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Combination Therapy of Pitavastatin and Sitagliptin Improves the Estimated Glomerular Filtration Rate in Patients with Type 2 Diabetes

Soichi Kurioka[1]*, Yasuo Ohyama[2], Akira Ichibangase[1], Hideho Murata[3], Nobuhiko Kataoka[4], Hiroaki Shimomura[4], Hideaki Sawaki[4], Tamaki Imai[4] and Shinichiro Ohashi[5]

[1]*Department of Diabetes, Komatsu Hospital, Osaka 572-8567, Japan*
[2]*Kadoma Keijinkai Clinic, Osaka 572-8567, Japan*
[3]*Murata Hospital, Osaka 572-8567, Japan*
[4]*Arisawa Hospital, Osaka 572-8567, Japan*
[5]*Ohashi Clinic, Osaka 572-8567, Japan*

Abstract

Objective: Previous studies have shown that statins improve kidney function in patients with chronic kidney disease. In this study, we examined the effect of combination therapy (statin and dipeptidylpeptidase IV inhibitor) on kidney function in patients with type 2 diabetes with hypercholesterolemia.

Research design and methods: The subjects were 81 patients with type 2 diabetes with hypercholesterolemia, of whom 29 were treated with 50 mg sitagliptin (combination therapy group) and 52 did not receive sitagliptin (control group). The patients received 2 mg pitavastatin for 6 months and the effects on estimated glomerular filtration rate (eGFR), lipid profile, and glycemic control were evaluated.

Results: After 6 months of pitavastatin treatment, there was a significant increase in eGFR in the combination therapy group (71.3 ± 23.2 to 84.2 ± 22.7 ml/min/1.73 m^2, $p<0.001$), but not in the control group (73.3 ± 20.1 to 76.1 ± 19.7 ml/min/1.73 m^2, $p=0.15$); and the changes in Cr and eGFR were significantly greater in the combination therapy group. Based on the CKD stage, patients with normal kidney function (G1 and G2) had no significant change in eGFR, but in patients with moderate kidney dysfunction (G3), the improvement in eGFR (from 48.6 ± 7.9 to 62.3 ± 18.9 mL/min/1.73 m^2) soon occurred after 1-month of combination therapy and then stabled. In multiple regression analysis, Cr, apoA-1, apoB, and sitagliptin were independently associated with the change in eGFR.

Conclusions: These findings suggest that combination therapy of pitavastatin and sitagliptin may have a kidney protective effect in patients with type 2 diabetes with hypercholesterolemia.

Keywords: Pitavastatin; Sitagliptin; eGFR

Introduction

Diabetic nephropathy is the leading cause of end-stage kidney disease (ESKD). Interventions that delay or prevent progression of diabetic nephropathy include tight control of blood pressure (BP) and blood glucose, and use of renin angiotensin system inhibitors such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin 2 receptor blockers (ARBs). However, even with optimal medical management in the context of clinical trials, patients with diabetic nephropathy are at risk for progressive loss of kidney function and for cardiovascular disease.

Hypercholesterolemia may play an important role in progression of chronic kidney disease (CKD) including diabetic nephropathy through toxic effects of lipids on mesangial cells or by promoting intrarenal atherosclerosis. A recent study showed that pitavastatin and rosuvastatin reduced the urinary excretion of albumin and improved glomerular hypertrophy in diabetic nephropathy in db/db mice [1]. In a sub-analysis of the LIVARO Effectiveness and Safety (LIVES) Study, pitavastatin was found to increase the estimated glomerular filtration rate (eGFR) by 5.6 mL/min/m^2 in patients with CKD (eGFR<60 mL/min/m^2); however, the increase in eGFR in patients with diabetes, hypertension and proteinuria was less than that in patients without these diseases [2].

Sitagliptin is a selective dipeptidylpeptidase IV (DPP-4) inhibitor that blocks inactivation and degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and is used to treat type 2 diabetes mellitus. Several studies have shown beneficial effects of GLP-1 on the cardiovascular system and on endothelial function. However, there is a lack of evidence for beneficial effects of DPP-4 inhibitors on kidney function, although sitagliptin has been shown to reduce albuminuria in patients with type 2 diabetes [3]. In this study, we examined the effects of combination therapy of pitavastatin and sitagliptin on the kidney in patients with type 2 diabetes with hypercholesterolemia.

Research Design and Methods

Subjects

This study was conducted as a prospective and open-labeled clinical trial. The subjects were 81 patients with type 2 diabetes with hypercholesterolemia, including 29 treated with 50 mg sitagliptin (combination therapy group) before pitavastatin administration and 52 patients who had not received sitagliptin (control group).

***Corresponding author:** Soichi Kurioka, 11-6 Kawakatsu-cho, Department of Diabetes, Komatsu Hospital, Osaka 572-8567, Japan, Tel: +81728231521; Fax: +81728217013; E-mail: kuriokas2471@msn.com

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The inclusion criterion was LDL-C ≥ 3.1 mmol/L and the exclusion criteria were age<20 years old and severe liver disease. All patients were treated with 2 mg pitavastatin for 6 months, after which effects on kidney function (serum creatinine level (Cr) and eGFR), lipid profile, and glycemic control were evaluated. The study was approved by the local research ethics committee and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Laboratory analysis

Fasting blood samples were collected from each patient after an overnight fast at baseline and after 1, 3 and 6 months of treatment. eGFR was assessed using the Japanese revised equation: eGFR (mL/min/1.73 m^2)=194×$Cr^{-1.094}$×$Age^{-0.287}$(×0.739, if female). Using the baseline eGFR, patients were classified into CKD stages as defined in the K/DOQI guidelines [4]: G1: ≥ 90, G2: ≥ 60-<90, G3: ≥ 30-<60, G4: ≥ 15-<30, and G5: <15 mL/min/1.73 m^2. For lipid profile analysis, the serum LDL-C concentration was estimated using the Friedewald formula (LDL-C=TC-HDL-C-TG0.2) [5] in patients with serum TG<4.5 mmol/L.

Statistical analysis

Patients were included in the data analysis set if eGFR values were available at enrollment and at follow-up after 6 months of treatment. Descriptive statistics were calculated. Comparisons of continuous variables between the sitagliptin and control groups were performed by ANOVA, and those between baseline and follow-up by repeated measures of ANOVA according to their distributions. Comparisons of categorical values between the two groups were performed by chi-square test. General linear models were used to assess relationships between the change in eGFR and several factors. We performed Pearson correlation analysis. Univariate and multivariate analyses were performed to assess the relationship between the change in eGFR and each potentially significant variable. Variables showing a correlation with the change of eGFR with p<0.1 in univariate analysis were included in multivariate analysis, which was conducted with backward model selection with p<0.05. Values are reported as means ± S.D, unless otherwise indicated. The significance level was 5% two-sided (2.5% one-sided) and all analyses were performed using JMP ver. 5.1.

Results

Baseline characteristics and a comparison of patients in the combination therapy group and the control group are shown in Table 1. Male gender, age, body mass index (BMI), systolic and diastolic blood pressure, current smoker, and hypertension did not differ significantly between the two groups. Of the 81 patients, 69 (86%) had received antidiabetic medication. Excluding sitagliptin, 56 patients (69%) had taken antidiabetic medication. Comparison between the combination therapy group and the control group showed significantly greater use of metformin in the control group (7% vs. 31%, p=0.0079), but no significant differences in use of sulfonylureas, α-glucosidase inhibitors, pioglitazone, and insulin. Antihypertensive medication had been used by 44 patients (54%). Use of ARBs or ACEIs, calcium antagonists, β-blockers, and diuretics did not differ significantly between the two groups.

Baseline biochemical characteristics and CKD stage are shown in Table 2. Total cholesterol (TC), triglyceride (TG), HDL-C, LDL-C, non-HDL-C, apolipoprotein A-1 (apoA-1), apolipoprotein B-100 (apoB), apoA-1/apoB, fasting plasma glucose (FPG), HbA1c, creatinine (Cr), eGFR, and CKD stage (G1, G2, and G3) did not differ significantly different between the two groups. No patients had a severe CKD stage of G4 or G5.

After 6 months of pitavastatin treatment, there was a significant increase in eGFR in the combination therapy group (71.3 ± 23.2 to 84.2 ± 22.7 ml/min/1.73 m^2, p<0.001), but not in the control group (73.3 ± 20.1 to 76.1 ± 19.7 ml/min/1.73 m^2, p=0.15). Changes in data from baseline at 6 months after pitavastatin are shown in Table 3. Changes of TC, TG, HDL-C, LDL-C, non-HDL-C, apoA-1, apoB, apoA-1/apoB, FPG, HbA1c, SBP, and DBP did not differ significantly between the two groups. Changes of Cr and eGFR were also significantly greater in the combination therapy group than in the control group. Based on the CKD stage, patients with normal kidney function (G1 and G2) had no significant change in eGFR, but in patients with moderate kidney dysfunction (G3), the improvement in eGFR (from 48.6 ± 7.9 to 62.3 ± 18.9 mL/min/1.73 m^2) soon occurred after 1-month of combination therapy and then stabled (Figure 1).

Changes in eGFR were correlated with apoA-1 (r=-0.29, p=0.014), apoB/apoA-1 (r=-0.29, p=0.013), serum creatinine (r=0.30, p=0.007), eGFR (r=-0.37, p=0.0006), and combination therapy (r=0.31, p=0.005). In multiple regression analysis (Table 4), serum creatinine, combination therapy, apoA-1, and apoB were independently associated with a change in eGFR.

Discussion

Several possible mechanisms may underlie the increase in eGFR induced by statins, including improvement of endothelial function

Item	All (n=81)	Combination Therapy (n=29)	Control (n=52)	P value
Male	45(56)	16(55)	29(56)	0.9584
Age (years)	63 ± 11	62 ± 12	63 ± 10	0.7119
BMI (kg/m^2)	26.2 ± 4.3	26.2 ± 5.0	26.1 ± 3.9	0.9071
SBP (mmHg)	135 ± 19	135 ± 17	135 ± 20	0.8839
DBP (mmHg)	78 ± 13	77 ± 11	78 ± 14	0.6793
Current smoker	9(11)	5(17)	4(8)	0.1997
Hypertension	44(54)	18(62)	26(50)	0.2941
Cerebral infarction	2(2)	0(0)	2(4)	0.1796
Peripheral artery disease	5(6)	2(7)	3(6)	0.8410
Coronary artery disease	5(6)	1(3)	4(8)	0.4268
Antidiabetic medication				
Sulfonylurea	36(45)	9(34)	27(52)	0.1285
α-glucosidase inhibitor	14(17)	3(10)	11(21)	0.2024
Pioglitazone	7(9)	2(7)	5(10)	0.6714
Metformin	18(22)	2(7)	16(31)	0.0079*
Insulin	10(12)	3(10)	7(13)	0.6792
Antihypertensive medication				
ARB or ACEI	37(46)	15(52)	22(42)	0.4150
Calcium antagonist	24(30)	11(38)	13(25)	0.2258
ß-blocker	7(9)	3(10)	4(8)	0.6871
Diuretic	3(4)	1(3)	2(4)	0.9272

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ARB: Angiotensin II Receptor Blocker; ACEI: Angiotensin Converting Enzyme Inhibitor. Data are means ± SD or n (%). * $p < 0.05$.

Table 1: Baseline characteristics and comparison of patients treated with or without sitagliptin.

Item	All (n=81)	Combination Therapy (n=29)	Control (n=52)	P value
TC (mmol/L)	6.4 ± 0.9	6.6 ± 1.0	6.3 ± 0.9	0.1951
TG (mmol/L)	2.1 ± 1.1	2.1 ± 1.1	2.0 ± 1.1	0.6187
HDL-C (mmol/L)	1.4 ± 0.4	1.4 ± 0.3	1.5 ± 0.4	0.6802
LDL-C (mmol/L)	4.1 ± 0.8	4.2 ± 0.9	4.0 ± 0.7	0.2227
Non-HDL-C (mmol/L)	5.0 ± 1.0	5.2 ± 1.1	4.9 ± 0.9	0.1550
ApoA-1 (g/L)	1.46 ± 0.26	1.46 ± 0.24	1.45 ± 0.28	0.9670
ApoB (g/L)	1.29 ± 0.22	1.34 ± 0.26	1.26 ± 0.20	0.1539
ApoA-1/ApoB ratio	0.92 ± 0.29	0.96 ± 0.37	0.90 ± 0.24	0.4149
FPG (mmol/L)	8.9 ± 3.2	9.9 ± 3.1	8.4 ± 3.2	0.0511
HbA1c (%)	7.6 ± 1.4	7.9 ± 1.4	7.5 ± 1.4	0.2058
IFCC (mmol/mol)	60 ± 15	63 ± 15	58 ± 15	
Creatinine (μmol/L)	71.6 ± 23.0	73.3 ± 23.9	69.8 ± 22.1	0.5730
eGFR (mL/min/1.73m^2)	72.6 ± 21.1	71.3 ± 23.2	73.3 ± 20.1	0.6917
CKD stage				
G1	19(24)	7(24)	12(23)	0.9141
G2	36(44)	11(38)	25(48)	0.3767
G3	26(32)	11(38)	15(29)	0.4038
G4 or G5	0(0)	0(0)	0(0)	-

Data are shown as means ± SD or n (%). IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.
G1 (≥90 mL/min/1.73 m^2), G2 (≥60 - <90 mL/min/1.73 m^2), G3 (≥30 - <60 mL/min/1.73 m^2), G4 (≥15 - <30 mL/min/1.73 m^2), G5 (<15 mL/min/1.73 m^2)

Table 2: Baseline biochemical characteristics and distribution of CKD stage.

Item	All (n=81)	Combination Therapy (n=29)	Control (n=52)	P value
TC (mg/dL)	-69 ± 37	-78 ± 36	-64 ± 37	0.0921
TG (mg/dL)	-10 ± 134	-25 ± 138	-1 ± 132	0.4278
HDL-C (mg/dL)	4 ± 13	5 ± 13	4 ± 13	0.7433
LDL-C (mg/dL)	-67 ± 35	-73 ± 35	-64 ± 34	0.2630
Non-HDL-C (mg/dL)	-73 ± 40	-83 ± 39	-67 ± 39	0.0913
Apo A-1 (mg/dL)	8 ± 20	7 ± 20	8 ± 20	0.7559
Apo B (mg/dL)	-39 ± 24	-46 ± 27	-34 ± 20	0.0538
Apo A-1/Apo B ratio	-0.32 ± 0.27	-0.36 ± 0.33	-0.29 ± 0.23	0.3571
FPG (mg/dL)	-10 ± 67	-21 ± 73	-3 ± 63	0.2586
HbA1c (%)	-0.2 ± 1.3	-0.6 ± 1.5	-0.02 ± 1.2	0.0598
Serum creatinine (mg/dL)	-0.07 ± 0.16	-0.13 ± 0.16	-0.03 ± 0.15	0.0079*
eGFR (mL/min/1.73m^2)	6.4 ± 15.7	12.9 ± 16.3	2.8 ± 14.2	0.0049*
SBP (mmHg)	-1 ± 33	5 ± 42	-4 ± 27	0.3092
DBP (mmHg)	-1 ± 11	1 ± 10	-1 ± 12	0.4514

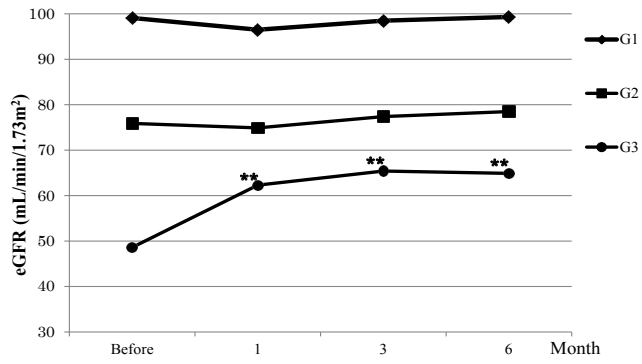
Data are means ± SD.
* p<0.05 , Combination Therapy vs Control.

Table 3: Changes in data from baseline at 6 months after pitavastatin.

[6]. Statins have also been suggested to increase renal blood flow and suppress monocyte recruitment, mesangial cell proliferation, and inflammation [7]. Nakamura et al. found that pitavastatin reduced urinary albumin and liver-type fatty acid-binding protein (L-FABP) in patients with early diabetic nephropathy, which might be attributable to the antioxidant effects of pitavastatin [8]. In spontaneously hypercholesterolemic Imai rats, pitavastatin has a renal protective effect via reduction of urinary protein and antioxidant actions, independent of lipid lowering effects [9]. Changes in serum lipids, such as higher total cholesterol, low-density lipoprotein (LDL) and triglycerides or lower high-density lipoprotein (HDL), are well-established risk factors for development of atherosclerotic cardiovascular disease. Evidence has also accumulated regarding these lipids as risk factors for CKD (10,11) [10,11]. Apolipoprotein A-1 is the major protein constituent of HDL, whereas apolipoprotein B is a constituent of intermediate-density lipoprotein (IDL), very low density lipoprotein (VLDL), and LDL particles [12,13]. Apolipoproteins can be measured independent of fasting status. Lower apoA-1 and higher apoB have been associated with CKD in several retrospective and prospective studies [10,14-19]. In the present study, multiple regression analysis revealed that apoA-1, apoB, and were independently associated with changes in eGFR. The basal levels of apoA-1 and apoB were identified as significant factors influencing changes in eGFR during pitavastatin treatment; therefore, an increase of apoA-1 and a decrease of apoB might be linked to the increase in eGFR.

There has been no previous report of a DPP-4 inhibitor or GLP-1 analog increasing eGFR in patients with diabetes. Sitagliptin has been found to reduce urinary albumin excretion (UAE) in patients with type 2 diabetes 3, with UAE, SBP, DBP, FPG, and HbA1c decreasing and eGFR being unchanged after 6 months of sitagliptin treatment. GLP-1 can improve endothelial function and prevent certain renal pathologies in diabetic rodents [20,21]. The GLP-1 receptor is abundant in the gastrointestinal tract and is found in the endothelium and kidney and may stimulate endothelial nitric oxide production [20,22,23].

Clinical guidelines emphasize hypercholesterolemia as a risk factor for progression of diabetic nephropathy. However, little is known about improvement of kidney function by statins in patients with type 2 diabetes. It has not been clarified that rationale of pitavastatin and sitagliptin combination therapy has improved eGFR in this study. The current study has several limitations, including a study population consisting only of Japanese patients, making it uncertain if the findings are generalizable to other ethnic groups; and the absence of data for UAE. However, to the best of our knowledge, this is the first study to investigate the effect of combination therapy of pitavastatin and sitagliptin on kidney function. In this study, sitagliptin group treated with a dose of 50 mg, a standard dose in Japanese patients with type 2 diabetes with normal kidney function. If we treated with a dose of 100 mg of sitagliptin, patients with normal kidney function (G1 and G2) may improve in eGFR.



G1	99.1 ± 13.0	96.5 ± 18.4	98.5 ± 15.5	99.3 ± 18.7
G2	75.9 ± 8.3	74.9 ± 13.0	77.4 ± 12.4	78.5 ± 14.5
G3	48.6 ± 7.9	62.3 ± 18.9**	65.4 ± 24.4**	64.9 ± 18.8**

Figure 1: Effect of pitavastatin on eGFR in subgroups based on the CKD stage. *p<0.05, **p<0.001 vs. before pitavastatin treatment. Values are shown as the mean ± SD. Patients with normal kidney function (stages G1 and G2) had no significant change in eGFR, but those with moderate kidney dysfunction (stage G3) had significantly improved eGFR.

Item	β	95%CI	p
creatinin	0.38	(10.7 to 39.1)	0.0008
Combination therapy	0.34	(2.4 to 9.3)	0.0018
ApoA1	0.25	(0.02 to 0.29)	0.0291
ApoB	-0.23	(-0.33 to -0.01)	0.0331

Multivariate analyses were performed to assess the relationship between the change in eGFR and each potentially significant variable. Variables showing a correlation with the change of eGFR with p<0.1 in univariate analysis were included in multivariate analysis, which was conducted with backward model selection with p<0.05.

Table 4: Results of multiple regression analysis for variables with an association with changes of eGFR.

Within the limitations, our results show that this therapy may have a kidney protective effect in patients with type 2 diabetes with hypercholesterolemia.

A major finding in this study is that a significant increase in eGFR occurred after 6 months of combination therapy of pitavastatin and sitagliptin in patients with type 2 diabetes with hypercholesterolemia. It has been clearly demonstrated that this combination therapy was not helpful in patients with baseline eGFR over 60 mL/min/1.73 m^2, but only helpful in patients with eGFR from 30 to 59 mL/min/1.73 m^2. The improvement in eGFR (from 48.6 ± 7.9 to 62.3 ± 18.9 ml/min/m^2) soon occurred after 1-month of pitavastatin and sitagliptin combination therapy and then stabled. As compared with previous studies showed a much slower (e.g. 1.22 ml/min per year slower in statin recipients [24] and insignificant improvement of GFR in statin users [25], the present result hinted that the pitavastatin and sitagliptin combination therapy dramatically and promptly improves eGFR in type 2 patients with CKD stage 3.

Study Limitations

There are several limitations in the study. These include the relatively small number of subjects, the lack of randomization, and the imbalanced subgroups.

Acknowledgments

The authors report no potential conflicts of interest relevant to this article. S.K. was involved in study design, coordination, subject recruitment, data collection and statistical analysis, and wrote the manuscript. Y.O., A.I., H.M., N.K., H. S., H.S., T.I., and S.O. were involved in study design and coordination, subject recruitment, and data collection.

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