

Impact of Diabetes Mellitus on the Aortic Wall Changes as Atherosclerosis Progresses: Aortic Dilatation and Calcification

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Aim: An inverse association between diabetes mellitus (DM) and aortic dilatation has recently been reported. However, little is known about the association between DM and the progression of aortic dilatation/calcification as atherosclerosis progresses.

Methods: We identified 216 patients who had undergone percutaneous coronary intervention (PCI) and abdominal computed tomography (CT) during the PCI and follow-up phases. The patients were classified into two groups: those with DM (DM+ group; $n=107$) and those without DM (DM- group; $n=109$). The infrarenal aortic diameter and aortic calcification index (ACI) were measured, and annual changes were calculated using measurement results obtained during the PCI and follow-up phases.

Results: Infrarenal aortic diameters were significantly shorter in the DM+ group than in the DM- group during the PCI phase, and no significant ACI differences were observed between the DM+ and DM- groups. The median duration between the PCI and follow-up phase CT was 3.0 years. The growth rate of the infrarenal aortic dilatation from the PCI phase in the DM+ group was similar to that in the DM- group. Annual ACI changes were significantly larger in the DM+ group than in the DM- group. Multivariate logistic regression analysis indicated that the prevalence of DM was an independent predictor of rapid aortic calcification progression (odds ratio: 2.51; 95% confidence interval: 1.23–5.14; $p=0.01$).

Conclusion: Our findings suggest that DM negatively affects aortic dilatation during an earlier phase of atherosclerosis progression and positively affects the progression of aortic calcification in a later phase.

Key words: Diabetes mellitus, Aortic dilatation, Aortic calcification, Coronary artery disease, Atherosclerosis

Introduction

Diabetes mellitus (DM) is a leading cause of atherosclerotic disease progression¹⁻³. The prevalence of abdominal aortic aneurysm (AAA) becomes higher with the progression of coronary artery disease⁴, a major atherosclerotic disease; therefore, aortic dilatation has been considered a process of atherosclerosis. However, recent studies have shown an inverse association between DM and aortic dilatation⁵⁻⁹ with DM patients having generally smaller aortic diameters and slower aortic dilatation growth rates, although little is

known about the time course.

On the contrary, vascular calcification is considered an important process in atherosclerosis. A prior report showed that patients with DM had a greater incidence of and absolute progression in coronary artery calcification¹⁰, although the relationship between DM and aortic calcification has not been fully elucidated.

The purpose of this study was to assess the impact of DM on the progression of aortic dilatation and calcification in patients with coronary artery disease (CAD).

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Methods

Patients

Among the patients who had undergone percutaneous coronary intervention (PCI) at our institution from January 2006 to December 2016, we identified the patients who underwent abdominal computed tomography (CT) during the PCI phase (within 6 months before or after PCI) and the follow-up phase (more than 1 year since the PCI phase CT). Patients were excluded if 1) the patient did not have either a PCI phase CT or a follow-up CT, 2) axial CT images with contiguous 5.0 mm-thick sections of the entire length were not available, or 3) the patient had already undergone surgical or endovascular aneurysm repair at the time of the PCI phase CT. Ultimately, we enrolled 216 patients who were classified into two groups: those with DM (DM+ group; $n=107$) and those without DM (DM- group; $n=109$) on the basis of baseline data during the PCI phase. DM was defined as a hemoglobin A1c level of $\geq 6.5\%$ (National Glycohemoglobin Standardization Program), a fasting glucose level of ≥ 126 mg/dL, a 2-hour glucose level of ≥ 200 mg/dL, a history of using any anti-hyperglycemic medication, or a previous diagnosis of DM. This study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the local ethics committee.

CT Measurement

Infrarenal aortic diameters were measured using abdominal CT. The short axial diameters of the outer contour were measured for all sections with contiguous 5.0 mm-thick axial images, and the largest short axial diameter of the infrarenal aorta was derived^{9,11}.

During CT, calcification appeared as an area of ≥ 1 mm² with a density of ≥ 130 Hounsfield units. The CT-based abdominal aortic calcification (AAC) scores were calculated by dividing the aorta into 12 segments (using 5 mm slices) from just under the renal artery to the bifurcation of the common iliac artery. The aortic calcification index (ACI) was calculated as follows: $ACI = (\text{total AAC scores on all slices}) / 12 \times 1 / (\text{number of slices}) \times 100$ (%)¹².

Annual changes of the aortic diameter and the ACI were calculated using measurement results from the PCI phase CT and follow-up phase CT. If surgical or endovascular aneurysm repair was performed within 1 year following the PCI phase CT, then the patient was excluded from the follow-up CT analysis. However, if performed after 1 year, then follow-up CT analysis was performed using the latest pre-repair CT images. Rapid progression of aortic dilatation and calcification was defined as being in the upper quartile of

annual changes for aortic diameter and ACI in the cohort of this study, respectively.

Statistical Analysis

Data are expressed as mean \pm standard deviation or median (interquartile ranges). Categorical variables are expressed as counts and percentages. Continuous data were compared using the unpaired *t*-test or the Mann–Whitney *U*-test. Categorical data were compared using the chi-squared or Fisher's exact test. Univariate logistic regression analyses were performed to determine contributing factors for rapid aortic dilatation and rapid progression of aortic calcification. The factors with $p < 0.1$ in the univariate analyses were entered into a multivariate logistic regression analysis. A p -value < 0.05 was considered statistically significant. All analyses were performed using the SPSS 24.0 software package (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of the patients are shown in **Table 1**. No significant differences were observed between the two groups with regard to age, sex, body mass index, hypertension, dyslipidemia, smoking status, the rate of previous PCIs, or coronary artery bypass grafting.

Measurement results of the largest short axial diameter of the infrarenal aorta and the ACI during PCI phase CT are shown in **Table 2**. Infrarenal aortic diameters during the PCI phase were significantly shorter in the DM+ group than those in the DM- group (21.3 mm [19.1–24.3 mm] vs. 23.6 mm [20.2–30.6 mm], $p < 0.001$), whereas ACI was similar between the DM+ and DM- groups (38.3% [16.3–52.5%] vs. 29.8% [17.6–51.9%], $p = 0.29$).

The median duration between the PCI phase CT and follow-up phase CT was 3.0 years (1.9–5.1 years). After excluding patients with surgical or endovascular aneurysm repair within 1 year of PCI phase CT, measurement results of follow-up CT were obtained in 100 DM+ patients and 94 DM- patients. The results of the infrarenal aortic dilatation growth rates and ACI are shown in **Table 2**. The growth rate of the infrarenal aortic dilatation was similar between the two groups (0.14 mm/year [–0.11–0.46] in DM+ vs. 0.15 mm/year [–0.09–0.56] in DM-, $p = 0.83$). No significant difference was seen in the rate of rapid aortic dilatation (defined as being in the upper quartile of annual aortic dilatation rates) between the two groups (23% vs. 27%, $p = 0.56$).

Annual ACI changes were significantly larger in the DM+ group than in the DM- group (2.56%/year [1.35–4.23] vs. 1.75%/year [0.69–3.25], $p = 0.02$).

Table 1. Baseline characteristics

	DM+ <i>n</i> = 107	DM- <i>n</i> = 109	<i>p</i> -value
Age, years	69.9 ± 10.9	72.2 ± 8.6	0.09
Male, <i>n</i> (%)	83 (77.6%)	87 (79.8%)	0.69
Body mass index, kg/m ²	23.3 ± 3.6	22.7 ± 3.6	0.19
Height, cm	161 ± 10	161 ± 9	0.81
Hypertension, <i>n</i> (%)	83 (77.6%)	82 (75.2%)	0.69
Dyslipidemia, <i>n</i> (%)	78 (72.9%)	72 (66.1%)	0.28
Current smoker, <i>n</i> (%)	24 (22.4%)	24 (22.0%)	0.94
Previous MI, <i>n</i> (%)	12 (11.2%)	23 (21.1%)	0.05
Previous PCI, <i>n</i> (%)	26 (24.3%)	25 (22.9%)	0.81
Previous CABG, <i>n</i> (%)	10 (9.3%)	10 (9.2%)	0.97
Dialysis, <i>n</i> (%)	9 (8.4%)	4 (3.7%)	0.14
LVEF (%)	60.0 ± 12.7	62.1 ± 12.3	0.23
eGFR, mL/min/1.73 m ²	58.8 ± 29.7	59.0 ± 21.3	0.96
eGFR < 30 mL/min/1.73 m ²	15 (15.0%)	11 (10.1%)	0.28
Triglyceride, mg/dL	126 ± 62	131 ± 67	0.55
HDL-cholesterol, mg/dL	45 ± 13	47 ± 12	0.24
LDL-cholesterol, mg/dL	97 ± 31	106 ± 30	0.03
HbA1c, %	7.2 ± 1.3	5.8 ± 0.4	<0.001
Hemoglobin, g/dL	12.4 ± 2.2	12.4 ± 2.6	0.98
Albumin, g/dL	3.7 ± 0.6	3.7 ± 0.5	0.34
C-reactive protein, mg/L	10 (5-35)	11 (6-31)	0.98
DM medication, <i>n</i> (%)			
No medication	39 (36.4%)	-	
OHA without insulin	39 (36.4%)	-	
Insulin	29 (27.1%)	-	
Statin, <i>n</i> (%)	77 (72.0%)	76 (69.7%)	0.72
ACEI or ARB, <i>n</i> (%)	67 (62.7%)	60 (55.0%)	0.26
Clinical presentation, <i>n</i> (%)			
Stable angina/ Silent ischemia	73 (68.2%)	79 (72.5%)	0.49
Unstable angina	16 (15%)	14 (12.8%)	0.65
Acute myocardial infarction	18 (16.8%)	16 (14.7%)	0.67

MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, LVEF=left ventricular ejection fraction, eGFR=estimated glomerular filtration rate, DM=diabetes mellitus, OHA=oral hypoglycemic agent, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker

Table 2. Baseline measurement and changes from baseline to follow-up in CT

	DM+ <i>n</i> = 107	DM- <i>n</i> = 109	<i>p</i> -value
Baseline CT measurements			
Maximum infrarenal aortic diameter, mm	21.3 (19.1–24.3)	23.6 (20.2–30.6)	0.001
Aortic calcification index, %	38.3 (16.3–52.5)	29.8 (17.6–51.9)	0.29
Changes from Baseline to follow-up CT	<i>n</i> = 100*	<i>n</i> = 94 ⁺	
Δ maximum infrarenal aortic diameter, mm/year	0.14 (-0.11–0.46)	0.15 (-0.09–0.56)	0.83
Rapid aortic dilatation, %	23 (23%)	25 (27%)	0.56
Δ aortic calcification index, %/year	2.56 (1.35–4.23)	1.75 (0.69–3.25)	0.02
Rapid progression in aortic calcification, %	33 (33%)	15 (16%)	0.006

*7 patients were excluded from assessment because received endovascular/ surgical abdominal aortic repair within 1 year of PCI phase CT

⁺15 patients were excluded from assessment because received endovascular/ surgical abdominal aortic repair within 1 year of PCI phase CT

Table 3. Logistic analyses to assess the predictors

A. Rapid aortic dilatation				
Variables	Univariate			
	OR (95%CI)	<i>p</i> -value		
Age	0.98 (0.95-1.02)	0.29		
Male	0.78 (0.36-1.67)	0.52		
Body mass index	0.98 (0.89-1.07)	0.66		
Hypertension	1.29 (0.59-2.84)	0.53		
Dyslipidemia	0.86 (0.43-1.73)	0.68		
Diabetes mellitus	0.82 (0.43-1.58)	0.56		
Current smoker	1.44 (0.68-3.05)	0.35		
Previous MI	0.66 (0.25-1.71)	0.39		
Previous PCI	0.51 (0.22-1.19)	0.12		
Previous CABG	1.46 (0.52-4.08)	0.47		
Left ventricular ejection fraction	1.01 (0.98-1.04)	0.43		
eGFR <30 mL/min/1.73 m ²	0.69 (0.25-1.95)	0.49		

B. Rapid progression of aortic calcification				
Variables	Univariate		Multivariate	
	OR (95%CI)	<i>p</i> -value	OR (95%CI)	<i>p</i> -value
Age	1.01 (0.98-1.05)	0.48		
Male	0.91 (0.42-1.98)	0.81		
Body mass index	1.02 (0.93-1.11)	0.74		
Hypertension	1.82 (0.78-4.23)	0.16	1.52 (0.63-3.65)	0.35
Dyslipidemia	0.98 (0.49-1.98)	0.96		
Diabetes mellitus	2.59 (1.30-5.18)	0.007	2.51 (1.23-5.14)	0.01
Current smoker	1.24 (0.58-2.66)	0.59		
Previous MI	0.83 (0.33-2.05)	0.68		
Previous PCI	0.72 (0.33-1.59)	0.42		
Previous CABG	0.79 (0.25-2.52)	0.7		
Left ventricular ejection fraction	0.99 (0.96-1.01)	0.27		
eGFR <30 mL/min/1.73 m ²	4.60 (1.95-10.84)	<0.001	4.12 (1.69-10.03)	0.002

OR=odds ratio, CI=confidence interval, MI=myocardial infarction, PCI=percutaneous coronary intervention, eGFR=estimated glomerular filtration rate

Rapid progression of aortic calcification (defined as being in the upper quartile of the ACI/year) was more frequently observed in the DM+ group than in the DM- group (33% vs. 16%, $p=0.006$).

Multivariate logistic regression analysis indicated the prevalence of DM (odds ratio [OR]: 2.51; 95% confidence interval [CI]: 1.23–5.14; $p=0.012$) and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (OR: 4.12; 95% CI: 1.69–10.03; $p=0.002$) were significant and independent predictors of rapid aortic calcification progression (Table 3).

Discussion

In this study, we confirmed the following: 1) an

inverse association between DM and abdominal aortic diameter at the time of PCI in patients with CAD exists, 2) the growth rate of aortic dilatation between patients with and without DM after PCI had no significant difference, 3) AAC between patients with and without DM at the time of PCI had no significant difference, 4) the growth rate of aortic calcification was significantly larger among patients with DM after PCI, and 5) DM and advanced renal dysfunction were independent predictors of rapid aortic calcification progression among patients with CAD.

Although many recent reports have described an inverse association between DM and aortic dilatation, the reports have significant DM time/phase differences. Newly diagnosed DM patients and those with-

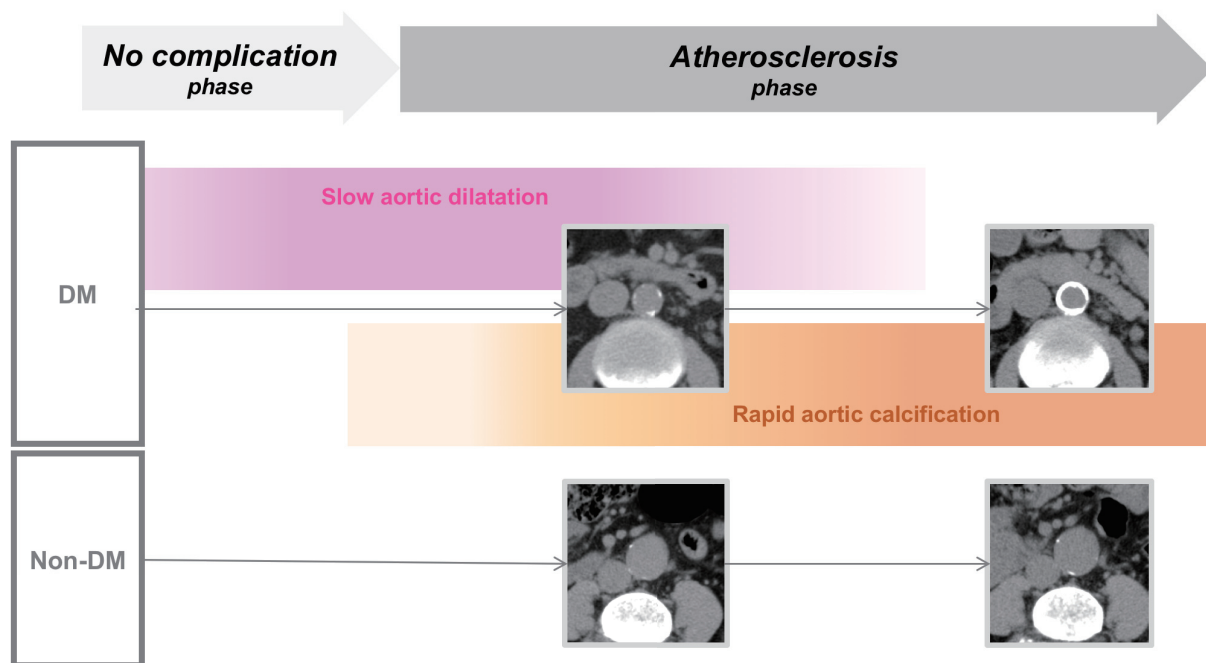


Fig. 1. Changes in influence of DM on aortic wall as atherosclerosis progresses

out systemic complications seem to have relatively smaller aortic diameter differences than non-DM patients^{6, 13}). As we previously reported⁹), DM patients with advanced atherosclerotic complications seem to have large diameter differences, and this report also demonstrated an obvious difference between DM and non-DM patients with CAD. These results may suggest that the early DM phase creates a negative aortic dilatation impact with larger differences occurring in the later phases.

With regard to the growth rate of aortic dilatation, a previous report showed that early DM had a slower aortic progression⁵). On the contrary, the growth rate of aortic dilatation was not significantly different after the PCI phase among patients with CAD in this study. Although this result can be attributed to the small number of patients, we can say that the DM influence on the aortic wall may be changing as atherosclerosis progresses (Fig. 1). Although definite mechanisms showing that DM suppresses aortic dilatation have not been elucidated, possible explanations include the inhibition of matrix metalloproteinases responsible for aortic wall degradation¹⁴⁻¹⁷). The progression of atherosclerosis changes aortic wall properties, which may lead to changes in aortic wall responses to various mechanisms.

In this study, the baseline degree of aortic calcification was similar between DM and non-DM with subsequent rapid progression of aortic calcification observed in patients with DM. Some reports have

showed an association between DM and coronary artery calcification^{10, 18}), but, to our knowledge, this is the first report showing a relationship between aortic calcification progression and DM among patients with CAD (Fig. 1). A prior report showed that the volume of aortic calcification did not predict AAA growth, refuting the earlier hypothesis that aortic calcification may be a cause of reduced AAA expansion in diabetic patients¹⁹). Our results, revealing a time course of aortic dilatation and calcification, support their conclusions.

We previously reported that advanced chronic kidney disease (CKD) was associated with the rapid progression of AAC among CKD patients²⁰). In this study, advanced renal dysfunction (eGFR < 30 mL/min/1.73 m²) and DM predicted the rapid progression of aortic calcification in patients with CAD. Our results may also indicate that vascular calcification is accelerated in patients with advanced CKD.

Nonetheless, this study has several limitations. First, this was a single-center study and the population was relatively small. Second, this study included any patient who received PCI in a population of atherosclerotic patients. However, the degree of atherosclerosis varied among the patients. Third, the effects of medication were not evaluated. Fourth, oral glucose tolerance test was not performed to newly diagnosed DM. Therefore, some undiagnosed patients in the non-DM group may be included. Notwithstanding these limitations, as limited studies focus on the rela-

relationship between aortic dilatation and calcifications exist, our data are of importance to this topic.

In conclusion, our findings suggest that DM negatively affects aortic dilatation in the early phase of atherosclerotic progression and positively affects progression of aortic calcification in the later phases. The effect of DM on the aortic wall may be changing as atherosclerosis progresses. Further investigations with various time phases should be required to explore the issue.

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Conflict of Interest

Hideki Ishii received lecture fees from Astellas Pharma Inc., Astrazeneca Inc., Daiichi-Sankyo Pharma Inc., and MSD K. K. Toyooki Murohara received lecture fees from Bayel Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Pfizer Japan Inc., Sanofi-aventis K. K., and Takeda Pharmaceutical Co., Ltd. Toyooki Murohara received unrestricted research grant for Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K. K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K. K., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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