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Original Article

Effects of sitagliptin on coronary atherosclerosis in patients with type 2 diabetes-A serial integrated backscatter-intravascular ultrasound study

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Abstract: Dipeptidyl peptidase-4 (DPP-4) inhibitors have demonstrated anti-inflammatory and anti-atherogenic effects in an animal model. However, the clinical usefulness of DPP-4 inhibitors, particularly its effects on coronary atherosclerosis, has not been evaluated thus far. Therefore, in this study, we evaluated the effects of sitagliptin, a DPP-4 inhibitor, on coronary atherosclerosis using integrated backscatter (IB)-intravascular ultrasound (IVUS) in patients with type 2 diabetes. This trial was a prospective, open-labeled, randomized, multicenter study. Twenty-eight patients with type 2 diabetes who underwent elective percutaneous coronary intervention (PCI) were randomly assigned to either the sitagliptin group (group S) or the control group (group C). Non-PCI lesions were evaluated using IB-IVUS at the time of PCI and at the 48-week follow-up. The primary endpoint was the percentage change in plaque volume measured using grayscale IVUS, and the secondary endpoint was changes in plaque composition evaluated using IB-IVUS. Grayscale IVUS analysis demonstrated that plaque volume tended to decrease in both groups (group S: -1.7±8.5%; group C: -3.2±12.2%), but a between-group difference was not observed. A decrease in the lipid plaque volume (group S: from 200.1±116.2 to 179.8±121.0 mm^3, P = 0.02; group C: from 298.3±363.0 to 256.6±386.1 mm^3, P = 0.1) and an increase in the calcified plaque volume (group S: from 2.1±0.9 to 3.2±1.8 mm^3, P = 0.06; group C: from 2.3±1.7 to 4.8±3.5 mm^3, P = 0.04) was observed on IB-IVUS analysis. Univariate and multivariate regression analyses showed that the percentage change in serum non-high-density lipoprotein (HDL) cholesterol level was an independent and significant predictor of a reduction in lipid plaque volume (β = 0.445, P = 0.04). In conclusions, sitagliptin did not significantly reduce coronary plaque volume in patients with type 2 diabetes. However, a decrease in the lipid plaque volume was observed in the sitagliptin group. A decrease in non-HDL cholesterol level was associated with a reduction in the lipid volume of coronary artery plaques.

Keywords: Coronary atherosclerosis, diabetes mellitus, dipeptidyl peptidase-4 inhibitor, intravascular ultrasound, sitagliptin

Introduction

The use of intravascular ultrasound (IVUS) has provided important insights into the progression and regression of coronary atherosclerosis and vessel remodeling [1]; however, grayscale IVUS has significant limitations in accurately assessing plaque composition. The integrated backscatter (IB)-IVUS system is more capable of characterizing fibrous lesions and lipid pools than is conventional grayscale IVUS [2, 3]. The lipid plaque volume evaluated using IB-IVUS provides information about the natural progression of narrowing of the coronary artery lumen [4].

Patients with diabetes mellitus (DM) are at high risk of developing coronary artery disease [5]. Although statin therapy is useful to prevent cardiovascular events [6, 7], the beneficial effects

of statins are diminished in patients with DM [8]. This is because the presence of diabetes attenuates the degree of regression of coronary artery plaques despite the use of statin therapy [9, 10]. Dipeptidyl peptidase-4 (DPP-4) inhibitors have demonstrated anti-inflammatory and anti-atherogenic effects in an animal model [11-13]. In addition, DPP-4 inhibitors improve endothelial function [14] as well as attenuate neointima formation after vascular injury [15]. However, the clinical usefulness of DPP-4 inhibitors, particularly its effects on coronary atherosclerosis, has not been evaluated. Therefore, in this study, we evaluated the effects of sitagliptin, a DPP-4 inhibitor, on coronary atherosclerosis using IB-IVUS in patients with type 2 DM.

Materials and methods

Study design and ethical considerations

The Trial of Atheroma Regression Evaluated with Integrated Backscatter Intravascular Ultrasound by Administering Sitagliptin (TRUST) study was a prospective, open-labeled, randomized, multicenter trial performed at 6 Japanese centers. The effects of sitagliptin on coronary artery plaque volume and composition were assessed using IB-IVUS with 48 weeks of invasive follow-up. Sitagliptin was selected because it was a commonly used DPP-4 inhibitor in Japan, and has shown favorable outcomes in terms of improved endothelial dysfunction in association with anti-inflammatory effects [16].

The primary endpoint was the percentage change in plaque volume (PV), measured using grayscale IVUS, from baseline to the 48-week follow-up. The secondary endpoint was quantitative changes in coronary artery plaques measured using IB-IVUS.

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the 6 participating institutions. The study has been registered with the University Hospital Medical Information Network (UMIN) (UMIN ID: 000007106).

Patient enrollment and randomization

Patients with type 2 DM who underwent successful elective percutaneous coronary intervention (PCI) under IB-IVUS guidance were screened. Patients who met the eligibility criteria for this study were invited to participate in this study. Inclusion and exclusion criteria have been described previously [17]. Eligible patients provided written informed consent and were then randomly assigned to either the sitagliptin group (group S) or the control group (group C).

The supervising physician administered 50 mg/day of sitagliptin in group S. In group C, the current anti-diabetic medications at the time of randomization were continued or glimepiride was added, if necessary. In cases of poor glycemic control (HbA1c ≥8.4%) at 24 weeks, additional glimepiride was administered in both groups, according to the physician's judgment. The IVUS examination and laboratory tests were performed at baseline and at the 48-week follow-up. An independent event assessment committee evaluated the occurrence of major adverse cardiac events, which was defined as cardiac death, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, target lesion revascularization, and coronary artery bypass grafting.

Intravascular ultrasound examination

The details of IVUS examination have been described previously [17]. The IVUS examination was performed for the culprit vessel in patients whose culprit vessel was the right coronary artery. In cases where the culprit vessel was the left coronary artery, we tried to perform the IVUS examination for both the left anterior descending and left circumflex coronary artery. All IVUS imaging data were stored in the console (VISIWAVE™; Terumo Co., Tokyo, Japan).

Intravascular ultrasound core laboratory analysis

The IVUS analysis was conducted at an independent core laboratory (Cardiocore Japan, Tokyo, Japan) by two independent and experienced investigators in a blinded manner. Offline analyses of acquired IVUS images were performed using planimetry software (VISIATLAS™, Terumo Co., Tokyo, Japan) [18]. Before the IVUS analysis, baseline and follow-up IVUS images were reviewed side-by-side on a display and the target lesions were selected with reference to a reproducible marker, such as side branches, calcification, and vein or stent edges. The target lesions of interest had >40% plaque burden

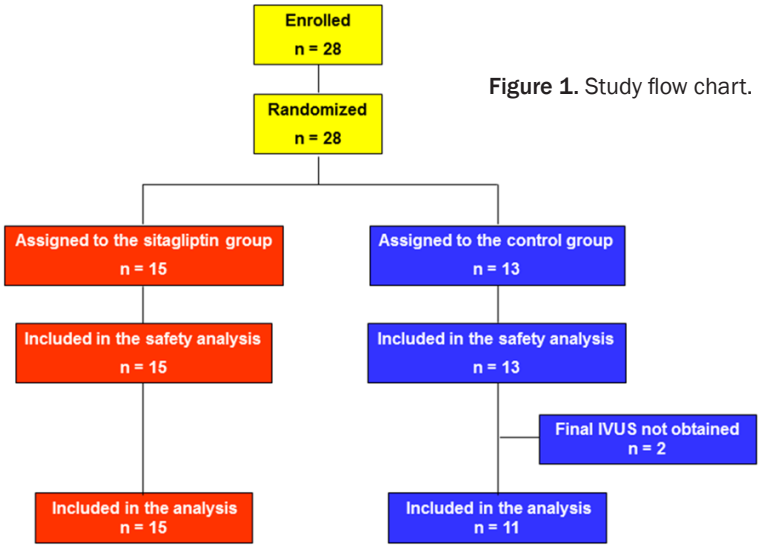

Figure 1. Study flow chart.

according to the IVUS findings. The plaques close to the PCI site, that is, those within 5 mm, were excluded. Semi-automated detection of both the lumen and the external elastic membrane (EEM) was performed at every 1-mm spaced segments within the analyzed lesion. The plaque area was defined as the EEM area minus the lumen area. Quantitative grayscale IVUS analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology [19].

The percentage change in PV was calculated as follows: PV (follow-up)-PV (baseline)/PV (baseline) × 100.

IB-IVUS analysis was performed according to the results of the grayscale border contour calculation. IB values for each category were determined by comparing the histologic images reported in a previous study [18]. On the IB-IVUS image, fibrous areas were marked in green, lipid in blue, dense fibrosis in yellow, and calcifications in red. An absolute and relative volume in each of the 4 plaque components was calculated automatically using VISIATLAS [2].

Laboratory data

The laboratory tests were performed at baseline and at the 48-week follow-up. The HbA1c levels were measured using high-performance liquid chromatography (Adams A1c HA-8160; Arkray Inc., Kyoto, Japan), and plasma glucose (PG) levels were measured using the glucose oxidation method (chemical reagent and Glucose AUTO and STAT GA-1160 analyzer; Arkray Inc.). Serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using standard enzymatic methods (AU2700; Beckman Coulter, CA, USA) and commercial enzymatic kits (Kyowa Medex, Tokyo, Japan). The serum high-sensitivity C-reactive protein (hs-CRP) levels were measured at a central clinical laboratory (SRL, Inc., Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using StatView, version 5.0 (SAS Institute, Cary, North Carolina, USA). Results are expressed as the mean ± standard deviation or median (range). Differences in continuous variables between the two groups were compared using the unpaired *t*-test when the variables had a normal distribution and the Mann-Whitney *U*-test when they did not. Differences in continuous variables within each group were compared using the paired *t*-test when the variables had a normal distribution and the Wilcoxon signed rank-sum test when they did not. Categorical variables between the two groups were compared using the chi-square test or the Fisher's exact test. Univariate and multivariate regression analyses were performed to assess the predictors associated with volume reduction in the lipid component. The variables with a p value <0.05 on the univariate analysis were entered into multivariate models. Statistical significance was set at $P<0.05$.

Results

The study flow chart is shown in **Figure 1**. A total of 28 patients were enrolled; 15 patients were randomized to group S and the remaining 13 to group C. IVUS images qualifying for evaluation both at baseline and at the follow-up were obtained for 15 patients in group S and 11 patients in group C.

There were no significant differences in patient clinical characteristics between the two groups (**Table 1**). Thirteen patients (87%) in group S

Table 1. Clinical characteristics of the subjects

	Sitagliptin (n = 15)	Control (n = 11)	*p* value
Age (years)	72±6	69±10	0.24
Male (%)	11 (73%)	10 (91%)	0.36
Body mass index (kg/m^2)	24.4±4.6	25.5±4.7	0.57
Hypertension (%)	10 (67%)	8 (73%)	>0.99
Dyslipidemia (%)	10 (67%)	9 (82%)	0.66
Smoking (%)	0 (0%)	2 (18%)	0.17
Medications at baseline			
Statins (%)	13 (87%)	8 (73%)	0.62
Aspirin (%)	15 (100%)	11 (100%)	-
Thienopyridines (%)	15 (100%)	11 (100%)	-
ACE inhibitors or ARBs (%)	10 (67%)	7 (64%)	>0.99
Ca channel blockers (%)	7 (47%)	4 (36%)	0.7
Beta-blockers (%)	5 (33%)	6 (55%)	0.43
Hypoglycemic medications			
Sulfonylureas (%)	4 (27%)	2 (18%)	>0.99
Biguanides (%)	2 (13%)	1 (9%)	>0.99
α-Glucosidase inhibitors (%)	4 (27%)	2 (18%)	>0.99
Insulin (%)	1 (7%)	1 (9%)	>0.99
Medications at follow-up			
Statins (%)	14 (93%)	9 (82%)	0.56
Aspirin (%)	15 (100%)	11 (100%)	-
Thienopyridines (%)	14 (93%)	11 (100%)	>0.99
ACE inhibitors or ARBs (%)	10 (67%)	7 (64%)	>0.99
Ca channel blockers (%)	8 (53%)	4 (36%)	0.45
Beta-blockers (%)	5 (33%)	5 (45%)	0.53
Hypoglycemic medications			
Sulfonylureas (%)	4 (27%)	6 (55%)	0.23
Biguanides (%)	2 (13%)	1 (9%)	>0.99
α-Glucosidase inhibitors (%)	4 (27%)	2 (18%)	>0.99
Insulin (%)	1 (7%)	1 (9%)	>0.99
DPP-4 inhibitor (%)	15 (100%)	0 (0%)	-

Data are expressed as mean ± standard deviation or number (%). CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DPP-4, dipeptidyl peptidase-4.

and 8 patients (73%) in group C were treated with statins at the time of randomization. During the study period, 1 patient in each group received additional treatment with statin. The statin regimen was changed from 10 mg of pravastatin to 10 mg of atorvastatin for 1 patient in group S. In group C, 2 patients (18%) had already received treatment with sulfonylureas, 1 patient with a biguanide, 2 patients with α-glucosidase inhibitors, and 1 patient with insulin at the time of randomization; the patients continued to take these drugs during the study period. Only 4 patients were treated with additional glimepiride therapy after randomization (0.5 mg in 3 patients and 1 mg in 1 patient). Therefore, 6 patients (55%) in group C were treated with sulfonylureas at the 48-week follow-up. No patients in either group were administered additional glimepiride therapy at 24 weeks because of poor glycemic control.

Serum LDL cholesterol levels decreased significantly in group S (from 99±33 to 81±23 mg/dL, P = 0.04), but the decrease in LDL cholesterol in group C could not reach statistical significance (from 106±25 to 94±20 mg/dL, P = 0.27). A decrease in the serum levels of non-HDL cholesterol (group S: from 116±36 to 99±26 mg/dL, P = 0.08; group C: from 120± 27 to 110±20 mg/dL, P = 0.29) and HbA1c (group S: from 7.5±0.8% to 7.0±1.2%, P = 0.06; group C: from 7.1±0.6% to 7.0±0.8%, P = 0.72) was observed, but without statistical significance. A significant reduction in hs-CRP levels was observed in both groups. Between-group differences at baseline and at follow-up, as well as percentage change, were not observed for PG, HbA1c, LDL-C, non-HDL-C, or hs-CRP levels (**Table 2**).

Grayscale IVUS analysis demonstrated that the EEM volume (group S: -1.3±7.0%, P = 0.34; group C: -4.6±8.9%, P = 0.48) and PV (group S: -1.7±8.5%, P = 0.3; group C: -3.2± 12.2%, P = 0.82) tended to decrease in both groups, but a between-group difference was not observed. On the IB-IVUS analysis, the lipid plaque volume decreased (group S: from 200.1±116.2 to 179.8±121.0 mm^3, P = 0.02; group C: from 298.3±363.0 to 256.6± 386.1 mm^3, P = 0.1) and the calcified plaque volume increased (group S: from 2.1±0.9 to 3.2±1.8 mm^3, P = 0.06; group C: from 2.3±1.7 to 4.8±3.5 mm^3, P = 0.04) in both groups. Significant increases in the fibrous and dense fibrosis plaque volume were observed only in group C (**Table 3**).

Table 2. Risk factor control at baseline and follow-up

	Sitagliptin (n = 15)			Control (n = 11)		
	Baseline	Follow-up	*p* value	Baseline	Follow-up	*p* value
Total cholesterol (mg/dL)	169±32	154±22	0.1	165±24	161±21	0.67
LDL cholesterol (mg/dL)	99±33	81±23	0.04	106±25	94±20	0.27
Triglycerides (mg/dL)	140 (79-297)	115 (57-379)	0.28	136 (64-209)	142 (89-254)	0.27
HDL cholesterol (mg/dL)	54±18	54±15	0.65	46±9	51±14	0.14
Non-HDL cholesterol (mg/dL)	116±36	99±26	0.08	120±27	110±20	0.29
hs-CRP (ng/mL)	2370 (236-8730)	918 (147-4530)	0.04	3670 (829-8060)	594 (132-3550)	0.008
PG (mg/dL)	134±34	142±56	0.64	134±45	129±49	0.64
HbA1c (%)	7.5±0.8	7.0±1.2	0.06	7.1±0.6	7.0±0.8	0.72
SBP (mmHg)	135±21	132±20	0.51	129±19	125±14	0.35
DBP (mmHg)	71±11	70±12	0.61	71±12	69±15	0.49
HR (beats/min)	66±9	67±10	0.8	67±13	69±15	0.71

Data are expressed as mean ± standard deviation or median (range). LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PG, plasma glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 3. The parameters evaluated using grayscale intravascular ultrasound and integrated backscatter-intravascular ultrasound

	Sitagliptin (n = 15)			Control (n = 11)		
	Baseline	Follow-up	*p* value	Baseline	Follow-up	*p* value
EEM (mm^3)	722.3±411.9	708.6±387.4	0.34	933.7±861.1	915.0±915.8	0.48
% change		-1.3±7.0			-4.6±8.9	
Plaque (mm^3)	325.6±172.6	316.4±158.1	0.3	437.8±481.6	433.2±530.5	0.82
% change		-1.7±8.5			-3.2±12.2	
Lumen (mm^3)	396.7±253.7	392.2±246.4	0.56	495.9±390.4	481.9±399.7	0.33
% change		-1.0±7.7			-5.5±10.7	
PAV (%)	45.6±7.7	45.4±7.9	0.73	43.8±10.9	44.3±11.3	0.65
Nominal change (%)		-0.2±2.0			0.5±3.5	
Absolute value						
Lipid (mm^3)	200.1±116.2	179.8±121.0	0.02	298.3±363.0	256.6±386.1	0.1
Fibrosis (mm^3)	103.3±62.9	110.2±51.1	0.52	144.2±134.6	177.4±160.7	0.01
Dense fibrosis (mm^3)	9.2±4.9	12.0±6.6	0.13	11.9±8.2	20.3±13.4	0.02
Calcification (mm^3)	2.1±0.9	3.2±1.8	0.06	2.3±1.7	4.8±3.5	0.04
Relative value						
Lipid (%)	62.9±8.5	57.9±17.2	0.35	59.2±13.0	49.0±8.4	0.06
Fibrosis (%)	33.2±7.4	36.6±13.8	0.44	36.1±9.3	43.8±5.8	0.04
Dense fibrosis (%)	3.1±1.1	4.3±2.8	0.17	3.9±2.8	5.8±2.3	0.14
Calcification (%)	0.7±0.2	1.2±1.0	0.08	0.9±1.1	1.4±0.7	0.25
Average length (mm)	44.1±21.9	43.3±20.8	0.17	53.1±35.2	52.8±35.1	0.5
Number of vessels/patient	1.5±0.5	1.5±0.5	-	1.4±0.5	1.4±0.5	-
Number of lesions/patient	1.8±0.6	1.8±0.6	-	1.7±0.6	1.7±0.6	-

Data are expressed as mean ± standard deviation. EEM, external elastic membrane; PAV, percent atheroma volume.

Univariate regression analyses showed that age and the percentage change in non-HDL cholesterol level were positively correlated and that male sex was negatively correlated with the percentage changes in the lipid plaque volume (**Table 4**; **Figure 2**). Glucose control (percentage change in PG and nominal change in HbA1c) as well as sitagliptin use did not correlate with the percentage changes in the lipid plaque volume. Multivariate regression analy-

Table 4. Predictors of the percentage change in the lipid component

	Univariate		Multivariate	
	r	*p* value	β	*p* value
Age	0.488	0.02	0.432	0.04
Sex	-0.447	0.04	-0.058	0.79
Hypertension	-0.221	0.32		
Smoking	-0.108	0.63		
Non-HDL cholesterol (% change)	0.505	0.02	0.445	0.04
Statin use	0.038	0.87		
hs-CRP (% change)	0.278	0.28		
PG (% change)	-0.185	0.41		
HbA1c (nominal change)	-0.162	0.47		
Sitagliptin use	0.027	0.91		

Male sex, hypertension, smoking, statin use, and sitagliptin use were assigned a value of 1. Female sex, normotension, non-smoking status, no-statin use, and no-sitagliptin use were assigned a value of 0. HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PG, plasma glucose; HbA1c, hemoglobin A1c.

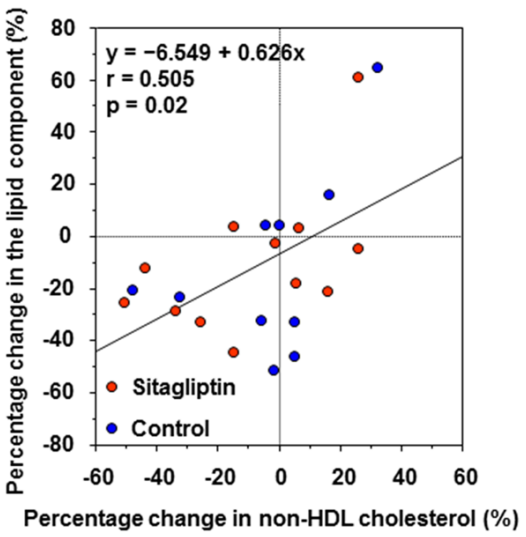

Figure 2. Correlation between the percentage change in non-HDL cholesterol and that in the lipid component. Significant positive correlations were observed between the percentage change in non-HDL cholesterol and that in the lipid component. HDL, high-density lipoprotein cholesterol.

sis showed that the percentage change in non-HDL cholesterol level was an independent and significant predictor of a reduction in the lipid plaque volume (**Table 4**).

There were no significant differences in the prevalence of major adverse cardiac events between the two groups (**Table 5**). Two patients in group S underwent target lesion revascularization at the 48-week follow-up.

Discussion

The major findings of the present study are as follows: (1) glycemic control using sitagliptin had no effects on coronary artery plaque volume; (2) a significant reduction in the lipid plaque volume and an increase in the calcified plaque volume were observed in both the sitagliptin and standard therapy groups; and (3) a decrease in non-HDL cholesterol, but not glycemic control, was associated with a reduction in the lipid volume of coronary artery plaques.

DM represents a residual risk for statin therapy, and patients with diabetes who are under treatment for secondary prevention of coronary artery disease are at high risk of a recurrence of cardiovascular events [20]. Intensive glycemic control in patients with DM reduces the risk of diabetes-related microvascular complications [21, 22], while the effects of glucose reduction on macrovascular complications remain elusive. Moreover, intensive glucose control does not seem to be beneficial in preventing major cardiovascular events when compared with standard therapy [23]. Although the new classes of anti-diabetic drugs, including GLP-1 and DPP-4 inhibitors, have demonstrated anti-inflammatory and anti-atherogenic effects in an animal model [11-13, 24], little is known about the influence of these agents, particularly DPP-4 inhibitors, on atherosclerosis-related cardiovascular disease in a clinical setting. Previous studies have reported that sitagliptin improves endothelial function [16, 25] and has a beneficial effect on carotid intima-media thickness [26]. However, Ishikawa et al. reported that the use of sitagliptin was not associated with a significant reduction in carotid intima-media thickness [26]. In our study too, the potential beneficial effects of sitagliptin on coronary artery plaque regression was not observed beyond its hypoglycemic action.

The quantity of the lipid component, as determined using IB-IVUS, provides information

Table 5. Major adverse cardiac events

	Sitagliptin (n = 15)	Control (n = 13)	*p* value
Cardiac death (%)	0 (0%)	0 (0%)	-
STEMI (%)	0 (0%)	0 (0%)	-
NSTEMI (%)	0 (0%)	0 (0%)	-
TLR (%)	2 (13%)	0 (0%)	0.48
CABG (%)	0 (0%)	0 (0%)	-

Data are expressed as number (%). STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; TLR, target lesion revascularization; CABG, coronary artery bypass grafting.

about the natural progression of luminal narrowing as well as post-procedural myocardial injury after stent implantation [4, 27]. A previous study has reported that the reduction in lipid plaque volume evaluated using IB-IVUS represents the plaque-stabilizing effects of statins [28]. In addition, statin therapy alters coronary artery plaque composition by significantly decreasing the lipid component and increasing the amount of calcification, evaluated by using virtual-histology IVUS [29]. Consistent with the findings of these previous studies, a significant reduction in the lipid plaque volume and an increase in the calcified plaque volume were observed in both groups. Furthermore, a significant increase in the fibrous plaque volume was observed in group C and this component tended to increase in group S. This could be attributable to increase in dense fibrous and elastic tissue due to statin therapy without plaque volume regression [30]. The percentage change in non-HDL cholesterol positively correlated with the percentage change in the lipid plaque volume. Thus, non-HDL cholesterol control is an important factor for plaque modification in patients with DM. Moreover, recent guidelines have emphasized the importance of non-HDL cholesterol as a predictor of cardiovascular risk [31].

Additional important results of the present study include the significant positive correlations observed between age and percentage changes in the lipid plaque volume. Age is a well-established risk factor for cardiovascular disease and silent atherosclerosis. In addition to the high likelihood of other cardiovascular risk factors prevalent in the elderly population, the aging process itself induces structural and functional changes in the vascular wall [32]. A previous study has reported that vascular responses to statin therapy were attenuated in the elderly patients compared to the non-elderly patients [33]. Thus, early plaques in the non-elderly patients would be more reversible than in the elderly patients.

Previous studies have reported that most of the anti-atherosclerotic effects of GLP-1 and DPP-4 inhibitors are mediated through the activation of intracellular cyclic AMP (cAMP) and protein kinase A (PKA) signaling [14, 24]. However, other studies have indicated that DPP-4 inhibitors might protect against endothelial inflammation and increase nitric oxide (NO) levels through other mechanisms, independent of the cAMP/PKA or phosphatidylinositide 3-kinase/AKT pathways [11, 34]. Thus, the mechanisms through which DPP-4 inhibitors attenuate the progression of atherosclerosis are complex and still not completely understood.

In two recent clinical trials, DPP-4 inhibitors (saxagliptin and alogliptin) did not increase or decrease the number of major adverse cardiovascular events [35, 36]. In the SAVOR-TIMI 53 trial, saxagliptin was associated with an increased risk of hospitalization for heart failure [35], whereas the EXAMINE trial showed a non-significant numerical imbalance in hospitalization rates for heart failure in the alogliptin group as compared with the placebo group [37]. In addition, in a recent randomized, double-blind study involving patients with type 2 DM and established cardiovascular disease, the addition of sitagliptin to the usual care regimen among patients with glycemic equipoise did not affect rates of major atherosclerotic cardiovascular events [38]. Thus, the effects of DPP-4 inhibitors on cardiovascular events and atherosclerosis remain controversial. However, recent meta-analyses have shown that DPP-4 inhibitors reduce the risk of cardiovascular events [39, 40]. A further, adequately powered, randomized, controlled trial is necessary to confirm the effects of DPP-4 inhibitors on cardiovascular events, particularly on coronary atherosclerosis.

Study limitations

This study had several limitations. First, the small sample size and short duration of follow-up yielded low statistical power. In addition, we

did not perform sample size calculation to achieve the primary endpoint. Furthermore, although baseline clinical characteristics did not differ between the two groups, selection bias may exist in the present study and have biased the conclusions. Second, we could not accurately evaluate the effects of other drugs that might be expected to influence coronary atherosclerosis, such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, because the number of patients included in the sub-analysis was too small. Although the frequency of statins therapy did not differ between the two groups, 1 patient in each group received additional treatment with statins. Furthermore, the type of statin was changed for 1 patient in group S during the study period. Third, we included patients with good glycemic control at random (HbA1c, 6.5-9.4%). Thus, the results of this study cannot be applied to general diabetic patients. Therefore, further studies, with a larger sample size and longer duration, would be necessary to confirm the effects of sitagliptin on coronary atherosclerosis.

Conclusions

Sitagliptin did not significantly reduce coronary plaque volume in patients with type 2 diabetes. However, a decrease in the lipid plaque volume was observed in the sitagliptin group. A decrease in non-HDL cholesterol level was associated with a reduction in the lipid volume of coronary artery plaques.

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Disclosure of conflict of interest

None.

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