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

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\textbf{Abstract}

\textbf{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.

\textbf{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.

\textbf{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\textsuperscript{2}, p<0.001), but not in the control group (73.3 ± 20.1 to 76.1 ± 19.7 ml/min/1.73 m\textsuperscript{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\textsuperscript{2}) soon occurred after 1-month of combination therapy and then stablized. In multiple regression analysis, Cr, apoA-1, apoB, and sitagliptin were independently associated with the change in eGFR.

\textbf{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.

\textbf{Keywords:} Pitavastatin; Sitagliptin; eGFR

\section{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\textsuperscript{2} in patients with CKD (eGFR<60 mL/ min/m\textsuperscript{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.

\section{Research Design and Methods}

\textbf{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).

\section*{Acknowledgments}

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\section*{Conflict of Interest}

The authors declare no potential conflict of interest.

\section*{References}


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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 m²)=194×Cr^{-1.094}×Age^{-0.287}×(1.21, if male). 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 m². 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. Combination between the 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 m², p<0.001), but not in the control group (73.3 ± 21.0 to 76.1 ± 19.7 ml/min/1.73 m², 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 m²) 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=0.006), and combination therapy (r=0.31, p=0.005). In multiple regression analysis (Table 4), serum creatinine, serum triglyceride (TG), and glycemic control were evaluated. The study was approved by the Institutional Review Board of the Tokyo Women's Medical University, and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

**Discussion**

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

<table>
<thead>
<tr>
<th>Item</th>
<th>All (n=81)</th>
<th>Combination Therapy (n=29)</th>
<th>Control (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>45(56)</td>
<td>16(55)</td>
<td>29(56)</td>
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<tr>
<td>Age (years)</td>
<td>63 ± 11</td>
<td>62 ± 12</td>
<td>63 ± 10</td>
<td>0.7119</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 4.3</td>
<td>26.2 ± 5.0</td>
<td>26.1 ± 3.9</td>
<td>0.9071</td>
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<tr>
<td>SBP (mmHg)</td>
<td>135 ± 19</td>
<td>135 ± 17</td>
<td>135 ± 20</td>
<td>0.8839</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78 ± 13</td>
<td>77 ± 11</td>
<td>78 ± 14</td>
<td>0.6793</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9(11)</td>
<td>5(17)</td>
<td>4(8)</td>
<td>0.1997</td>
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<td>Hypertension</td>
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<td>18(62)</td>
<td>26(50)</td>
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<td>Cerebral infarction</td>
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<td>0(0)</td>
<td>2(4)</td>
<td>0.1796</td>
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<tr>
<td>Peripheral artery disease</td>
<td>5(6)</td>
<td>2(7)</td>
<td>3(6)</td>
<td>0.8410</td>
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<tr>
<td>Coronary artery disease</td>
<td>5(6)</td>
<td>1(3)</td>
<td>4(8)</td>
<td>0.4268</td>
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<td>Antidiabetic medication</td>
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<td></td>
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<td></td>
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<td>Sulfonylurea</td>
<td>36(45)</td>
<td>9(34)</td>
<td>27(52)</td>
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</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>14(17)</td>
<td>3(10)</td>
<td>11(21)</td>
<td>0.2024</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>7(9)</td>
<td>2(7)</td>
<td>5(10)</td>
<td>0.6714</td>
</tr>
<tr>
<td>Metformin</td>
<td>18(22)</td>
<td>2(7)</td>
<td>16(31)</td>
<td>0.0079*</td>
</tr>
<tr>
<td>Insulin</td>
<td>10(12)</td>
<td>3(10)</td>
<td>7(13)</td>
<td>0.6792</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB or ACEI</td>
<td>37(46)</td>
<td>15(52)</td>
<td>22(42)</td>
<td>0.4150</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>24(30)</td>
<td>11(38)</td>
<td>13(25)</td>
<td>0.2258</td>
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<tr>
<td>β-blocker</td>
<td>7(9)</td>
<td>3(10)</td>
<td>4(8)</td>
<td>0.6871</td>
</tr>
<tr>
<td>Diuretic</td>
<td>3(4)</td>
<td>1(3)</td>
<td>2(4)</td>
<td>0.9272</td>
</tr>
</tbody>
</table>

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.
for development of atherosclerotic cardiovascular disease. Evidence has also accumulated regarding these lipids as risk factors for CKD [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 apoA-I/apoB ratio 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, 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 sitatiglin 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 progression of diabetic nephropathy. However, little is known about improvement of kidney function by sitatiglin 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 progression of diabetic nephropathy. However, little is known about improvement of kidney function by sitatiglin 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.
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 in 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 in multivariate analysis, which was conducted with backward model selection with $p<0.05$.

<table>
<thead>
<tr>
<th>Item</th>
<th>$\beta$</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>creatinin</td>
<td>0.38</td>
<td>(10.7 to 39.1)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>0.34</td>
<td>(2.4 to 9.3)</td>
<td>0.0018</td>
</tr>
<tr>
<td>ApoA1</td>
<td>0.25</td>
<td>(0.02 to 0.29)</td>
<td>0.0291</td>
</tr>
<tr>
<td>ApoB</td>
<td>-0.23</td>
<td>(-0.33 to -0.01)</td>
<td>0.0331</td>
</tr>
</tbody>
</table>

Table 4: Results of multiple regression analysis for variables with an association in multivariate analysis, which was conducted with backward model selection with $p<0.05$.

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.

References