Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
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ORIGINAL RESEARCH

Anti-atherosclerotic effects of sitagliptin in patients with type 2 diabetes mellitus

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
27 July 2015
Number of times this article has been viewed

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Background: Advanced glycation end products, selectins, and adiponectin play important roles in the development of atherosclerosis in individuals with diabetes. Sitagliptin has been shown to reduce the concentration of glycated hemoglobin in diabetic patients. However, its effects on soluble receptor for advanced glycation end products (sRAGEs), selectins, and adiponectin in these patients are poorly understood. This study was conducted to assess the effects of sitagliptin on the circulating levels of sRAGEs, monocyte chemoattractant protein-1 (MCP-1), selectins, and adiponectin in patients with type 2 diabetes.

Methods: Diabetic patients eligible for sitagliptin monotherapy or combination therapy (eg, sitagliptin plus a sulfonylurea) were administered sitagliptin (50 mg/day) for 6 months. Levels of soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1), MCP-1, sRAGEs, and adiponectin were measured by ELISA at baseline and after 3 and 6 months of treatment.

Results: At baseline, the levels of MCP-1, sP-selectin, sE-selectin, and sVCAM-1 were higher and the level of adiponectin was lower in diabetic patients than in nondiabetic patients. Sitagliptin therapy for 3 and 6 months significantly reduced plasma levels of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline, while significantly increasing adiponectin levels. sRAGEs did not exhibit a statistical significance, although there was an increasing tendency. Furthermore, the reductions in sP-selectin, sE-selectin, sVCAM-1, and MCP-1 during sitagliptin therapy were significantly greater in responders, defined as patients with a significant increase in adiponectin levels, than in nonresponders. In contrast, responders showed a significant increase in the plasma concentration of sRAGEs.

Conclusion: Sitagliptin shows an adiponectin-dependent anti-atherothrombotic effect, which may be beneficial for primary prevention of atherothrombosis, in patients with type 2 diabetes.

Keywords: type 2 diabetes mellitus, sitagliptin, sRAGE, selectins, sVCAM-1, adiponectin

Introduction

The development of atherosclerosis in patients with type 2 diabetes mellitus (T2DM) may be due to hypercoagulability and platelet hyperaggregability,[1,2] along with increased levels of platelet activation markers. These changes have been associated with increased risks of cardiovascular events.[3,4] Diabetes is also characterized by the increased expression of cell adhesion molecules,[5] which may play a role in the microvascular complications of this disease. The first step in the process of leukocyte migration into the subendothelial space is the adhesion of circulating leukocytes to the endothelium, which may involve adhesion molecules such as P-selectin, E-selectin, and vascular cell adhesion molecule-1 (VCAM-1). These molecules have been associated with vascular

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complications, with higher serum levels of soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), and soluble VCAM-1 (sVCAM-1) in patients with diabetes.[6,7] Patients with postprandial hyperglycemia often have accompanying postprandial hyperinsulinemia. However, the postprandial increase in blood glucose level itself is now considered a risk factor for the progression of atherosclerosis.[8]

Adiponectin, the most abundant adipose tissue-specific protein, is exclusively expressed in and secreted by adipose tissue.[9] Plasma adiponectin concentrations, which are normally high, have been shown to be reduced in obese individuals[9,10] and those with T2DM,[11] and to be closely related to insulin sensitivity.[12] Adiponectin has been shown to stimulate nitric oxide (NO) production in vascular endothelial cells, ameliorating endothelial function.[13,14] These observations suggest that the anti-atherogenic properties of adiponectin may involve its NO-dependent antiplatelet effects.

Advanced glycation end products (AGEs), the final products of the nonenzymatic glycation of proteins,[15] bind to activate receptor for AGEs (RAGEs), enhancing inflammation.[16,17] RAGEs also promote chronic inflammation, as observed in diabetes and atherosclerosis.[18,19] In contrast, soluble RAGE (sRAGE), a RAGE isoform lacking the transmembrane domain, is an inhibitor of AGE–RAGE-mediated pathological effects.[20] For example, sRAGE was shown to protect blood vessels against AGE–RAGE-mediated microvascular damage in patients with T2DM.[21]

Dipeptidyl peptidase-4 is an enzyme involved in the degradation of the intact (active) incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide, to their inactive metabolites. GLP-1 and glucose-dependent insulinotropic peptide are released by the intestine into the circulation in response to a meal, and both the hormones increase glucose-dependent insulin secretion by inhibiting the degradation of active incretins. Sitagliptin is the first dipeptidyl peptidase-4 inhibitor that increases active incretin concentrations, thereby enhancing their glucoregulatory effects.[22–24] Many clinical trials have shown that sitagliptin reduces glycated hemoglobin (HbA_{1c}) concentrations.[25,26] However, the effects of sitagliptin on sP-selectin, adiponectin, and sRAGE in patients with T2DM are poorly understood. To determine whether sitagliptin has anti-atherosclerotic effects, we assessed its effects on sP-selectin, adiponectin, and sRAGE concentrations in patients with T2DM.

Materials and methods

Patients

The study cohort included 72 nondiabetic and 113 diabetic patients (Table 1), selected from among those admitted to our hospital between April 2011 and March 2014 for the treatment of hypertension, hyperlipidemia, and diabetes. The study protocol was approved by the Institutional Review Board of Kansai Medical University, and written informed consent was obtained from each patient. Individuals were excluded if they had a history (within 3 months prior to enrollment) of inflammatory, coronary artery, or cerebrovascular disease; or if they had clinically detectable hepatic dysfunction (elevated transaminases), infection (fever or an elevated white blood cell count), or malignancy (detected on ultrasound or computed tomography). Of the included patients, 20 were taking aspirin because of a previous cerebral infarction or angina pectoris, 69 were taking angiotensin II receptor blockers, 47 were taking Ca antagonists, and 48 were taking statins (Table 1). The doses of these drugs were not adjusted, and there were no other changes to drug therapy, during the present study.

Table 1 Demographic and clinical characteristics of the diabetic patients and nondiabetic controls

	Nondiabetes	Diabetes	*P*-value
n	72	113	
Men/women (n)	39/33	60/53	
Age (years)	62±6	63±8	NS
BMI (kg/m^2)	26.1±3.9	27.9±4.6	NS
FBG (mg/dL)	102±21	239±57	<0.001
HbA_{1c} (%)	5.1±0.9	7.6±1.5	<0.01
TC (mg/dL)	220±28	236±37	NS
HDL-C (mg/dL)	47±12	44±13	NS
LDL-C (mg/dL)	133±32	141±42	NS
Complications, n (%)			
Angina pectoris	9 (12.5)	16 (14.2)	NS
Heart failure	5 (6.9)	7 (6.2)	NS
Cerebral infarction	4 (5.6)	10 (8.8)	NS
Medication, n (%)			
Statins	21 (29.2)	27 (23.9)	NS
ARBs	30 (41.7)	39 (34.5)	NS
Ca antagonists	21 (29.2)	26 (23.0)	NS
Aspirin	7 (9.7)	13 (11.5)	NS

Notes: Data are shown as mean ± SD. *P*-value, diabetic patients versus nondiabetic controls.

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ARBs, angiotensin II receptor blockers; NS, not significant; SD, standard deviation.

Study design

Patients were eligible for sitagliptin monotherapy if their diet/exercise therapy had continued unchanged for 3 months. Patients who had used a biguanide (metformin), a sulfonylurea (glibenclamide or glimepiride), a thiazolidinedione (glitazone), or insulin for 3 months were eligible for combination therapy with that agent plus sitagliptin. Patients with almost normal renal function (serum creatinine

[S-CRTN] <2.0 mg/dL) were administered sitagliptin (50 mg/day) once daily for 6 months. Clinical and biochemical data were obtained before and 3 and 6 months after starting sitagliptin treatment.

Measurement of soluble molecules and adiponectin

Blood samples from patients and controls under fasting conditions were collected into tubes with or without sodium citrate and allowed to clot at room temperature for a minimum of 1 hour. Citrated plasma or serum was isolated by centrifugation at 1,000× *g* for 20 minutes at 4°C and stored at −30°C until analyzed. Plasma concentrations of sP-selectin, sE-selectin, sVCAM-1, and monocyte chemoattractant protein-1 (MCP-1) were measured using monoclonal antibody-based ELISA kits (Invitrogen Inc., Camarillo, CA, USA), plasma adiponectin was measured with adiponectin ELISA kits (Otsuka Pharmaceutical Co., Ltd. Tokyo, Japan), and serum sRAGE was measured using sRAGE ELISA kits (Quantikine; R&D Systems, Minneapolis, MN, USA). The recombinant products and standard solutions provided with each kit were used as positive controls in each assay, and all the procedures were performed according to the manufacturers' instructions.

Diabetic patients were divided into two subgroups based on their adiponectin responses to sitagliptin treatment. Responders were defined as patients showing a ≥1.5-fold increase in plasma adiponectin levels, relative to baseline, after sitagliptin treatment, whereas nonresponders were defined as those with a <1.5-fold increase in plasma adiponectin.

Statistics

Data were expressed as mean ± standard deviation and were analyzed using multivariate regression analysis, as appropriate. Between-group comparisons were analyzed using the Newman–Keuls test and Scheffe's test. The correlation between uric acid concentration and continuous variables was assessed using multivariate linear regression analysis. The significance of differences among variables was determined by analysis of variance (ANOVA). *P*-values less than 0.05 were considered statistically significant. All the analyses were performed using the Stat Flex program (V 6.0).

Results

Patient demographic and clinical characteristics were similar in the diabetic and nondiabetic groups, except for fasting blood glucose and HbA_{1c} concentrations (Table 1).

The levels of blood urea nitrogen, S-CRTN, C-reactive protein, MCP-1, sP-selectin, sE-selectin, and sVCAM-1 were higher in diabetic than in nondiabetic patients (Table 2). However, adiponectin was lower in diabetic than in nondiabetic patients (Table 2).

Using univariate and multivariate regression analyses, we investigated the associations between 16 variables and HbA_{1c} concentration in diabetic patients (Table 3). Univariate analysis showed that body mass index, angina pectoris, low-density lipoprotein cholesterol, sP-selectin, sE-selectin, sVCAM-1, MCP-1, sRAGE, and adiponectin were factors significantly associated with HbA_{1c}, whereas sP-selectin, sVCAM-1, MCP-1, and adiponectin were significantly correlated with HbA_{1c} in multivariate analysis.

Renal function was almost normal (S-CRTN <2.0 mg/dL) in 65 of the 113 diabetic patients. Administration of sitagliptin to these 65 patients for 3 months significantly reduced fasting blood glucose and HbA_{1c} (data not shown), and administration for 6 months significantly reduced plasma concentrations of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline ($P<0.05$ each; Figure 1A–D). Sitagliptin treatment significantly increased adiponectin concentrations after 3 ($P<0.05$) and 6 ($P<0.01$) months relative to baseline (Figure 1F). Sitagliptin also increased sRAGE concentration relative to baseline, although the differences were not statistically significant (Figure 1E).

Table 2 Plasma levels of soluble factors, chemokines, and adiponectin in the nondiabetic controls and diabetic patients

	Nondiabetes	Diabetes	*P*-value
n	72	113	
BUN (mg/dL)	18.9±8.8	26.6±14.9	<0.05
S-CRTN (mg/dL)	0.62±0.19	1.95±1.07	<0.05
AST (mg/dL)	30±12	34±15	NS
ALT (mg/dL)	28±14	32±19	NS
T-BIL (mg/dL)	0.71±0.34	0.87±0.51	NS
LD (U/L)	218±66	232±82	NS
CRP (mg/dL)	0.82±0.79	1.24±0.85	<0.05
MCP-1 (pg/mL)	344±82	566±129	<0.01
sP-selectin (ng/mL)	232±73	278±104	<0.05
sE-selectin (ng/mL)	72±39	95±48	<0.05
sVCAM-1 (ng/mL)	632±139	924±148	<0.01
sRAGE (pg/mL)	1,030±478	1,220±670	NS
Adiponectin (μg/mL)	4.54±1.01	2.52±1.43	<0.01

Notes: Data are shown as mean ± SD. *P*-value, diabetic patients versus nondiabetic controls.

Abbreviations: BUN, blood urea nitrogen; S-CRTN, serum creatinine; AST, aspartate aminotransferase; ALT, alanine transaminase; T-BIL, total bilirubin; LD, lactate dehydrogenase; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; sP-selectin, soluble P-selectin; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhesion molecule-1; sRAGE, soluble receptor for advanced glycation end product; NS, not significant; SD, standard deviation.

Table 3 Multiregression analysis on HbA_{1c} in diabetic patients

Analysis	Univariate		Multivariate	
	β	*P*-value	*β*	*P*-value
Age (years)	0.2155	0.08793		
Sex (men)	–0.0775	0.36417		
BMI (kg/m^2)	0.3847	0.00917*	0.2755	0.73116
Angina pectoris (%)	0.3277	0.04726*	0.2311	0.10339
Heart failure (%)	0.1753	0.26354		
Cerebral infarction (%)	0.2346	0.06617		
TC (mg/dL)	–0.0896	0.25331		
HDL-C (mg/dL)	–0.1279	0.36972		
LDL-C (mg/dL)	0.4533	0.00172*	0.3159	0.05379
CRP (mg/dL)	0.2374	0.07223		
sP-selectin (ng/mL)	0.4377	0.00188*	0.3284	0.04549*
sE-selectin (ng/mL)	0.3982	0.00774*	0.2863	0.06127
sVCAM-1 (ng/mL)	0.4328	0.00196*	0.3218	0.04673*
MCP-1 (pg/mL)	0.5985	0.00017*	0.4233	0.01163*
sRAGE (pg/mL)	–0.3699	0.01029*	–0.2611	0.07356
Adiponectin (μg/mL)	–0.6172	<0.00001*	–0.5672	0.00234*

Note: *β* indicates standardized regression coefficients. * indicates statical significance ($P<0.05$)

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; sP-selectin, soluble P-selectin; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; sRAGE, soluble receptor for advanced glycation end product.

We divided diabetic patients into two subgroups according to their adiponectin response to sitagliptin treatment. Responders showed significant reductions in plasma concentrations of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline ($P<0.01$ for each; Figure 2A–D), and all the four concentrations were significantly lower in responders than in nonresponders after 6 months of sitagliptin treatment (two-factor ANOVA; $P<0.05$ each). However, responders showed a significant increase in plasma concentration of sRAGE and adiponectin (Figure 2E and F).

Discussion

Postprandial hyperglycemia is an early manifestation of T2DM and is caused by the loss of early-phase insulin response.[27] Chronic hyperglycemia is also associated with accumulation of AGEs.[28] Diabetic complications may be due to inflammatory and oxidative stresses to endothelial cells caused by AGEs, mainly through RAGE. Circulating concentrations of both cleaved-type sRAGE and endogenous secretory RAGE (esRAGE) are increased in diabetic patients.[29–31] sRAGE concentrations are linked to reactions between AGE and RAGE, and are affected by various clinical features in T2DM.[31–33] Interestingly, esRAGE concentration was reported to be negatively correlated with the development of atherosclerosis in patients with T2DM,[34] with esRAGE increasing after statin treatment.[35] This study showed that sitagliptin treatment tended to increase sRAGE, although the increase was not statistically significant. However, adiponectin responders showed a significant increase in sRAGE following sitagliptin treatment, in agreement with previous findings.[35] In addition, sitagliptin treatment also reduced the concentrations of the endothelial cell activation markers

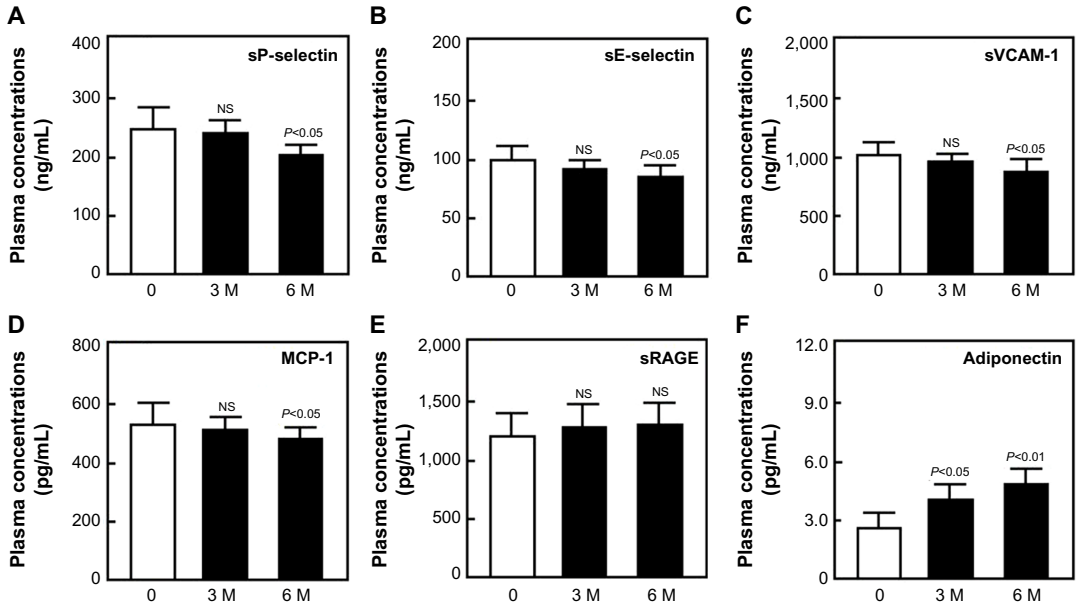

Figure 1 Plasma concentrations of sP-selectin (**A**), sE-selectin (**B**), sVCAM-1 (**C**), MCP-1 (**D**), sRAGE (**E**), and adiponectin (**F**) before and after sitagliptin treatment in diabetic patients.

Notes: Data are shown as mean ± SD. *P*-value, 0 versus 3 or 6 months (M).

Abbreviations: sP-selectin, soluble P-selectin; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; sRAGE, soluble receptor for advanced glycation end product; NS, not significant; SD, standard deviation.

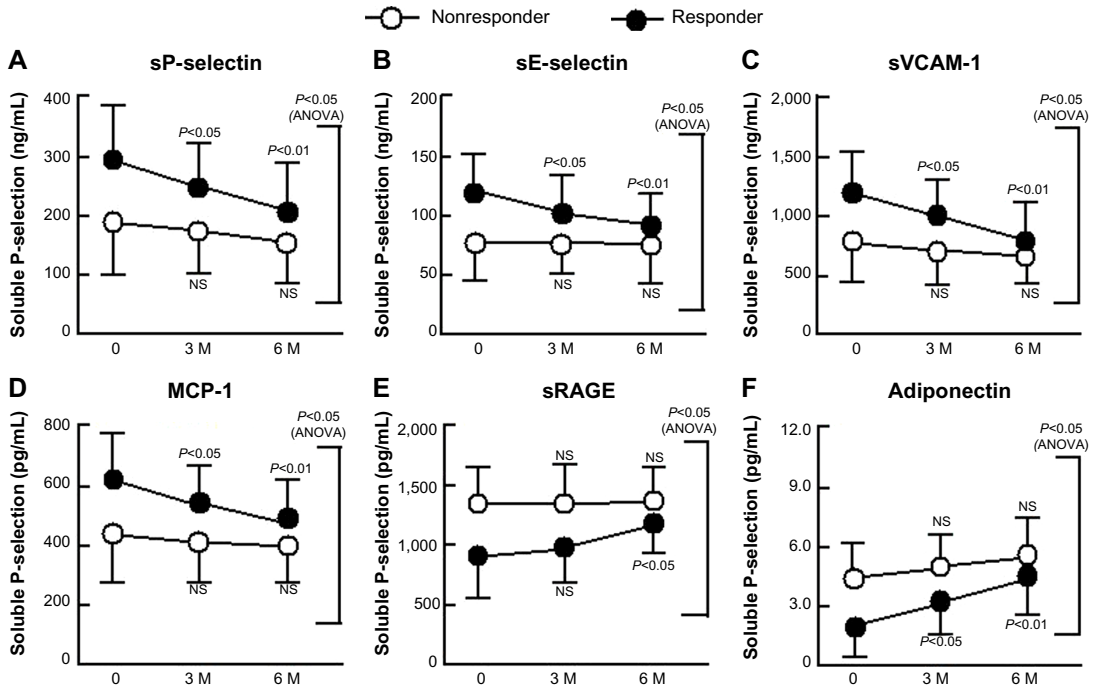

Figure 2 Changes in sP-selectin (**A**), sE-selectin (**B**), sVCAM-1 (**C**), MCP-1 (**D**), sRAGE (**E**), and adiponectin (**F**) in response to treatment with sitagliptin of patients with type 2 diabetes with and without significant improvements in adiponectin.

Notes: Responder: with a significant improvement of adiponectin. Nonresponder: without a significant improvement of adiponectin. Bars show the mean ± SD. 0, before 3 and 6 months (M) after. *P*-values are for comparison with each baseline parameter (0 vs 3 and 6 M). ANOVA: nonresponder versus responder.

Abbreviations: sP-selectin, soluble P-selectin; ANOVA, analysis of variance; NS, not significant; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; sRAGE, soluble receptor for advanced glycation end product; SD, standard deviation.

sE-selectin and sVCAM-1 in patients with diabetes, suggesting that sitagliptin has an effect on atherosclerosis related to sRAGE and endothelial cell activation. Further investigations are needed, because our assay of sRAGE could not measure esRAGE specifically.

Postprandial hyperglycemia in diabetic patients may be associated with the activation of endothelial cells. Postprandial hyperglycemia induces oxidative stress via various biochemical pathways, generating superoxide, which reacts with NO to form peroxynitrite.[36] The resulting decreases in NO concentrations and activity may accelerate vascular inflammation by enhancing the expression of various cytokines and growth factors.[37] Treatment with sitagliptin was shown to significantly reduce body mass index and waist circumference,[38,39] as well as to prevent nephropathic complications in patients with T2DM.[40] Thus, our results suggest that sitagliptin causes the improvement of endothelial dysfunction and atherosclerosis.

Plasma concentrations of adiponectin are lower in obese than in nonobese individuals[9] and are closely related to whole-body insulin sensitivity.[11] Plasma adiponectin concentrations are also reduced in patients with T2DM.[11] Adiponectin has been reported to suppress the attachment of monocytes to endothelial cells[37] and to play a role in protection against vascular injury, suggesting that hypoadiponectinemia is associated with endothelial dysfunction.[41] Hypoadiponectinemia has also been associated with platelet activation. The level of NO, which regulates platelet activation, is reduced by hypoadiponectinemia, because adiponectin stimulates NO production by vascular endothelial cells.[13,14,42] Thus, platelet activation due to low NO concentrations occurs in individuals with hypoadiponectinemia. Therefore, the sitagliptin-induced increase in adiponectin may have an antiplatelet effect by enhancing NO production,[43] as shown by the significant reduction in sP-selectin in diabetic patients treated with sitagliptin.

Various posttranslational modifications, including the glycosylation of lysine residues, have been shown to be necessary for the multimerization of adiponectin.[44] These intracellular posttranslational processes may be affected by hyperglycemia, leading to functional impairment at the organ level in diabetic patients.[45–47] Therefore, the sitagliptin-induced improvement in postprandial hyperglycemia may alter the posttranslational modification of adiponectin.

This study also found that sitagliptin reduced sP-selectin, sE-selectin, sVCAM-1, and MCP-1 concentrations. Grouping of the diabetic patients into two subgroups according to the adiponectin response to sitagliptin treatment showed that the plasma levels of these four markers were significantly reduced in adiponectin

responders, suggesting that sitagliptin induces adiponectin-dependent improvements in the plasma levels of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 in diabetic patients.

The exact mechanism by which sitagliptin treatment increases circulating adiponectin concentrations remains unclear, although the gut-derived incretin hormone GLP-1 is likely involved. GLP-1-based therapies have been shown to reduce glucose concentrations and have antiobesity effects in patients with T2DM.[48] Sitagliptin was found to enhance the secretion of active GLP-1, suggesting that the antidiabetic properties of sitagliptin depend, in part, on GLP-1.[49] In addition, GLP-1 was shown to promote adiponectin secretion.[50,51] Our findings suggest that the effects of sitagliptin on sP-selectin, sE-selectin, sVCAM-1, and MCP-1 concentrations depend on adiponectin. Therefore, sitagliptin may inhibit the progression of atherothrombosis by promoting adiponectin-dependent reductions in plasma sP-selectin, sE-selectin, sVCAM-1, and MCP-1. However, further studies are necessary to elucidate the effects of sitagliptin itself on adiponectin production.

This study had two potential strengths. First, despite the treatment of many T2DM patients with sitagliptin, no previous study had assessed the effects of sitagliptin on serum markers of the disease. Second, it showed that investigation of appropriate serum markers can be used to address atherosclerosis. However, this study also had several limitations. First, changes in clinical parameters such as body mass index were not routinely recorded. Second, we could not identify causative differences in groups of adiponectin responders and nonresponders. Responders had poorer serum values at the onset of sitagliptin treatment, suggesting a genetic/environmental factor associated with these differences. Third, we could not clarify the significance of sRAGE relative to atherosclerosis after sitagliptin treatment. Confirmation of these findings in larger and more particular studies would be useful.

In conclusion, sitagliptin increased circulating sRAGE and adiponectin concentrations in patients with T2DM. In addition, sitagliptin treatment reduced sP-selectin, sE-selectin, sVCAM-1, and MCP-1 levels. Sitagliptin may be beneficial in the primary prevention of atherothrombosis in patients with T2DM.[52] However, large clinical trials are required to test this hypothesis.

Acknowledgments

This study was partly supported by a grant from the Japan Foundation of Neuropsychiatry and Hematology Research, a Research Grant for Advanced Medical Care from the Ministry of Health and Welfare of Japan, and a Grant (13670760 to SN) from the Ministry of Education, Science and Culture of Japan.

Disclosure

The authors report no conflicts of interest in this work.

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