Changes in coronary atherosclerosis, composition, and fractional flow reserve evaluated by coronary computed tomography angiography in patients with type 2 diabetes☆

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ARTICLE INFO

ABSTRACT

Background: The use of coronary computed tomography angiography (CCTA) for noninvasive anatomic detection of coronary artery disease is increasing. Recently, fractional flow reserve (FFR) assessment using routinely acquired CCTA datasets (FFR_{CT}) has been developed. However, there are no reports about changes in coronary atherosclerosis, composition, and FFR_{CT} in patients with type 2 diabetes.
Methods: This prospective, multicenter, observational trial evaluated changes in coronary atherosclerosis after alogliptin therapy in patients with type 2 diabetes. Fifty-one patients with type 2 diabetes who underwent CCTA examination and having intermediate coronary artery stenosis were treated with 25 mg of alogliptin. After 48 weeks, CCTA examination was repeated. The primary endpoint was changes in FFR_{CT}, and the secondary endpoint was changes in total atheroma volume (TAV) from the baseline to the 48-week follow-up.
Results: The FFR_{CT} decreased from the baseline to follow-up, but not significantly. A significant increase in TAV (from 658.5 mm^3 to 668.9 mm^3, $p = 0.048$) was observed. Vessel volume tended to increase, whereas percentage atheroma volume and lumen volume did not change. A significant negative correlation was observed between percentage change in TAV and change in FFR_{CT} ($r = -0.185$, $p = 0.048$). A significant increase in calcified plaques ($p = 0.01$) and a decrease in intermediate-attenuation plaques ($p = 0.006$) was observed.
Conclusions: In Japanese patients with diabetes and intermediate coronary artery stenosis, alogliptin could not improve FFR_{CT} or reduce atheroma volume, whereas the plaque composition changed. A progression of atheroma volume was associated with a reduction in FFR_{CT}.

1. Introduction

The use of coronary computed tomography angiography (CCTA) for noninvasive anatomic detection or exclusion of coronary artery disease (CAD) is increasing [1–3]. However, the diagnostic performance of CCTA is hampered by beam-hardening and blooming artifacts because of the presence of calcified plaques in the coronary artery wall. These artifacts can be caused by an enlargement of the calcified plaque and lead to overestimation or paradoxical underestimation of stenosis severity [1,4]. Furthermore, stenosis severity evaluated by CCTA does not correlate with functional ischemia assessed using invasive fractional flow reserve (FFR) [5]. Recently, a method using computational fluid dynamics to calculate coronary blood flow, pressure, and FFR using routinely acquired CCTA datasets (FFR_{CT}) has been developed [6,7]. The FFR_{CT} provides high diagnostic performance for the diagnosis of ischemic lesions of intermediate stenosis severity [7–9].

Diabetes mellitus (DM) is an established major risk factor for CAD [10]. Furthermore, CAD is the major cause of mortality and morbidity in patients with DM [11]. Therefore, the prevention of subclinical CAD is important in patients with DM. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been reported to attenuate the progression of carotid intima-media thickness [12,13], while sitagliptin has no effect on plaque volume in the coronary arteries as evaluated by intravascular ultrasound

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(IVUS) [14]. Thus, the effect of this class of drugs on atherosclerosis is controversial. Examination using CCTA is frequently performed to detect subclinical CAD in patients with DM. Therefore, in this study, we evaluated changes in coronary atherosclerosis using the newly-developed FFR$_{CT}$ as the primary endpoint after alogliptin therapy. We further evaluated quantitative changes in atheroma and vessel volume, as well as qualitative changes in plaque composition after alogliptin therapy.

2. Methods

2.1. Study design and ethical considerations

The Treatment of Alogliptin on Coronary Atherosclerosis Evaluated by Computed Tomography-Based Fractional Flow Reserve (TRACT study) was a prospective, multicenter, observational trial performed in Japan. Quantitative and qualitative changes in coronary atherosclerosis using CCTA were evaluated after 48-week alogliptin therapy in patients with type 2 DM.

The primary endpoint was changes in FFR$_{CT}$, and the secondary endpoint was the change in total atheroma volume (TAV) from baseline to the 48-week follow-up. In addition, changes in plaque composition, as well as serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, plasma glucose (PG), and hemoglobin A1c (HbA1c) were evaluated. Changes in blood pressure and heart rate were also evaluated.

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the three participating institutions. The study has been registered with the University Hospital Medical Information Network (UMIN; UMIN ID: 000015381).

2.2. Patient enrollment

Patients with type 2 DM who were suspected of having CAD and underwent CCTA examination 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 [15]. Briefly, patients with type 2 DM who had intermediate coronary artery stenosis (diameter stenosis <70%) as evaluated by CCTA were included in this trial. Eligible patients provided written informed consent. The supervising physician administered 25 mg of alogliptin within 2 weeks after CCTA examination. Patients who had been previously treated with another type of DPP-4 inhibitors were changed to alogliptin treatment. The patients continued alogliptin until the end of study, until certain adverse events had occurred, or until they decided to discontinue participation in this study. The CCTA examination and laboratory tests were performed at baseline and at the 48-week follow-up. During the study period, there were no lifestyle changes, and anti-hypertensive and lipid-lowering medications used at enrollment were continued without modification of the dose. An independent event assessment committee evaluated adverse events.

2.3. Examination with CCTA and image acquisition

The details of CCTA examination have been described previously [15]. Each center performed CCTAs in accordance with the Society of Cardiovascular Computed Tomography Guidelines on Performance of CCTA with a variety of different 64-detector row computed tomography scanner platforms [16]. Follow-up images were acquired using the same machine for every patient. Helical or axial scan data were obtained with retrospective or prospective electrocardiographic gating, respectively. Image acquisition was prescribed to include the coronary arteries, left ventricle, and proximal ascending aorta.

2.4. The CCTA core laboratory analysis

The CCTA images recorded on DVD were transmitted to the core laboratory (HeartFlow Inc., Redwood City, California, USA) for computational analysis of FFR$_{CT}$. Computation of FFR$_{CT}$ was performed in a blinded manner. The FFR$_{CT}$ was calculated after semi-automated segmentation of the coronary arteries and left ventricular mass [6]. Briefly, 3-dimensional (3D) blood flow simulations in the coronary vasculature were performed using proprietary software with quantitative image quality analysis, image segmentation, and physiological modeling using computational fluid dynamics. Coronary blood flow and pressure were calculated under conditions simulating maximal hyperemia. The FFR$_{CT}$ was obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure. The results provided a complete spatial distribution of FFR$_{CT}$ in the coronary arteries.

Quantitative changes in the coronary artery were analyzed at another independent core laboratory (Cardiocore Japan, Tokyo, Japan) in accordance with the Society of Cardiovascular Computed Tomography Guidelines on CCTA interpretation [17]. The quantitative atheroma analyses were performed by independent, experienced observers who were blinded to FFR$_{CT}$ results and clinical data. All reconstructed datasets were transferred to an offline workstation to perform quantitative coronary atheroma volume analysis using dedicated software with a semi-automated 3D contour detection algorithm (QAngioCT, vs. 2.1 RC4, MEDIS™, Leiden, The Netherlands) [18]. The reconstructed image was set at a window width of 740 and a window level of 220 for quantitative coronary artery assessment. All three coronary vessels, >2.0 mm in diameter, were analyzed (QAngioCT, vs. 2.1 RC4, MEDIS™) according to an AHA 17 segment model. Only the major coronary vessels were considered for analysis (segments 1, 2, 3, 6, 7, 8, 11, 13, and 15). Automated luminal and vessel border detection was manually corrected when necessary. We defined quantitative atheroma volume indices as follows: TAV = (total vessel volume − total lumen volume), percentage atheroma volume (PAV) = (TAV / total vessel volume) × 100, and percentage change in TAV (% change in TAV) = [(TAV follow up − TAV baseline) / TAV baseline] × 100. Segments at baseline and follow-up were synchronized using the branch points as the landmarks. All plaques were characterized based on Hounsfield units (HU) into low-attenuation plaques (<30 HU), intermediate-attenuation plaques (30 to 150 HU), and calcified plaques (>150 HU) [19], and the volume of each component was measured.

2.5. 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 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, LDL cholesterol, triglycerides, and HDL cholesterol 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).

2.6. Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). Results are expressed as the mean ± standard deviation or median (range). Differences in continuous variables 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. Univariate regression analyses were performed to assess the parameters associated with change in FFR$_{CT}$. Statistical significance was set at $p < 0.05$.

3. Results

The study flow chart is shown in Fig. 1. A total of 51 patients were enrolled in this study. One patient was lost to follow-up. Therefore, quantitative analysis of CCTA images was performed on 143 vessels from 50 patients. The FFR value could not be measured in 11 patients because of poor CCTA image quality. Finally, we obtained FFR values for 117 vessels from 39 patients.

Baseline characteristics of the patients are shown in Table 1. Twenty-one patients (54%) were male sex with a mean age of 71 years. The frequency of hypertension and dyslipidemia was 85% and 62%, respectively. Seventeen patients (44%) were treated with statins and 5 patients (13%) with ezetimibe. Twenty-one patients (54%) were already treated with another type of DPP-4 inhibitor at baseline. Therefore, these medications were changed to alogliptin. Thirteen patients (33%) had alogliptin added to their baseline medications.

Risk factor control at baseline and follow-up is shown in Table 2. Serum levels of total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, PG, and HbA1c levels did not change. Furthermore, serum hs-CRP levels did not decrease after alogliptin therapy.

Quantitative and qualitative changes in coronary atherosclerosis in the 3 coronary arteries are shown in Table 3. The FFR_{CT} decreased from 0.86 to 0.85, but this reduction was not statistically significant. A significant increase in TAV (from 658.5 mm^3 to 668.9 mm^3, $p = 0.048$) was observed. Vessel volume tended to increase, whereas PAV and lumen volume did not change. The absolute volume of calcified plaques increased significantly (from 234.4 mm^3 to 259.6 mm^3, $p = 0.006$), while volume of low- and intermediate-attenuation plaques tended to decrease. As a result, a significant increase in the relative value of calcified plaques (from 35.8% to 40.4%, $p = 0.01$) and a decrease in intermediate-attenuation plaques was observed (from 50.6% to 46.9%, $p = 0.006$).

A significant negative correlation was observed between the percentage change in TAV and change in FFR_{CT} ($r = -0.185$, $p = 0.048$) (Fig. 2), whereas changes in HbA1c and LDL cholesterol from baseline did not correlate with changes in FFR_{CT} (Table 4). The use of statin did not affect the change in FFR_{CT}.

No adverse events related to alogliptin were observed during the study period.

4. Discussion

The major findings of the present study are as follows: (1) glycemic control using alogliptin could not improve FFR_{CT}, (2) the TAV increased,
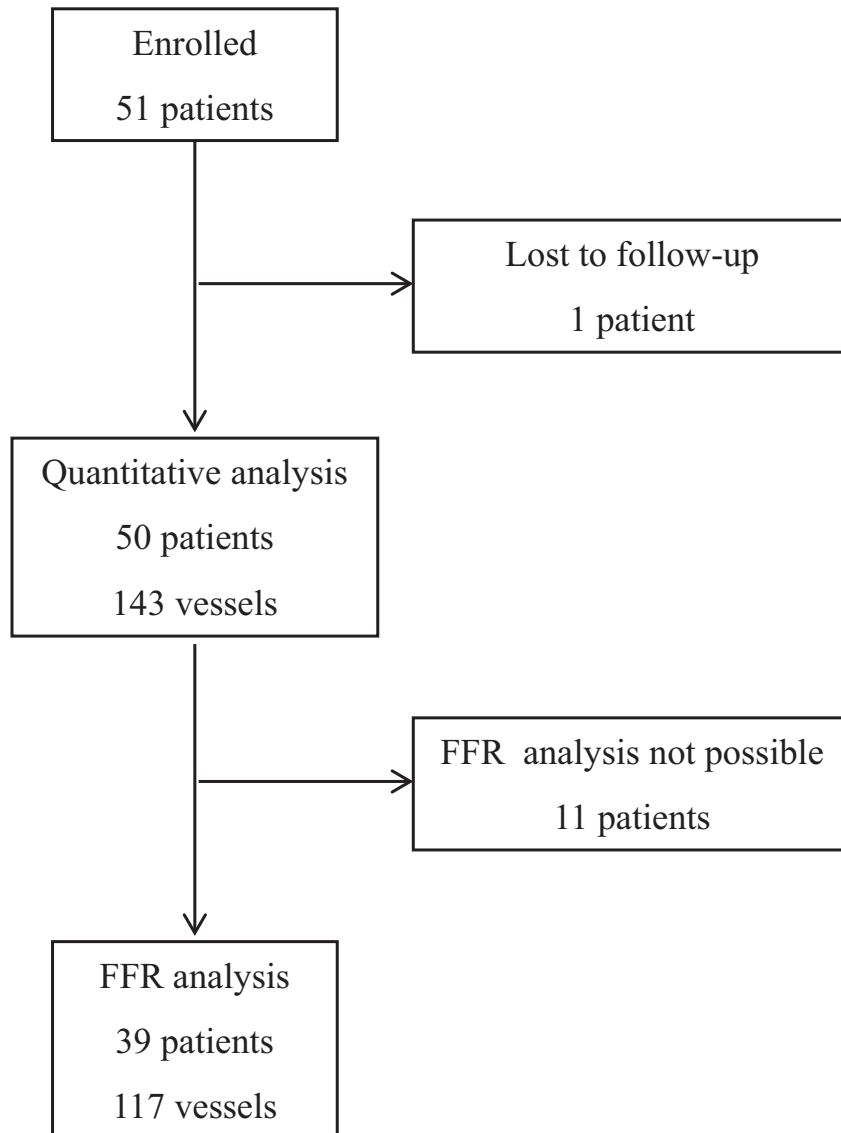

Fig. 1. Study flow chart. FFR, fractional flow reserve.

Table 1
Baseline characteristics of the subjects.

Age (years)	71 ± 9
Male (%)	21 (54%)
Body mass index (kg/m^2)	24.7 ± 3.4
Hypertension (%)	33 (85%)
Dyslipidemia (%)	24 (62%)
Smoking (%)	8 (21%)
Statin (%)	17 (44%)
Ezetimibe (%)	5 (13%)
Antiplatelet (%)	8 (21%)
ACE inhibitor or ARB (%)	17 (44%)
Beta-blocker (%)	8 (21%)
Hypoglycemic medications at baseline	
DPP-4 inhibitor (%)	21 (54%)
Sulfonylurea (%)	11 (28%)
Biguanide (%)	10 (26%)
α-Glucosidase inhibitor (%)	4 (10%)
Glinide	2 (5%)
Thiazolidine	1 (3%)
Insulin (%)	0 (0%)
Treatment pattern of alogliptin	
Add to baseline medications (%)	13 (33%)
Change some drugs (%)	26 (67%)
Hypoglycemic medications at follow-up	
DPP-4 inhibitor (%)	39 (100%)
Sulfonylurea (%)	10 (26%)
Biguanide (%)	8 (21%)
α-Glucosidase inhibitor (%)	2 (5%)
Glinide	1 (3%)
Thiazolidine	1 (3%)
Insulin (%)	0 (0%)

Data are expressed as mean ± SD or number (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DPP-4, dipeptidyl peptidase-4.

and percentage change in TAV negatively correlated with change in FFR$_{CT}$ after alogliptin therapy, and (3) plaque composition was changed after alogliptin therapy (an increase in calcified plaques and a decrease in intermediate-attenuation plaques).

In an animal model, DPP-4 inhibitors have been shown to have anti-inflammatory and anti-atherogenic effects [20–23]. However, the effects of this class of drug on the progression of atherosclerosis are controversial in the clinical setting. Previous studies have reported that sitagliptin improves endothelial function [24,25] and has a beneficial effect on carotid intima-media thickness [13,26]. Furthermore, it has been reported that alogliptin attenuates the progression of carotid intima-media thickness [12]. However, another study has reported that sitagliptin has no effect on plaque volume in the coronary arteries as evaluated by IVUS [14]. Consistent with this report, the potential beneficial effects of alogliptin on atheroma volume and vessel remodeling in the coronary arteries were not observed beyond its hypoglycemic action. Furthermore, FFR$_{CT}$ did not improve after alogliptin therapy. An additional important result of the present study was that a significant

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

	Baseline (n = 39)	Follow-up (n = 39)	p value
Total cholesterol (mg/dL)	199 ± 30	197 ± 30	0.76
LDL cholesterol (mg/dL)	120 ± 31	117 ± 31	0.53
Triglycerides (mg/dL)	146 (36–442)	154 (26–477)	0.69
HDL cholesterol (mg/dL)	63 ± 15	64 ± 17	0.35
hs-CRP (mg/L)	0.68 (0.65–8.97)	0.61 (0.58–11.70)	0.45
PG (mg/dL)	140 ± 46	146 ± 56	0.5
HbA1c (%)	7.1 ± 0.8	7.1 ± 1.1	0.64
SBP (mmHg)	139 ± 19	139 ± 21	0.8
DBP (mmHg)	83 ± 13	82 ± 14	0.75
HR (beats/min)	63 ± 10	64 ± 10	0.71

Data are expressed as mean ± SD 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
Quantitative and qualitative changes of coronary atherosclerosis in the 3 coronary arteries.

	Baseline (n = 39)	Follow-up (n = 39)	p value
FFR$_{CT}$	0.86 ± 0.09	0.85 ± 0.10	0.19
Vessel volume (mm^3)	1267.2 ± 728.7	1277.2 ± 722.4	0.14
% change		1.4 ± 6.4	
TAV (mm^3)	658.5 ± 390.5	668.9 ± 397.3	0.048
% change		2.2 ± 9.6	
Lumen volume (mm^3)	608.7 ± 405.9	608.3 ± 397.8	0.95
% change		0.8 ± 12.1	
PAV (%)	52.9 ± 10.9	53.3 ± 11.2	0.31
Nominal change (%)		0.4 ± 3.9	
Plaque characteristics			
Absolute value			
Low-attenuation (mm^3)	93.0 ± 84.1	88.9 ± 88.0	0.5
Intermediate-attenuation (mm^3)	317.1 ± 194.3	306.9 ± 189.9	0.1
Calcified (mm^3)	234.4 ± 218.4	259.6 ± 228.8	0.006
Relative value			
Low-attenuation (%)	13.7 ± 10.0	12.7 ± 9.7	0.27
Intermediate-attenuation (%)	50.6 ± 13.8	46.9 ± 15.6	0.006
Calcified (%)	35.8 ± 19.2	40.4 ± 21.9	0.01

Data are expressed as mean ± SD.
FFR, fractional flow reserve; TAV, total atheroma volume; PAV, percentage atheroma volume.

negative correlation was observed between percentage changes in TAV and change in FFR$_{CT}$. This simply means that plaque progression is associated with a reduction in FFR$_{CT}$. However, a significant reduction in FFR$_{CT}$ was not observed, and the mean FFR$_{CT}$ at follow-up was 0.85. A previous study reported that care guided by FFR$_{CT}$ was associated with low clinical event rate over 1-year follow-up [27]. Thus, optimal medical therapies for atherosclerosis may prevent cardiac events over time in these patients.

With advancements in imaging technology, we can identify vulnerable plaques using IVUS, angioscopy, optical coherence tomography, CCTA, and magnetic resonance imaging. Quantitative and qualitative analysis of coronary artery plaques detected by 64 detector CT scans is accurate compared to other modalities [28]. Thus, CCTA can assess the progression of coronary atherosclerosis and be used for non-invasive monitoring of pharmacological interventions in CAD [18]. The features of high-risk plaques evaluated by CCTA are low-attenuation plaque,
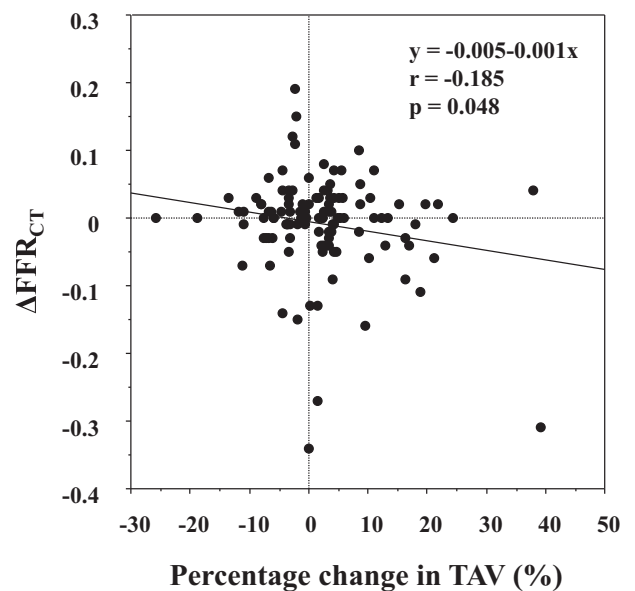

Fig. 2. Correlation between change in FFR$_{CT}$ and percentage change in TAV. A significant negative correlation is observed between change in FFR$_{CT}$ and percentage change in TAV. Δ, change; FFR, fractional flow reserve; TAV, total atheroma volume.

Table 4
Correlation between changes in FFR_{CT} and other parameters.

	r	p value
ΔHbA1c	−0.017	0.86
ΔLDL cholesterol	0.001	0.99
Use of statin	0.004	0.96
% change of vessel volume	−0.131	0.16
% change of TAV	−0.185	0.048
% change of lumen volume	0.080	0.4
ΔPAV	−0.139	0.14

Δ, change; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; TAV, total atheroma volume; PAV, percentage atheroma volume.

spotty calcification, and positive vessel remodeling [29,30]. Indeed, a previous prospective study reported that patients with these characteristics of plaques on CCTA were at a higher risk of acute coronary syndrome developing over time when compared with patients without these plaques [19]. Thus, plaque characteristics identified with CCTA are useful for detection of vulnerable plaques and high-risk patients. A lipid-lowering therapy with statins can significantly reduce the incidence of CAD. Although the mechanisms of this effect are not clearly understood, regression and stabilization of coronary artery plaques is presumed, in part, to play an important role. On the basis of IVUS analysis, a decrease in lipid volume and increases in stable components such as fibrous and calcified plaque components, are plaque stabilizing effects of statins [31,32]. According to the previous studies using CCTA, statins produce regression of low-attenuation plaque [33] and are associated with an increased prevalence and extent of calcified plaques [34]. Although alogliptin could not improve FFR_{CT} and produce the regression of coronary artery plaques, changes in coronary artery plaque composition were observed. In the previous study using integrated backscatter IVUS, sitagliptin decreased the lipid plaque volume and increased the calcified plaque volume [14]. Thus, DPP-4 inhibitors may be able to change coronary artery plaque composition and lead to the prevention of future coronary events, even if apparent plaque regression does not occur.

5. Study limitations

This study had several limitations. First, this study was an observational, non-randomized study and had no control group. The sample size was too small without sample size calculation to achieve the primary endpoint. In addition, the follow-up duration was short. These factors yield low statistical power. Second, we could not accurately evaluate the effects of other drugs, particularly statins, on coronary atherosclerosis. Only 40% of the patients were treated with stain. Thus, baseline medical therapies for atherosclerosis were poor. Third, changes in plaque composition may be the natural course of plaque progression/regression, because of the absence of control group. Fourth, a selection bias existed, because we included patients with intermediate coronary artery stenosis. Furthermore, patients included in this study were suspected of having CAD and underwent CCTA examination. Therefore, the results of this study cannot be applied to general diabetic patients. However, to the best to our knowledge, this is the first study to evaluate changes in coronary atherosclerosis using FFR_{CT} as the primary endpoint in patients with type 2 DM. Further large randomized studies with a longer duration are necessary to confirm these conclusions.

6. Conclusions

In this pilot study of Japanese diabetic patients with intermediate coronary artery stenosis, alogliptin could not improve FFR_{CT} or reduce atheroma volume, whereas the plaque composition changed. A progression of atheroma volume was associated with a reduction of FFR_{CT}.

Funding

Disclosure

None.

Conflict of interests

The authors declare that they have no competing interests.

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