA using the microplate reader EMax (Molecular Devices, Tokyo, Japan) at both hospitals (reference range 0.6–2.8 pg/mL).

Calculations

The CPR index, a measure of insulin secretion capacity that was previously reported to be a useful marker for basal insulin secretion in patients with type 2 diabetes [11, 12], was calculated as follows: $100 \times [\text{fasting CPR (ng/mL)}/\text{FPG (mg/dL)}]$.

The homeostatic model assessment 2 insulin resistance (HOMA2-IR) value was calculated using the HOMA2 calculator, version 2.2 (<http://www.dtu.ox.ac.uk/homa-calculator/index.php>).

Statistical analysis

The sample size was calculated based on the hypothesis that HbA1c had a standard deviation of 0.7% and a non-inferiority margin of 0.4%. Briefly, in a study comparing the efficacy of simvastatin to rosuvastatin and of colestimide to pravastatin, the standard deviation of HbA1c levels at baseline was 0.7% [13, 14], which was thus the hypothesized standard deviation of HbA1c at baseline for this study. The noninferiority margin of 0.4% was chosen as a clinically meaningful exacerbation of diabetes control in clinical practice. To detect a significant difference between baseline and 24 weeks in a statistical situation with a power greater than 80% and a two-sided type 1 error rate of 0.05, at least 38 patients were required for enrollment [15].

Missing baseline data on patients were imputed as mean or median values. The last observation carried forward (LOCF) method was used to address missing treatment course data. Results were expressed as mean \pm standard deviation or median (interquartile range). Statistical analysis of changes between baseline and 24 weeks for normally distributed data was performed using the paired *t* test, whereas non-normally distributed data were compared using the Wilcoxon rank sum test. We performed simple linear regression between change in HbA1c level and baseline clinical and biochemical characteristics and parameters. Next, we performed multiple linear regression analyses to determine the independent influences of parameters on the change in HbA1c by calculating the coefficients adjusted for baseline clinical characteristics,

biochemical characteristics, and parameters. A receiver operating characteristic (ROC) analysis was performed to define the cutoff value indicative of impairment of glucose metabolism. *P* values of <0.05 were considered significant in all statistical analyses performed. JMP 11 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Patient background

A total of 50 patients were recruited. Five of these patients could not complete pretrial evaluation satisfactorily, three declined participation prior to the start of the trial because of personal circumstances, and two patients were excluded because the results of their blood tests before the start of the trial met the exclusion criteria.

Ultimately, data from 32 patients at Yokohama City University Hospital and 13 patients at Fujisawa Shounandai Hospital were analyzed. Rosuvastatin therapy was stopped in six of these patients due to myalgia, and two patients were administered an oral hypoglycemic agent due to a significant deterioration in blood glucose control. However, these eight patients were included in the intention-to-treat (ITT) analysis.

The clinical characteristics and baseline diabetes and dyslipidemia medications of the patients enrolled in this trial are shown in Table 1. The mean age was 65.8 ± 9.3 years and the mean body mass index (BMI) was 25.8 ± 5.0 kg/m² (Table 1a). The most common baseline treatment for dyslipidemia was rosuvastatin (2.5 mg/day) (Table 1b). The majority of the patients (80%) were taking oral hypoglycemic agents (Table 1c). Two patients were being treated with dietary and exercise therapy only, 36 patients were taking oral hypoglycemic agents, and 7 patients were receiving insulin therapy.

Changes in glucose and lipid metabolism

Table 2 shows the changes in the components of the lipid profile and the HbA1c level during the course of the study. At the switch to rosuvastatin, the mean HbA1c level was $7.1 \pm 0.7\%$. Eight weeks after switching, the mean HbA1c level had increased significantly, and a further increase to $7.5 \pm 0.9\%$ was observed after 24 weeks of rosuvastatin therapy.

The TC, LDL-C, and non-HDL-C levels were significantly reduced at 24 weeks after the statins were switched, but no changes in TG or HDL-C levels were noted. Furthermore, no significant changes in HbA1c levels were observed among patients whose rosuvastatin dose was doubled from 2.5 to 5 mg/day or among those whose statin

Table 1 Clinical characteristics

a (<i>Clinical characteristics</i>)	
Number	45
Male, <i>n</i> (%)	31 (68.9)
Age (years)	65.8 ± 9.3
Body mass index (kg/m ²)	25.8 ± 5.0
Systolic blood pressure (mmHg)	125.3 ± 10.8
Diastolic blood pressure (mmHg)	72.5 ± 7.5
Duration of diabetes (years)	13.0 ± 8.5
FPG (mg/dL)	149.0 ± 35.6
HbA1c (%)	7.1 ± 0.7
Fasting CPR (ng/mL)	2.5 ± 1.2
CPR index	1.70 ± 0.79
HOMA2-IR	4.39 ± 3.29
LDL-C (mg/dL)	108.9 ± 16.5
Non-HDL-C (mg/dL)	134.4 ± 15.7
Serum creatinine (mg/dL)	0.79 ± 0.27
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m ²)	72.7 ± 24.2
Microalbuminuria (mg/gCr)	16.0 (7.4, 39.9)
b (<i>Baseline treatment of dyslipidemia</i>)	
Pravastatin	
5 mg/day, <i>n</i> (%)	4 (8.9)
10 mg/day, <i>n</i> (%)	8 (17.8)
Simvastatin	
5 mg/day, <i>n</i> (%)	2 (4.4)
Fluvastatin	
20 mg/day, <i>n</i> (%)	1 (2.2)
Rosuvastatin	
2.5 mg/day, <i>n</i> (%)	12 (26.7)
Pitavastatin	
1 mg/day, <i>n</i> (%)	8 (17.8)
2 mg/day, <i>n</i> (%)	3 (6.7)
Atorvastatin	
5 mg/day, <i>n</i> (%)	3 (6.7)
10 mg/day, <i>n</i> (%)	4 (8.9)
c (<i>Baseline treatment of diabetes mellitus</i>)	
Dietary therapy, <i>n</i> (%)	2 (4.4)
Oral hypoglycemic agents, <i>n</i> (%)	
Sulfonylurea, <i>n</i> (%)	21 (46.7)
Metformin, <i>n</i> (%)	16 (35.6)
Thiazolidinedione, <i>n</i> (%)	14 (31.1)
Alpha-glucosidase inhibitor, <i>n</i> (%)	14 (31.1)
Glinide, <i>n</i> (%)	3 (6.7)
Dipeptidyl peptidase-4 inhibitors (DPP4 inhibitors), <i>n</i> (%)	23 (51.1)
Insulin therapy, <i>n</i> (%)	7 (15.6)

Data are expressed either as numbers (%) or means (± SD), except for microalbuminuria, which is expressed as median (interquartile range)

SD standard deviation, FPG fasting plasma glucose, HbA1c hemoglobin A1c, Fasting CPR fasting C-peptide immunoreactivity, CPR index C-peptide immunoreactivity index, HOMA2-IR homeostatic model assessment 2 insulin resistance, LDL-C low-density lipoprotein cholesterol, Non-HDL-C non-high-density lipoprotein cholesterol

Table 2 Temporal changes in hemoglobin A1c and the components of the lipid profile

	Baseline	Week 8	Week 16	Week 24	Week 24 – baseline
HbA1c (%)	7.1 ± 0.7	7.3 ± 0.9 (<i>P</i> = 0.016)	7.4 ± 0.9 (<i>P</i> < 0.001)	7.5 ± 0.9 (<i>P</i> < 0.001)	0.4 ± 0.6
TC (mg/dL)	194.6 ± 21.3	184.4 ± 27.8 (<i>P</i> = 0.011)	185.5 ± 29.0 (<i>P</i> = 0.038)	174.5 ± 29.4 (<i>P</i> < 0.001)	–20.0 ± 32.0
LDL-C (mg/dL)	108.9 ± 16.5	98.2 ± 22.7 (<i>P</i> = 0.018)	100.1 ± 24.6 (<i>P</i> = 0.061)	91.6 ± 24.5 (<i>P</i> < 0.001)	–17.3 ± 29.9
HDL-C (mg/dL)	60.1 ± 13.2	60.5 ± 13.9 (<i>P</i> = 0.700)	61.3 ± 14.9 (<i>P</i> = 0.429)	59.4 ± 15.7 (<i>P</i> = 0.643)	–0.7 ± 10.5
TG (mg/dL)	127.4 ± 50.8	128.7 ± 52.2 (<i>P</i> = 0.830)	130.9 ± 52.6 (<i>P</i> = 0.574)	117.6 ± 42.1 (<i>P</i> = 0.145)	–9.8 ± 44.1
Non-HDL-C (mg/dL)	134.4 ± 15.7	128.4 ± 22.5 (<i>P</i> = 0.044)	127.9 ± 26.3 (<i>P</i> = 0.854)	116.5 ± 26.2 (<i>P</i> < 0.001)	–17.9 ± 30.2

Data are expressed as mean ± SD

SD standard deviation, HbA1c hemoglobin A1c, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, Non-HDL-C non-high-density lipoprotein cholesterol

Table 3 Comparison of the changes in hemoglobin A1c in the doubled and switched groups

	Doubled group	Switched group	<i>P</i> value
HbA1c at baseline (%)	7.1 ± 0.7	7.1 ± 0.7	0.981
HbA1c at week 24 (%)	7.5 ± 0.9	7.6 ± 1.0	0.871
Change in HbA1c (%) from baseline to week 24	0.4 ± 0.4	0.5 ± 0.6	0.818

Data are expressed as mean ± SD. The doubled group included patients whose rosuvastatin dose was doubled from 2.5 to 5 mg/day (*n* = 12). The switched group included patients whose treatment was switched from another statin to 5 mg/day rosuvastatin (*n* = 33)

SD standard deviation

Table 4 Changes in insulin secretion and resistance and the components of lipid profile

	Baseline	Week 24	<i>P</i> value
FPG (mg/dL)	149.0 ± 35.6	158.3 ± 46.8	0.114
Fasting CPR (ng/mL)	2.5 ± 1.2	2.4 ± 1.3	0.718
CPR index	1.70 ± 0.79	1.63 ± 0.98	0.571
HOMA2-IR	4.39 ± 3.29	4.96 ± 4.30	0.339
Oxidized LDL (U/L)	139.3 ± 33.0	115.8 ± 33.0	<0.001
Sd-LDL (mg/dL)	37.0 ± 10.8	31.9 ± 11.6	0.004
TNF-α (pg/mL)	1.63 ± 1.38	1.56 ± 1.22	0.383
High-molecular-weight adiponectin (μg/mL)	5.09 ± 5.61	5.07 ± 5.66	0.909
ApoB (mg/dL)	94.0 ± 11.1	81.7 ± 16.3	<0.001
ApoA-1 (mg/dL)	144.0 ± 22.3	145.8 ± 22.7	0.291
ApoB/ApoA-1 ratio	0.67 ± 0.13	0.57 ± 0.15	<0.001

Data are expressed as mean ± SD

SD standard deviation, FPG fasting plasma glucose, CPR C-peptide immunoreactivity, HOMA2-IR homeostasis model assessment 2 insulin resistance, Sd-LDL small dense low-density lipoprotein, TNF-α tumor necrosis factor alpha, ApoB apolipoprotein B, ApoA-1 apolipoprotein A-1

regimen was switched from another statin to 5 mg/day rosuvastatin (Table 3). Since pitavastatin has been shown to improve glycosylated hemoglobin levels in patients with type 2 diabetes [16], we divided patients into a pitavastatin

group and a nonpitavastatin group. The HbA1c levels of the two groups did not differ significantly (data not shown).

An assessment of the changes in parameter values associated with insulin secretion and resistance and the

Table 5 Results of simple linear regression analyses between change in hemoglobin A1c and baseline clinical and biochemical characteristics and parameters

	R^2	β	SE	P value
FPG (mg/dL)	0.1531	0.006	0.002	0.008
Fasting CPR (ng/mL)	0.0301	-0.085	0.073	0.255
CPR index	0.1000	-0.236	0.108	0.034
Male sex	0.0070	0.105	0.190	0.585
Age (years)	0.0097	0.006	0.011	0.520
Duration of diabetes (years)	0.0029	-0.004	0.011	0.726
BMI (kg/m ²)	0.0181	-0.016	0.018	0.379
HOMA2-IR	0.0228	-0.027	0.027	0.322
LDL-C (mg/dL)	0.0180	-0.005	0.005	0.379

SE standard error, FPG fasting plasma glucose, CPR C-peptide immunoreactivity, BMI body mass index, HOMA2-IR homeostasis model assessment 2 insulin resistance, LDL-C low-density lipoprotein cholesterol

lipid profile revealed that there were no significant changes in FPG, CPR index (reflecting insulin secretion ability), or HOMA2-IR (reflecting insulin resistance) after 24 weeks of treatment with rosuvastatin (Table 4). Conversely, the levels of oxidized LDL and sd-LDL decreased significantly, and a qualitative improvement in LDL-C was observed at the end of the study. The apoB levels and apoB/apoA-1 ratio were significantly reduced with rosuvastatin. Furthermore, simple linear regression analysis showed that there were significant correlations between the change in apoB or apoB/apoA-1 and the change in LDL-C [apoB: correlation coefficient (R^2) = 0.64, α = 0.31; β = 1.44, standard error (SE) = 0.1, P < 0.001; apoB/apoA-1 ratio: R^2 = 0.54, α = -1.00, β = 176; SE = 24.7, P < 0.001].

Table 6 Results of multiple linear regression analysis between change in hemoglobin A1c and baseline clinical and biochemical characteristics and parameters

Model 1	β	SE	95% CI	P value
FPG (mg/dL)	0.008	0.002	0.004 to 0.013	0.001
Male sex	0.143	0.174	-0.211 to 0.496	0.418
Age (years)	0.007	0.001	-0.013 to 0.027	0.490
Duration of diabetes (years)	-0.008	0.010	-0.029 to 0.013	0.442
BMI (kg/m ²)	-0.030	0.019	-0.068 to 0.008	0.122
LDL-C (mg/dL)	-0.005	0.005	-0.015 to 0.006	0.370
Model 2	β	SE	95% CI	P value
CPR index	-0.308	0.133	-0.577 to -0.038	0.026
Male sex	0.078	0.187	-0.025 to 0.020	0.679
Age (years)	-0.002	0.011	-0.025 to 0.020	0.829
Duration of diabetes (years)	-0.013	0.012	-0.036 to 0.011	0.286
BMI (kg/m ²)	-0.005	0.020	-0.045 to 0.035	0.800
LDL-C (mg/dL)	-0.005	0.006	-0.016 to 0.007	0.410

SE standard error, FPG fasting plasma glucose, BMI body mass index, CPR index C-peptide immunoreactivity index, LDL-C low-density lipoprotein cholesterol

To identify predictors of the changes in HbA1c levels in these patients, we examined the relationships between HbA1c and the predictors derived from clinical and biochemical characteristics as well as parameters obtained at the start of the trial before the switch to rosuvastatin. Simple linear regression analysis showed that the change in HbA1c level was positively correlated with the FPG level at baseline and was negatively correlated with the CPR index at baseline (Table 5). Multiple linear regression analysis revealed that the change in HbA1c level was significantly and positively correlated with FPG level at baseline [β = 0.008, 95% confidence interval (CI) 0.004–0.013, P = 0.001] (Table 6, model 1), and was significantly and negatively correlated with the CPR index at baseline (β = -0.308, 95% CI -0.577 to -0.038, P = 0.026) (Table 6, model 2) after adjustment for sex, age, duration of diabetes, BMI, and LDL-C. We conducted a ROC analysis to explore the relationships of the change in HbA1c level with FPG and the CPR index (Fig. 1). Patients were stratified based on the degree of change in HbA1c into those with a change in HbA1c of <0.4% and those with a \geq 0.4% change in HbA1c. FPG was a significant predictor of the change in HbA1c level (area under the curve: 0.72), whereas CPR index was not a significant predictor (area under the curve: 0.52). The FPG cutoff value of 168 mg/dL had a sensitivity and a specificity of 47 and 93%, respectively, and positive and negative predictive values of 93 and 47%, respectively.

Analysis of safety endpoint parameters indicated that body weight and BMI did not increase with the switch to low-dose rosuvastatin. While creatine kinase was somewhat elevated, the increase was not significant (Table 7).

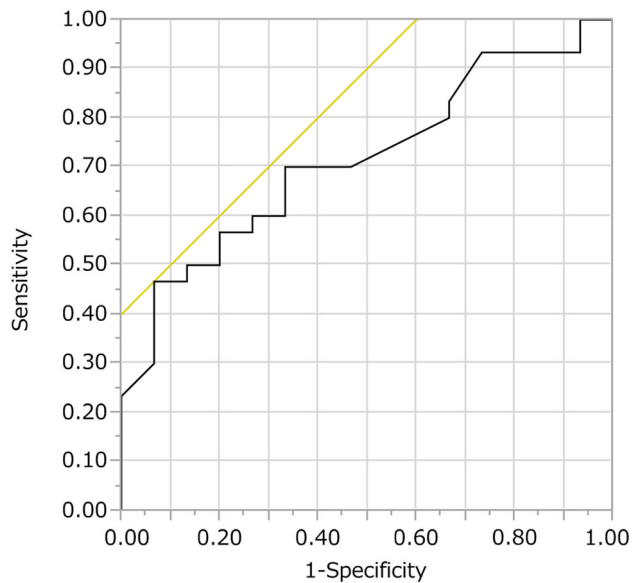


Fig. 1 Receiver operating characteristic curve analysis of changes in hemoglobin A1c and fasting plasma glucose levels. Fasting plasma glucose was a significant predictor of increased HbA1c (area under the curve: 0.72). The cutoff value for plasma glucose (168 mg/dL) had a sensitivity of 47% and a specificity of 93%

Table 7 Safety endpoint parameters

	Baseline	Week 24	<i>P</i> value
Body weight (kg)	68.9 ± 14.9	68.6 ± 15.6	0.623
BMI (kg/m ²)	25.8 ± 5.0	25.6 ± 5.1	0.556
CK (IU/L)	89.0 (70.5, 168.0)	99.0 (70.5, 160.0)	0.526
AST (IU/L)	26.5 ± 14.0	23.8 ± 10.2	0.056
ALT (IU/L)	24.8 ± 12.0	24.1 ± 10.7	0.594
γ-GTP (IU/L)	33.8 ± 21.7	33.6 ± 24.2	0.922
Myalgia (n%)	0 (0)	6 (13.3)	0.012

Data are expressed as mean ± SD except for CK, which is shown as median (interquartile range)

SD standard deviation, BMI body mass index, CK creatine kinase, AST aspartate aminotransaminase, ALT alanine aminotransaminase, γ-GTP gamma-glutamyltransferase

Discussion

In the present study, switching from other statins to low-dose rosuvastatin at 5 mg/day led to further reductions in TC, LDL-C, and non-HDL-C levels. Therefore, low-dose rosuvastatin should be considered for intensive statin therapy in Japanese patients with type 2 diabetes and dyslipidemia. The change in LDL-C following rosuvastatin treatment was previously reported for Asian patients [17]: in patients switching to the statin, the mean LDL-C level was significantly reduced by 24.5%, from 132.7 ± 36.9 to 97.6 ± 35.1 mg/dL, which was a larger reduction than that observed in the present study. This discrepancy might be

due to the different rosuvastatin doses used in the studies: 10 mg/day was used in the previous study. Furthermore, in that retrospective observational study, changes in FPG and HbA1c levels were not determined.

Originally, statin was reported to reduce oxidized LDL and sd-LDL [18, 19]. Conversely, impaired glucose tolerance was shown to increase oxidized LDL and sd-LDL [20, 21]. In our study, the HbA1c level increased; however, there was no significant correlation between the change in HbA1c and the change in oxidized LDL or sd-LDL (oxidized LDL: $R^2 = 0.0043$, $\alpha = 0.4168$, $\beta = -0.0011$, $SE = 0.592$, $P = 0.670$; sd-LDL: $R^2 = 0.0035$, $\alpha = 0.4264$, $\beta = -0.0031$, $SE = 0.592$, $P = 0.700$). On the other hand, a significant positive correlation was observed between the change in LDL-C and that of oxidized LDL or sd-LDL (oxidized LDL: $R^2 = 0.2562$, $\alpha = -7.2738$, $\beta = 0.4293$, $SE = 26.113$, $P < 0.001$; sd LDL: $R^2 = 0.4363$, $\alpha = -8.2968$, $\beta = 1.7635$, $SE = 22.737$, $P < 0.001$). Oxidized LDL and sd-LDL decreased in parallel with the decrease in LDL-C but not with the decrease in glucose tolerance.

Statins reduce the risk of cardiovascular diseases [1]. In a previous report, the apoB/apoA-1 ratio was reported to be a high population-attributable risk (54%) with a high odds ratio (1.59, 95% CI 1.53–1.64) for the risk of myocardial infarction [22]. The report suggested that rosuvastatin might reduce the risk of myocardial infarction. Our study also showed that the change in LDL-C level was positively correlated with the change in apoB/apoA-1 ratio. The administration of rosuvastatin (20 mg/day) or atorvastatin (80 mg/day) was also reported to reduce apoB and the apoB/apoA-1 ratio [23]. In agreement with these studies, we also found that rosuvastatin (5 mg/day) reduced both apoB and apoB/apoA-1 in Japanese patients with type 2 diabetes and dyslipidemia.

One of the results of JUPITER, a large-scale clinical trial, was the identification of a relationship between statins and glucose metabolism; the investigators found increased incidence of new-onset diabetes with rosuvastatin [3, 4]. The dose of rosuvastatin used in that trial, 20 mg/day, was higher than that used in Japan, and it was unclear whether rosuvastatin would affect glucose metabolism at the dose used in Japanese patients or in patients already diagnosed with type 2 diabetes. In contrast, a retrospective study found that switching to a stronger statin or doubling the original statin dose did not increase HbA1c levels in Japanese patients with type 2 diabetes and dyslipidemia who failed to achieve lipid control targets [24]. In a prospective study, rosuvastatin (5 mg/day) and atorvastatin (10 mg/day) given to Japanese patients with type 2 diabetes and dyslipidemia increased HbA1c levels by 0.11 and 0.12%, respectively; and there was no significant difference in HbA1c levels between the two groups at 12 months [25]. Furthermore, in a subgroup analysis, FPG levels were

reported to decrease significantly in patients with a BMI ≥ 25 kg/m² and increase in those with BMI < 25 kg/m² [26]. However, these studies were conducted within the limits of daily clinical practice and without setting a standard treatment for diabetes.

In our study, 5 mg/day of rosuvastatin, which is considered a moderate dose in Japan, was administered to patients with type 2 diabetes. Our results showed a significant decrease in LDL-C levels and a significant increase in HbA1c levels (Table 2). According to simple linear regression analysis, there was no significant correlation between the change in HbA1c level and the change in LDL-C level ($R^2 = 0.0012$, $\alpha = 0.4535$, $\beta = 0.0007$, $SE = 0.030$, $P = 0.820$). Based on our results, it is highly probable that impaired glucose tolerance—which was potentially masked in previous reports by the favorable effects of lifestyle guidance and changes in diabetes treatment—was observed in our study. We did not provide such guidance and followed a standardized treatment for diabetes as part of the study design. Thus far, three major mechanisms have been proposed for new-onset diabetes related to statins [27]. First, certain statins affect insulin secretion through direct, indirect, or combined effects on calcium channels in pancreatic β cells. Second, reduced translocation of glucose transporter 4 to the plasma membrane in response to statin treatment results in hyperglycemia and hyperinsulinemia. Third, statin therapy decreases other important downstream products, such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and dolichol, and their depletion leads to reduced intracellular signaling. In patients with type 2 diabetes, atorvastatin (10 mg/day) was reported to decrease the HOMA2 percent β -cell function and increase the HOMA2-IR compared with the baseline values; the differences, however, were not statistically significant [28]. Our study revealed a tendency for decreased insulin secretion (determined by the CPR index) and increased insulin resistance (as reflected by the HOMA2-IR value; Table 4) in patients that switched to rosuvastatin; however, these changes, which are considered indicators of impaired glucose tolerance, were not statistically significant.

Our study showed that FPG was a significant predictor of change in HbA1c level based on ROC analysis. Therefore, a high FPG value could be a predictor of exacerbated glucose metabolism in patients switching to rosuvastatin (5 mg/day). However, there is the possibility that a high FPG level could affect glucose metabolism and therefore increase the HbA1c level.

The outcomes of this study suggest that statin dose should be adjusted based on individual cardiovascular disease risk and carefully monitored in Japanese patients with type 2 diabetes and dyslipidemia who typically have high FPG levels.

A limitation of our study was the lack of a control group. FPG was a significant predictor; however, the possibility

remains that high FPG levels may affect glucose metabolism, thereby increasing HbA1c levels in patients in this study.

Conclusions

Switching from other statins to rosuvastatin (5 mg/day) further reduced LDL-C and apoB/apoA-1 levels but significantly increased HbA1c levels after 24 weeks in Japanese patients with type 2 diabetes and dyslipidemia. The intensity of statin therapy should be carefully controlled in Japanese patients with type 2 diabetes and dyslipidemia who typically have high FPG levels.

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Compliance with ethical standards

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Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later versions.

Informed consent Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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