Since the introduction of sitagliptin in 2006, a large body of evidence suggesting the effectiveness of dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of patients with type 2 diabetes has been accumulated [1, 2]. A low risk of hypoglycemia, minimal effects on body weight, and a general lack of gastrointestinal and other side effects make DPP-4 inhibitors preferable to some other classes of oral hypoglycemic agents in some patients. Experimental and clinical studies suggest that DPP-4 inhibitors might preserve and possibly reverse the progressive elimination of pancreatic β-cells and loss of insulin secretory capacity characteristic of type 2 diabetes [3, 4]. Long-term studies in patients with type 2 diabetes, however, are required to determine the clinical significance of these findings. Furthermore, the extra-pancreatic effects of DPP-4 inhibitors, including their impact on the macro- and microvasculature, should be evaluated. We report here the inhibitory effect of sitagliptin on albuminuria in patients with type 2 diabetes.

Materials and Methods

Study design

Patients with type 2 diabetes whose HbA1c was higher than 6.5% (according to the National Glycohaemoglobin Standardisation Programme [NGSP]) despite receiving education on diet and exercise and medical treatment for at least 6 months at our clinic and whose estimated glomerular filtration rate (eGFR) was more than 60 mL/min/1.73 m² were enrolled in this study. Forty consecutive patients fulfilling above criteria were enrolled irrespective of age, body mass index (BMI), severity of diabetic vascular complications, and the level of albuminuria. Sitagliptin (50 mg) was administered orally once daily. Physical examinations (including measurement of blood pressure and body weight) and blood or urine tests were performed 6 months before this study, at the starting point, and every month after starting sitagliptin treatment. Fasting blood glucose, HbA1c, and glycated albumin were measured every month after

Abstract. We investigated the inhibitory effect of sitagliptin on albuminuria in patients with type 2 diabetes. Thirty-six patients (19 men and 17 women) whose HbA1c was higher than 6.5% (NGSP) despite receiving education on diet and exercise and medical treatment for at least 6 months at our clinic were enrolled into this study and were successfully followed over 6 months of sitagliptin treatment. Sitagliptin (50 mg/day) treatment significantly lowered both systolic and diastolic blood pressures, fasting blood glucose and postprandial blood glucose, HbA1c, and glycated albumin at 3 months and 6 months. Significant reductions in highly sensitive C-reactive protein and soluble vascular cell adhesion molecule 1 were also observed at 6 months. Urinary albumin excretion (measured as urinary albumin-to-creatinine ratio (ACR: mg/g Cr)) did not change in the 6 months before sitagliptin treatment (ΔACR: 2.3 ± 19.9) and decreased in the 6 months after sitagliptin treatment (ΔACR: -20.6 ± 24.6); these differences were statistically significant. At 6 months, the ACR decreased from 11.6 ± 8.4 to 4.5 ± 5.0 in 13 patients with normoalbuminuria (ACR<30), from 98.4 ± 79 to 24.9 ± 20 in 15 patients with microalbuminuria (30<ACR<300), and from 1263 ± 492 to 561 ± 89 in 8 patients with macroalbuminuria (ACR>300). Thus, the present findings strongly suggest that sitagliptin reduces albuminuria without lowering the estimated glomerular filtration rate, most likely depending on known factors such as blood sugar reduction, blood pressure reduction, and inflammation reduction, as well as yet undetermined factors caused by an increase in active glucagon-like peptide-1.

Key words: DPP-4 inhibitor, Albuminuria, eGFR
starting sitagliptin. Postprandial blood glucose (at 2 h after a standard breakfast (450 Kcal)) and the urinary albumin-to-creatinine ratio (ACR) were measured at -6, 0, 3, and 6 months after starting sitagliptin. Highly sensitive C-reactive protein (hsCRP) and soluble vascular cell adhesion molecule 1 (sVCAM-1) were measured before and at 6 months after starting sitagliptin treatment. Blood glucose was measured using Accu-chek (Roche Diagnostics K.K, Tokyo, Japan), and all other biochemical data were obtained by measurement in our laboratory except sVCAM-1 which was measured in SRL, Inc (Tokyo, Japan).

Before entering the study, 7 patients had been treated with diet and exercise alone as anti-diabetic therapy. Twenty-four had been receiving glimepiride, and it was reduced to 2 mg/day or less upon entry. Furthermore, glimepiride was reduced by half or stopped when HbA1c was reduced by more than 0.5% per month. Metformin (n=12) and pioglitazone (n=4) that patients had been taking before this study started were continued throughout the study without changing the dosing. Alpha-glucosidase inhibitors and glinides had been discontinued at least 3 months before this study started. Angiotensin II receptor blockers were administered to 13 patients and statins were administered to 8 patients; both of these were continued throughout the study.

The protocol for this study was approved by the Ethics Committees of the hospital and the research was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Data are expressed as mean ± SD. Differences between groups were compared for significance using Wilcoxon signed-rank test in Statview-J4.5. P values of less than 0.017 (=0.05/3) were considered statistically significant.

**Patient profile**

Forty patients were enrolled into this study, of whom 36 (19 men and 17 women) with a mean age of 62.3 years at the beginning of the study were successfully followed over 6 months of sitagliptin treatment. Mean body mass index (BMI) was 22.5 ± 3.1 kg/m² and mean duration of diabetes was 9.5 ± 4.8 years among these 36 patients at the beginning of the study.

**Results**

No significant changes in body weight, BMI, or waist circumference were observed from the onset to 3 or 6 months of sitagliptin administration. In this study, HbA1c decreased to lower than 6.5% in 29 of 36 patients. Although we did not determine in the protocol how to manage patients with regard to hypoglycemia in the study, no hypoglycemia or related signs and symptoms occurred during the study period. Sitagliptin treatment for 3 months significantly lowered both systolic and diastolic blood pressures, an effect which continued for 6 months. A reduction in fasting blood glucose was observed at 3 months (from 149 ± 32 mg/dL to 129 ± 16 mg/dL) and 6 months (129 ± 20 mg/dL), and a reduction in postprandial blood glucose (at 2 h) was observed at 3 months (from 244 ± 66 mg/dL to 212 ± 64 mg/dL) and 6 months (197 ± 54 mg/dL). A reduction in HbA1c was also observed at 3 months (6.9 ± 0.85% to 6.3 ± 0.46%) and 6 months (6.2 ± 0.61%), and a reduction in glycated albumin was observed at 3 months (21.7 ± 3.4% to 18.4 ± 2.2%) and 6 months (18.0 ± 2.4%). Triglyceride, total cholesterol, HDL-cholesterol, and LDL-cholesterol were not altered by sitagliptin treatment. Finally, significant reductions in highly sensitive C-reactive protein (hs-CRP) from 448 ± 314 ng/mL to 203 ± 126 ng/mL and soluble vascular cell adhesion molecule 1 (sVCAM-1) from 723 ± 236 ng/mL to 634 ± 173 ng/mL were observed at 6 months (Table 1). It is notable that a dramatic improvement in retinopathy was observed in 2 patients during sitagliptin treatment.

Urinary albumin excretion (measured as urinary albumin-to-creatinine ratio (ACR: mg/g Cr)) did not change in the 6 months before sitagliptin treatment (∆ACR: 2.3 ± 19.9) and decreased in the 6 months after sitagliptin treatment (∆ACR: -20.6 ± 24.6); these differences were statistically significant (p=0.0014) (Fig. 1). Estimated glomerular filtration rate was 75.3 ± 17.8 mL/min/1.73 m² at 6 months before sitagliptin treatment, 73.3 ± 16.3 mL/min/1.73 m² at the start of sitagliptin treatment, and 77.0 ± 19.4 mL/min/1.73 m² at 6 months after sitagliptin treatment (Fig. 1). Thirteen patients with normoalbuminuria (defined as an ACR of less than 30 at baseline) had a reduction in ACR at 6 months from 11.6 ± 8.4 to 4.5 ± 5.0, suggesting a preventive effect of sitagliptin on the occurrence of microalbuminuria. Eleven patients with microalbuminuria (defined as an ACR of 30 to 299 at the outset) had a reduction in ACR from 98.4 ± 79 to 24.9 ± 20, suggesting the beneficial effect of sitagliptin in the early stage of diabetic nephropathy. Six patients with macroalbuminuria (defined as an ACR of more than 300 at the outset) had a reduction in ACR from 1263 ± 492 to
Sitagliptin reduces albuminuria

Discussion

Because DPP-4 inhibitors are weight-neutral and associated with a low risk for hypoglycemia, they may be appropriate to obtain good glycemic control in patients for whom weight gain and hypoglycemia are undesirable. Both of these are thought to be associated with risk of vascular events and death [5]. In the present study, sitagliptin treatment reduced fasting blood sugar as well as postprandial blood sugar without changing weight and without causing hypoglycemia.

To the best of our knowledge, this is the first report to show that DPP-4 inhibitor sitagliptin reduces albuminuria. One of the mechanisms of albuminuria reduction might be induction of satisfactory control of blood sugar. Attenuating glucose swing by reducing not only fasting blood sugar but also postprandial blood sugar might lead to the inhibition of vascular inflammation [6]. Another mechanism might be increased active glucagon-like peptide-1 (GLP-1) levels, which could inhibit vascular inflammation. Indeed, it has been

$561 \pm 89$, suggesting a trend toward benefit in progressive diabetic nephropathy (Table 2).

Table 1 Blood pressure, blood glucose markers, and inflammatory markers at baseline and follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>140 ± 18</td>
<td>129 ± 13*</td>
<td>129 ± 17*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77 ± 10</td>
<td>73 ± 7*</td>
<td>73 ± 7*</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>149 ± 32</td>
<td>129 ± 16*</td>
<td>129 ± 20*</td>
</tr>
<tr>
<td>PBS (mg/dL)</td>
<td>244 ± 66</td>
<td>212 ± 64</td>
<td>197 ± 54*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.9 ± 0.85</td>
<td>6.3 ± 0.46*</td>
<td>6.2 ± 0.61*</td>
</tr>
<tr>
<td>GA (%)</td>
<td>21.7 ± 3.4</td>
<td>18.4 ± 2.2*</td>
<td>18.0 ± 2.4*</td>
</tr>
<tr>
<td>hsCRP (ng/mL)</td>
<td>448 ± 314</td>
<td>203 ± 126*</td>
<td></td>
</tr>
<tr>
<td>sVCAM (ng/mL)</td>
<td>723 ± 236</td>
<td>634 ± 173*</td>
<td></td>
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</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; PBS, postprandial blood sugar; GA, glycated albumin; ACR, albumin-to-creatinine ratio; hsCRP, highly sensitive C-reactive protein; sVCAM-1, soluble vascular cell adhesion molecule 1. *p < 0.017.

Table 2 Albumin-to-creatinine ratio at baseline and 6 months after starting sitagliptin treatment

<table>
<thead>
<tr>
<th>Albuminuric Grade</th>
<th>Baseline</th>
<th>Follow-up (6 M)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuric (ACR&lt;30)</td>
<td>11.6 ± 8.4</td>
<td>4.5 ± 5.0</td>
<td>p=0.0012</td>
</tr>
<tr>
<td>Microalbuminuric (30&lt;ACR&lt;300)</td>
<td>98.4 ± 79</td>
<td>24.9 ± 20</td>
<td>p=0.0152</td>
</tr>
<tr>
<td>Macroalbuminuric (ACR&lt;300)</td>
<td>1263 ± 492</td>
<td>561 ± 89</td>
<td>p=0.0211</td>
</tr>
</tbody>
</table>

ACR, albumin-to-creatinine ratio (mg/g Cr).

Fig. 1 Changes in urinary albumin excretion (dACR: albumin-to-creatinine ratio) estimated glomerular filtration rate at 6 months before sitagliptin treatment (-6 M), at the start of sitagliptin treatment (0 M), and at 6 months after sitagliptin treatment (6 M). *p < 0.017 compared with change before sitagliptin.
reported that GLP-1 inhibits advanced glycation end-product-induced up-regulation of VCAM-1 mRNA levels in vascular endothelial cells at concentrations which sitagliptin treatment has been shown to reach [7]. In this report, GLP-1 receptor was shown to be present on human umbilical vein endothelial cells. We confirmed the presence of GLP-1 receptor on human glomerular microvascular endothelial cells as well (unpublished data). Thus, sitagliptin might exert anti-inflammatory action in the kidney through GLP-1 receptor by increasing active GLP-1, possibly leading to the reduction of albuminuria. Another anti-inflammatory property of GLP-1 including involvement of the cAMP/PKA pathway might also contribute to reducing albuminuria [8]. It has been reported that treatment with lixisludide resulted in a clinically significant reduction in blood pressure, which could not be fully accounted for by the reduction in body weight [9, 10]. Treatment with sitagliptin might cause a similar effect on blood pressure by increasing GLP-1 levels; this could probably not be achieved in every patient, but might be feasible in well-educated patients in whom sitagliptin is considerably effective in glycemic control. Tight blood pressure control with inhibition of the renin angiotensin aldosterone system and multifactorial intervention (such as glycemic and lipid control) are warranted for secondary prevention and treatment of chronic kidney disease in diabetes [11]. Therefore, the significant reduction in blood pressure with sitagliptin in this study might contribute to some extent to lowering urinary albumin secretion.

DPP-4 cleaves behind a penultimate N-terminal proline or alanine and thus degrades several physiologically important neuropeptides, hormones, and cytokines [12, 13]. Therefore, by preventing the degradation of those important peptides, including GLP-1, sitagliptin might have direct beneficial effects on the microvasculature, which could be consistent with the observed reduction in albuminuria as well as the improvement in retinopathy seen in 2 patients. In fact, chronic sitagliptin treatment corrected the glycemic dysmetabolism, hypertriglyceridemia, inflammation, and hypertension, reduced the severity of the histopathological lesions of pancreatic endocrine and exocrine tissues, and created a favorable redox status, which might be a further advantage in the management of diabetes and its proatherogenic comorbidities in an animal model of type 2 diabetes (ZDF rat) [14].

Although this was an uncontrolled study, the reduction of albuminuria was statistically significant at 6 months after sitagliptin treatment compared with the change in the 6 months before sitagliptin treatment. All of the patients were well-educated about the importance of diet and physical exercise and most of them were stably treated with oral anti-diabetic drugs for at least 6 months. Therefore, it is unlikely that the decrease in blood sugar levels, blood pressure, and low-grade inflammation, as well as the reduction in albuminuria, were caused by factors other than sitagliptin treatment. Angiotensin II receptor blockers could also reduce albuminuria [15], but they had been provided to these 13 patients for more than 2 and half years prior to the start of the present study. Indeed, no difference in the reduction of albuminuria was observed between patients with and without angiotensin II receptor blockers.

In conclusion, the present findings strongly suggest that sitagliptin reduces albuminuria without decreasing the estimated glomerular filtration rate through its anti-diabetic and anti-inflammatory actions.

Conflicts of Interests

The author has no competing interests to declare.

References


