Supplementary Material

An Inconvenient Relationship of Hemoglobin A1c Level with Endothelial Function in Type 2 Diabetes in A Cross-sectional Study

Short title: Low HbA1c and endothelial function

Takayuki Yamaji, MD;[1] Takahiro Harada, MD;[1] Yu Hashimoto, MD;[1] Yuji Takaeko, MD;[1] Masato Kajikawa, MD, PhD;[2] Yiming Han, MS;[1] Tatsuya Maruhashi, MD, PhD;[1] Shinji Kishimoto, MD, PhD;[1] Haruki Hashimoto, MD;[1] Yasuki Kihara, MD, PhD;[1] Eisuke Hida, PhD;[3] Kazuaki Chayama, MD, PhD;[4] Chikara Goto, PhD;[5] Farina Mohamad Yusoff, MD;[6] Ayumu Nakashima, MD, PhD;[7] Yukihito Higashi, MD, PhD, FAHA[2,6]

[1]Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan
[2]Division of Regeneration and Medicine, Medical Center for Translational and Clinical Research, Hiroshima University Hospital, Hiroshima, Japan
[3]Department of Biostatistics and Data Science, Osaka University Graduate School of Medicine, Osaka, Japan
[4]Department of Gastroenterology and Metabolism, Institute of Biomedical and Health Sciences, Graduate School of Biomedical and Health Sciences, Hiroshima University Hiroshima, Japan
[5]Hiroshima International University, Hiroshima, Japan
[6]Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan
[7]Department of Stem Cell Biology and Medicine, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

Address for correspondence: Yukihito Higashi, MD, PhD, FAHA
Department of Cardiovascular Regeneration and Medicine,
Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University
1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Phone: +81-82-257-5831 Fax: +81-82-257-5831
E-mail: yhigashi@hiroshima-u.ac.jp

Supplementary Methods

Measurement of FMD and NID

Subjects fasted the previous night and abstained from alcohol, smoking, caffeine, antioxidant vitamins, and all medications including hypertensive drugs, lipid-lowering drugs and antidiabetic drugs on the day of the FMD and NID examinations, and only drinking water was given to the subjects. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature of 23°C to 26°C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. At least 20 min after maintaining the supine position, baseline brachial artery diameter was measured. Then FMD and NID were measured. The observers were blind to the form of examination.

A blood pressure cuff was placed around the forearm of each subjects. The brachial artery was scanned longitudinally 5 to 10 cm above the elbow. When the clearest B-mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained, the transducer was held at the same point throughout the scan by using a special probe holder (UNEX Co.) to ensure consistency of the imaging. Depth and gain setting were set to optimize the images of the arterial lumen wall interface. When the tracking gate was placed on the intima, the artery diameter was automatically tracked, and the waveform of diameter changes over the cardiac cycle was displayed in real time using the FMD mode of the tracking system. This allowed the ultrasound images to be optimized at the start of the scan and the transducer position to be adjusted immediately for optimal tracking performance throughout the scan. Pulsed Doppler flow was assessed at baseline and during peak hyperemic flow, which was confirmed to occur within 15 seconds after cuff deflation. Blood flow velocity was calculated from the color Doppler data and was displayed as a waveform in real time. Baseline longitudinal images of the artery were acquired for 30 seconds, and then the blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 minutes. Blood flow volume was calculated by multiplying the Doppler flow velocity (corrected for the angle) by heart rate and vessel cross-sectional area ($-r^2$). Reactive hyperemia was calculated as the maximum percentage increase in flow after cuff deflation compared with baseline flow. The correlation coefficient between FMD analyzed at the core laboratory and participant institutions was 0.84 ($p<0.001$).

The response to nitroglycerine was used for assessment of endothelium-independent vasodilation. After acquiring baseline rest images for 30 seconds, a sublingual tablet (nitroglycerine, 75 μg) was given and imaging of the artery was done continuously for 5 minutes. NID was automatically calculated as a percentage change in peak vessel diameter from the baseline. Percentage of NID [(Peak diameter-Baseline diameter)/Baseline diameter] was used for analysis.

Online Supplementary Tables

Table 1. Clinical Characteristics of Patients with Type 2 Diabetes in Four Groups on the Basis on HbA1c Level

Variables	Total (n=1215)	HbA1c <6.5% (n=474)	HbA1c 6.5-6.9% (n=333)	HbA1c 7.0-7.9% (n=272)	HbA1c ≥8.0% (n=136)	P value
Age, yr	62±10	65±10	61±10	62±10	57±11	<0.001
Gender, men/women	870/345	301/173	240/93	220/52	119/22	<0.001
Body mass index, kg/m^2	25.3±4.3	24.7±4.0	25.7±4.3	25.7±4.4	25.7±4.3	0.002
Heart rate, bpm	68±11	69±12	68±11	67±11	69±12	0.3
Systolic blood pressure, mmHg	133±17	130±18	134±16	135±18	136±17	<0.001
Diastolic blood pressure, mmHg	79±11	76±11	80±11	80±11	81±13	<0.001
Total cholesterol, mg/dL	188±37	180±33	194±35	186±38	202±46	<0.001
Triglycerides, mg/dL	148±109	130±81	147±111	164±130	177±133	<0.001
HDL-C, mg/dL	54±15	57±16	55±15	51±14	51±14	<0.001
LDL-C, mg/dL	107±32	101±29	112±31	106±32	118±39	<0.001
Creatinine, mg/dL	0.84±0.29	0.86±0.31	0.82±0.24	0.84±0.30	0.83±0.31	0.26
Uric acid, mg/dL	5.7±1.4	5.8±1.4	5.8±1.4	5.6±1.4	5.3±1.4	<0.001
Glucose, mg/dL	138±46	119±27	130±26	149±37	202±78	<0.001
Hemoglobin A1c, %	6.8±1.1	5.9±0.4	6.7±0.1	7.3±0.3	9.1±1.2	<0.001
Medical history, n (%)						
Hypertension	969 (79.8)	378 (79.8)	266 (79.9)	226 (83.1)	99 (72.8)	0.12
Dyslipidemia	953 (78.4)	371 (78.3)	251 (75.4)	226 (83.1)	105 (77.2)	0.13
CVD, n (%)	409 (33.7)	150 (31.7)	98 (29.4)	104 (38.2)	57 (41.9)	0.02
Current Smoking, n (%)	290 (24.1)	104 (21.9)	73 (22.3)	73 (27.3)	40 (29.6)	0.12
Medication, n (%)						
Antihypertensive drugs	852 (70.1)	365 (77.0)	227 (68.2)	181 (66.5)	79 (58.1)	<0.001
Lipid-lowering drugs	680 (56.0)	298 (62.9)	168 (50.5)	154 (56.6)	60 (44.1)	0.001
Antidiabetic drugs	866 (71.3)	373 (78.7)	184 (55.3)	205 (75.4)	104 (76.5)	<0.001

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 2. Univariate Analysis of Relationships among FMD, HbA1c Level and Variables

Variables	FMD		HbA1c	
	r	P value	r	P value
Age, yr	-0.30	<0.001	-0.21	<0.001
Body mass index, kg/m^2	0.01	0.63	0.07	0.01
Heart rate, bpm	-0.03	0.27	-0.01	0.73
Systolic blood pressure, mmHg	0.04	0.13	0.13	<0.001
Diastolic blood pressure, mmHg	0.17	<0.001	0.14	<0.001
Total cholesterol, mg/dL	0.03	0.33	0.18	<0.001
Triglycerides, mg/dL	-0.04	0.15	0.18	<0.001
HDL-C, mg/dL	-0.01	0.6	-0.14	<0.001
LDL-C, mg/dL	0.04	0.2	0.16	<0.001
Creatinine, mg/dL	-0.09	0.002	0.004	0.88
Uric acid, mg/dL	-0.01	0.62	-0.11	<0.001
Glucose, mg/dL	-0.02	0.44	0.57	<0.001
HbA1c, %	0.08	0.004		
FMD, %			0.08	0.004
NID, %	0.33	<0.001	-0.02	0.70

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.
Univariate analysis of the relations among FMD, HbA1c levels and variables (Pearson's correlation analysis).

Table 3. Multivariate Analysis of Relationships among Low Quartiles of FMD and NID and Low HbA1c Level

	Low quartile of FMD		Low quartile of NID	
Variables	OR (95% CI)	P value	OR (95% CI)	P value
Model 1	2.50 (1.93-3.27)	<0.001	1.17 (0.74-1.84)	0.50
Model 2	2.04 (1.55-2.69)	<0.001	1.00 (0.61-1.61)	0.99
Model 3	2.03 (1.53-2.69)	<0.001	1.07 (0.65-1.75)	0.80

Model 1: unadjusted model
Model 2: adjusted for age, gender and body mass index
Model 3: adjusted for age, gender, body mass index, current smoking, creatine, and presence of hypertension, dyslipidemia and CVD

FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation; OR, odds ration; CI, confidence interval; CVD, cardiovascular disease.
Low quartile of FMD indicates less than 2.1%. Low quartile of NID indicates less than 6.2%.

Table 4. Clinical Characteristics of Type 2 Diabetes Patients with HbA1c of <6.5% and with HbA1c of 6.5-6.9%

Variables	HbA1c <6.5% (n=238)	HbA1c 6.5-6.9% (n=238)	P value
Age, yr	63±10	63±10	0.94
Gender, men/women	171/67	162/76	0.37
Body mass index, kg/m^2	25.2±4.2	25.3±4.1	0.75
Heart rate, bpm	67±11	68±11	0.6
Systolic blood pressure, mmHg	132±17	132±16	0.92
Diastolic blood pressure, mmHg	78±10	78±11	0.96
Total cholesterol, mg/dL	188±33	189±34	0.63
Triglycerides, mg/dL	126±60	130±69	0.51
HDL-C, mg/dL	56±14	56±16	0.84
LDL-C, mg/dL	108±29	109±30	0.94
Creatinine, mg/dL	0.82±0.21	0.82±0.26	0.58
Uric acid, mg/dL	5.8±1.3	5.8±1.4	0.95
Glucose, mg/dL	119±26	130±26	<0.001
Hemoglobin A1c, %	5.9±0.4	6.7±0.1	<0.001
Medical history, n (%)			
Hypertension	191 (80.3)	192 (80.7)	0.91
Dyslipidemia	174 (73.1)	183 (76.9)	0.34
CVD, n (%)	76 (31.9)	76 (31.9)	1.00
Current Smoking, n (%)	53 (22.3)	56 (23.5)	0.74
Medication, n (%)			
Antihypertensive drugs	39 (79.6)	36 (73.4)	0.47
Lipid-lowering drugs	131 (55.0)	135 (56.7)	0.71
Antidiabetic drugs	186 (78.2)	140 (58.8)	<0.001

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 5. Clinical Characteristics of Type 2 Diabetes Patients with HbA1c of <6.5% and with HbA1c of 7.0-7.9%

Variables	HbA1c <6.5% (n=192)	HbA1c 7.0-7.9% (n=192)	P value
Age, yr	63±10	63±9	0.96
Gender, men/women	163/29	151/41	0.11
Body mass index, kg/m^2	25.3±3.9	25.4±4.2	0.80
Heart rate, bpm	67±11	67±12	0.99
Systolic blood pressure, mmHg	133±18	133±16	0.94
Diastolic blood pressure, mmHg	79±11	79±10	0.74
Total cholesterol, mg/dL	178±33	181±37	0.36
Triglycerides, mg/dL	135±76	132±84	0.72
HDL-C, mg/dL	52±13	53±15	0.54
LDL-C, mg/dL	101±29	104±32	0.29
Creatinine, mg/dL	0.88±0.30	0.84±0.29	0.16
Uric acid, mg/dL	5.8±1.4	5.7±1.4	0.32
Glucose, mg/dL	118±21	146±36	<0.001
Hemoglobin A1c, %	5.9±0.4	7.3±0.3	<0.001
Medical history, n (%)			
Hypertension	162 (84.4)	158 (82.3)	0.58
Dyslipidemia	150 (78.1)	157 (81.8)	0.37
CVD, n (%)	75 (39.1)	77 (40.1)	0.84
Current Smoking, n (%)	49 (25.5)	45 (23.4)	0.64
Medication, n (%)			
Antihypertensive drugs	138 (71.9)	135 (70.3)	0.74
Lipid-lowering drugs	111 (57.8)	117 (60.9)	0.53
Antidiabetic drugs	159 (82.8)	146 (76.0)	0.10

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 6. Clinical Characteristics of Type 2 Diabetes Patients with HbA1c of <6.5% and with HbA1c of ≥8.0 %

Variables	HbA1c <6.5% (n=93)	HbA1c ≥8.0% (n=93)	P value
Age, yr	58±11	58±10	0.78
Gender, men/women	68/25	71/22	0.61
Body mass index, kg/m^2	24.9±4.9	25.1±4.1	0.78
Heart rate, bpm	68±12	67±12	0.76
Systolic blood pressure, mmHg	136±18	134±17	0.61
Diastolic blood pressure, mmHg	80±11	80±13	0.86
Total cholesterol, mg/dL	193±40	190±39	0.58
Triglycerides, mg/dL	129±59	139±72	0.28
HDL-C, mg/dL	54±14	53±15	0.67
LDL-C, mg/dL	114±34	110±35	0.41
Creatinine, mg/dL	0.85±0.36	0.85±0.33	1.00
Uric acid, mg/dL	5.3±1.2	5.4±1.1	0.88
Glucose, mg/dL	118±22	189±72	<0.001
Hemoglobin A1c, %	5.9±0.4	9.0±1.2	<0.001
Medical history, n (%)			
Hypertension	62 (66.7)	65 (69.9)	0.64
Dyslipidemia	65 (69.9)	67 (72.0)	0.75
CVD, n (%)	33 (35.5)	39 (41.9)	0.37
Current Smoking, n(%)	25 (26.9)	27 (29.0)	0.74
Medication, n (%)			
Antihypertensive drugs	54 (58.1)	59 (63.4)	0.45
Lipid-lowering drugs	43 (46.2)	43 (46.2)	1.00
Antidiabetic drugs	80 (86.0)	73 (78.5)	0.18

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 7. Clinical Characteristics of Patients with Type 2 Diabetes Not Taking Antidiabetic Drugs

Variables	Total (n=349)	HbA1c <6.5% (n=101)	HbA1c ≥6.5% (n=248)	P value
Age, yr	61±10	66±10	60±10	<0.001
Gender, men/women	245/104	59/42	186/62	0.002
Body mass index, kg/m^2	25.4±4.2	24.6±4.1	25.7±4.3	0.03
Heart rate, bpm	69±11	70±11	68±11	0.06
Systolic blood pressure, mmHg	133±17	128±18	135±16	<0.001
Diastolic blood pressure, mmHg	80±11	77±12	82±10	<0.001
Total cholesterol, mg/dL	199±39	186±33	204±40	<0.001
Triglycerides, mg/dL	169±139	133±82	183±154	0.002
HDL-C, mg/dL	54±15	57±15	52±15	0.005
LDL-C, mg/dL	116±32	110±30	119±32	0.02
Creatinine, mg/dL	0.8±0.3	0.85±0.37	0.79±0.20	0.07
Uric acid, mg/dL	5.8±1.5	6.0±1.7	5.7±1.5	0.10
Glucose, mg/dL	137±46	119±28	143±50	<0.001
Hemoglobin A1c, %	6.8±1.0	5.9±0.4	7.2±1.0	<0.001
Medical history, n (%)				
Hypertension	266 (76.2)	75 (74.3)	191 (77.0)	0.58
Dyslipidemia	275 (78.8)	79 (78.2)	196 (79.0)	0.87
CVD, n (%)	79 (22.6)	27 (26.7)	52 (21.0)	0.24
Current Smoking, n (%)	79 (22.6)	20 (19.8)	59 (23.8)	0.37
Medication, n (%)				
Antihypertensive drugs	217 (62.2)	78 (77.2)	139 (56.1)	<0.001
Lipid-lowering drugs	144 (41.3)	59 (58.4)	85 (34.3)	<0.001
Antidiabetic drugs	0 (0)	0 (0)	0 (0)	

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 8. Univariate Analysis of Relationships among FMD, HbA1c Level and Variables in Patients with Type 2 Diabetes Not Taking Antidiabetic Drugs

Variables	FMD		HbA1c	
	r	P value	r	P value
Age, yr	-0.24	<0.001	-0.2	<0.001
Body mass index, kg/m^2	0.09	0.08	0.06	0.28
Heart rate, bpm	0.05	0.33	-0.01	0.82
Systolic blood pressure, mmHg	0.10	0.048	0.17	0.001
Diastolic blood pressure, mmHg	0.19	<0.001	0.12	0.02
Total cholesterol, mg/dL	0.02	0.66	0.22	<0.001
Triglycerides, mg/dL	-0.02	0.64	0.23	<0.001
HDL-C, mg/dL	-0.05	0.30	-0.19	<0.001
LDL-C, mg/dL	0.03	0.59	0.14	0.01
Creatinine, mg/dL	-0.03	0.62	-0.07	0.20
Uric acid, mg/dL	0.08	0.15	-0.10	0.07
Glucose, mg/dL	-0.08	0.12	0.70	<0.001
HbA1c, %	0.05	0.40		
FMD, %			0.05	0.40
NID, %	0.36	<0.0001	-0.02	0.78

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 9. Clinical Characteristics of Type 2 Diabetes Patients with HbA1c of <6.5% and with HbA1c of 6.5-6.9%

Variables	HbA1c <6.5% (n=49)	HbA1c 6.5-6.9% (n=49)	P value
Age, yr	64±9	66±7	0.29
Gender, men/women	29/20	26/23	0.54
Body mass index, kg/m^2	25.3±3.7	24.8±3.6	0.51
Heart rate, bpm	69±9	68±10	0.5
Systolic blood pressure, mmHg	131±17	129±16	0.46
Diastolic blood pressure, mmHg	78±11	76±9	0.30
Total cholesterol, mg/dL	189±35	190±28	0.95
Triglycerides, mg/dL	126±48	132±86	0.66
HDL-C, mg/dL	56±13	58±16	0.47
LDL-C, mg/dL	112±30	108±24	0.52
Creatinine, mg/dL	0.79±0.22	0.76±0.18	0.49
Uric acid, mg/dL	5.6±1.2	5.3±1.3	0.32
Glucose, mg/dL	117±18	124±22	0.14
Hemoglobin A1c, %	5.8±0.4	6.7±0.2	<0.001
Medical history, n (%)			
Hypertension	39 (79.6)	39 (79.6)	1.00
Dyslipidemia	37 (75.5)	40 (81.6)	0.46
CVD, n (%)	12 (24.5)	12 (24.5)	1.00
Medication, n (%)			
Antihypertensive drugs	39 (79.6)	36 (73.4)	0.47
Lipid-lowering drugs	29 (59.2)	30 (61.2)	0.84
Antidiabetic drugs	0 (0)	0 (0)	
Current Smoking, n (%)	12 (24.5)	10 (20.4)	0.63

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 10. Clinical Characteristics of Type 2 Diabetes Patients with HbA1c of <6.5% and with HbA1c of 7.0-7.9%

Variables	HbA1c <6.5% (n=29)	HbA1c 7.0-7.9% (n=29)	P value
Age, yr	63±10	65±8	0.37
Gender, men/women	19/10	20/9	0.78
Body mass index, kg/m^2	24.9±3.8	24.8±3.9	0.91
Heart rate, bpm	70±10	68±11	0.4
Systolic blood pressure, mmHg	133±17	134±14	0.74
Diastolic blood pressure, mmHg	80±12	81±8	0.78
Total cholesterol, mg/dL	189±31	183±39	0.51
Triglycerides, mg/dL	168±116	146±143	0.51
HDL-C, mg/dL	49±12	51±15	0.47
LDL-C, mg/dL	114±28	108±32	0.48
Creatinine, mg/dL	0.80±0.24	0.78±0.22	0.68
Uric acid, mg/dL	5.7±1.4	5.4±1.5	0.40
Glucose, mg/dL	119±23	136±32	0.02
Hemoglobin A1c, %	5.8±0.4	7.3±0.3	<0.001
Medical history, n (%)			
Hypertension	25 (86.2)	27 (93.1)	0.39
Dyslipidemia	23 (79.3)	23 (79.3)	1.00
CVD, n (%)	8 (27.6)	9 (31.0)	0.77
Current Smoking, n (%)	8 (27.6)	5 (17.2)	0.34
Medication, n (%)			
Antihypertensive drugs	24 (82.7)	19 (65.5)	0.13
Lipid-lowering drugs	18 (62.1)	15 (51.7)	0.43
Antidiabetic drugs	0 (0)	0 (0)	

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Table 11. Clinical Characteristics of Type 2 Diabetes Patients with HbA1c of <6.5% and with HbA1c of ≥8.0%

Variables	HbA1c <6.5% (n=20)	HbA1c ≥8.0% (n=20)	P value
Age, yr	59±11	58±11	0.82
Gender, men/women	15/5	16/4	0.71
Body mass index, kg/m^2	24.9±4.5	25.4±4.6	0.71
Heart rate, bpm	72±10	67±8	0.11
Systolic blood pressure, mmHg	138±20	136±21	0.80
Diastolic blood pressure, mmHg	84±14	82±11	0.65
Total cholesterol, mg/dL	199±40	213±40	0.31
Triglycerides, mg/dL	149±73	203±142	0.13
HDL-C, mg/dL	56±16	48±14	0.10
LDL-C, mg/dL	126±38	125±32	0.89
Creatinine, mg/dL	0.76±0.16	0.85±0.34	0.30
Uric acid, mg/dL	5.8±1.4	6.0±1.7	0.67
Glucose, mg/dL	116±17	212±63	<0.001
Hemoglobin A1c, %	6.0±0.4	9.4±1.2	<0.001
Medical history, n (%)			
Hypertension	14 (70.0)	15 (75.0)	0.72
Dyslipidemia	13 (65.0)	16 (80.0)	0.29
CVD, n (%)	5 (25.0)	3 (15.0)	0.43
Medication, n (%)			
Antihypertensive drugs	12 (60.0)	11 (55.0)	0.75
Lipid-lowering drugs	5 (25.0)	4 (20.0)	0.71
Antidiabetic drugs	0 (0)	0 (0)	
Current Smoking, n (%)	6 (30.0)	4 (20.0)	0.47

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; NID, nitroglycerine-induced vasodilation.

Online Supplementary Figures

Figure 1

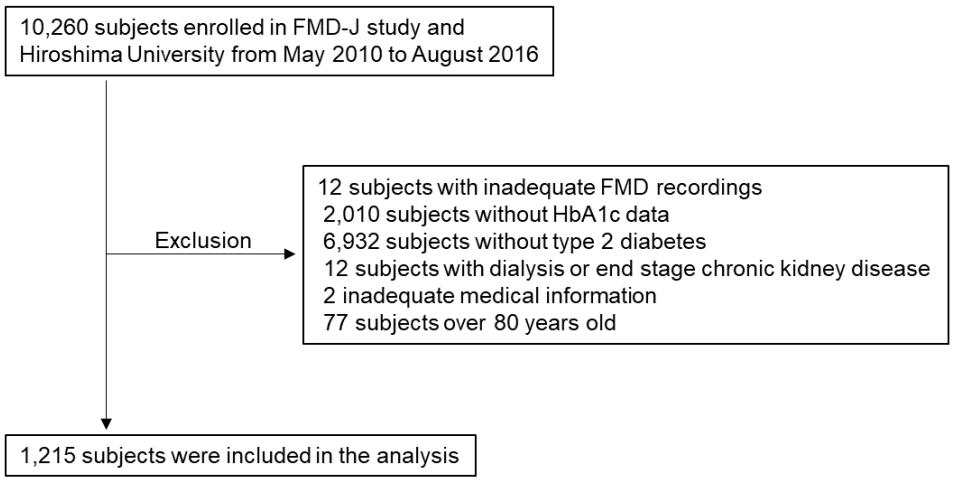

Figure 1. Flow chart of the study design.

Figure 2

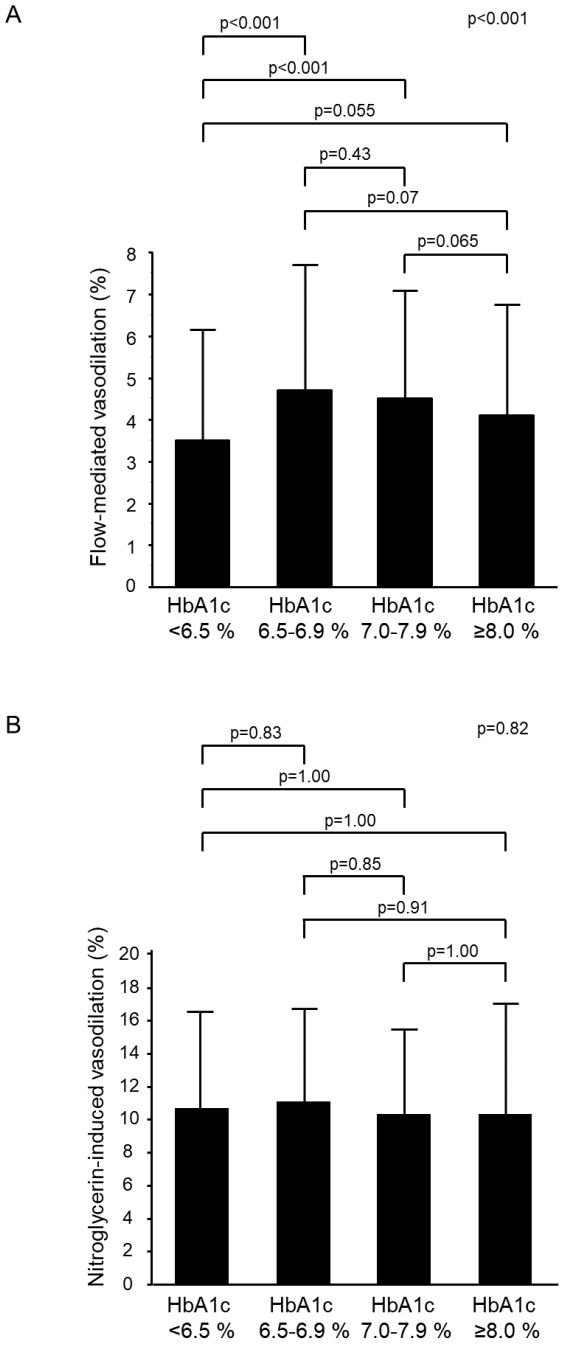

Figure 2. Bar graphs show flow-mediated vasodilation (A) and nitroglycerine-induced vasodilation (B) in 4 groups according to HbA1c levels.

Figure 3

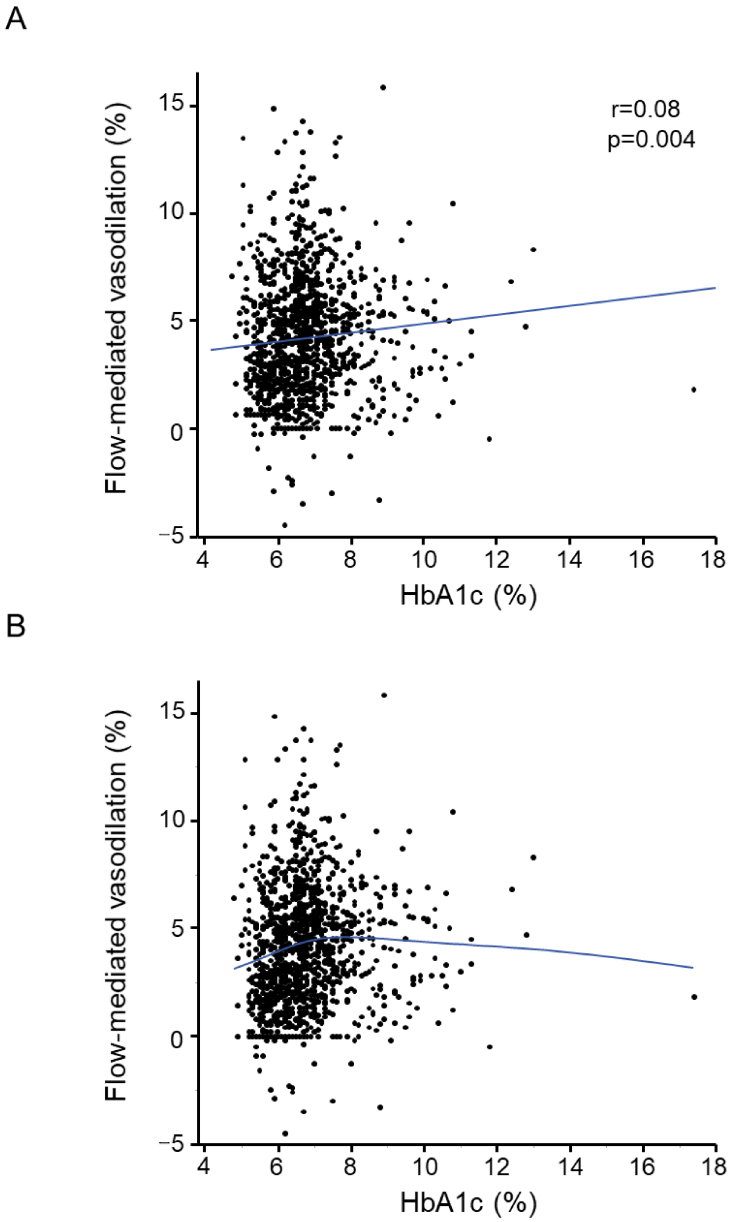

Figure 3. Scatter plots show the relationship between flow-mediated vasodilation and serum HbA1c levels in all patients (A) and locally weighted regression smoothing (Lowess) plot (B)

Figure 4

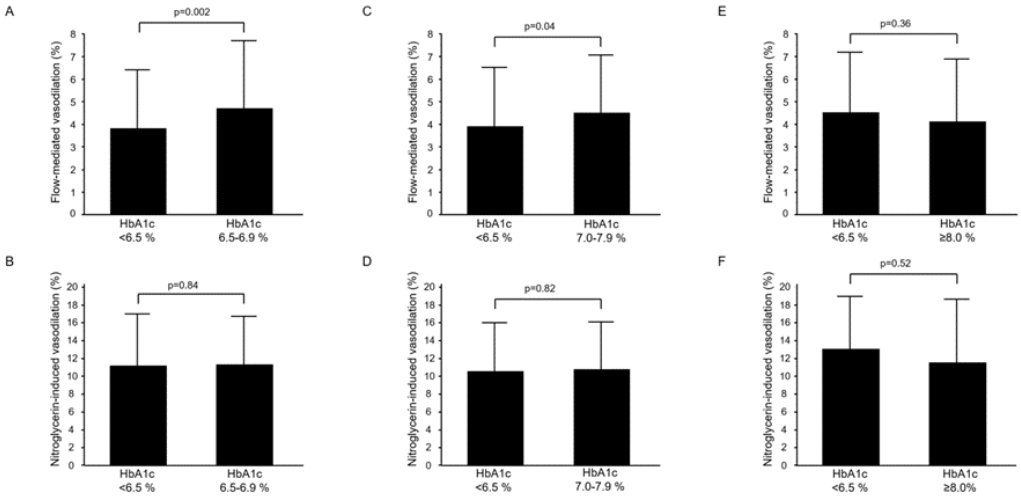

Figure 4. Bar graphs show flow-mediated vasodilation (A) and nitroglycerine-induced vasodilation (B) in patients with HbA1c of <6.5% and patients with HbA1c of 6.5%-6.9%, flow-mediated vasodilation (C) and nitroglycerine-induced vasodilation (D) in patients with HbA1c of <6.5% and patients with HbA1c of 7.0%-7.9%, and flow-mediated vasodilation (E) and nitroglycerine-induced vasodilation (F) in patients with HbA1c of <6.5% and patients with HbA1c of ≥8.0% in a propensity score-matched population.

Figure 5

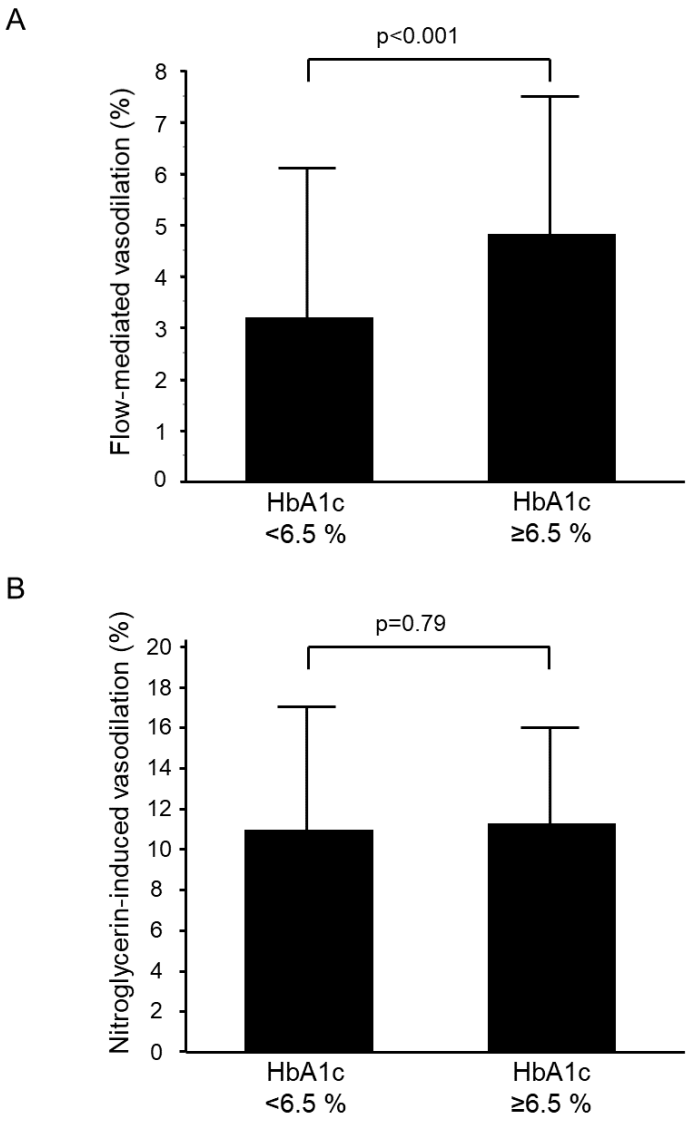

Figure 5. Bar graphs show flow-mediated vasodilation (A) and nitroglycerine-induced vasodilation (B) in patients with HbA1c of <6.5% and patients with HbA1c of ≥6.5% who were not receiving antidiabetic drug treatment.

Figure 6

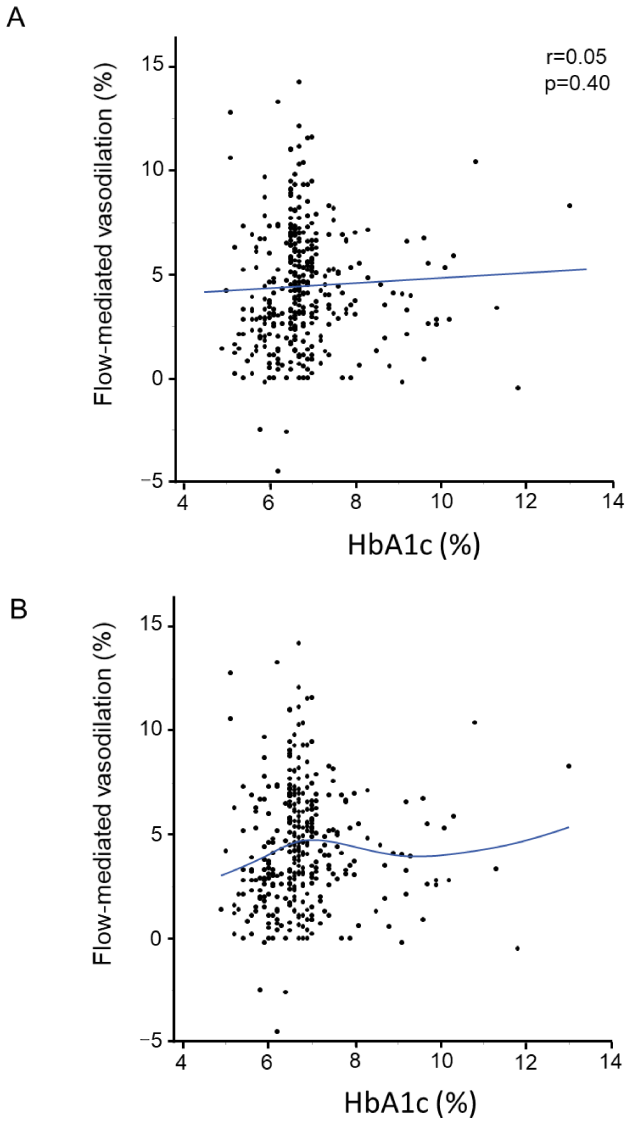

Figure 6. Scatter plots show the relationship between flow-mediated vasodilation and serum HbA1c levels in patients not receiving antidiabetic drug treatment (A) and locally weighted regression smoothing (Lowess) plot (B）.

Figure 7

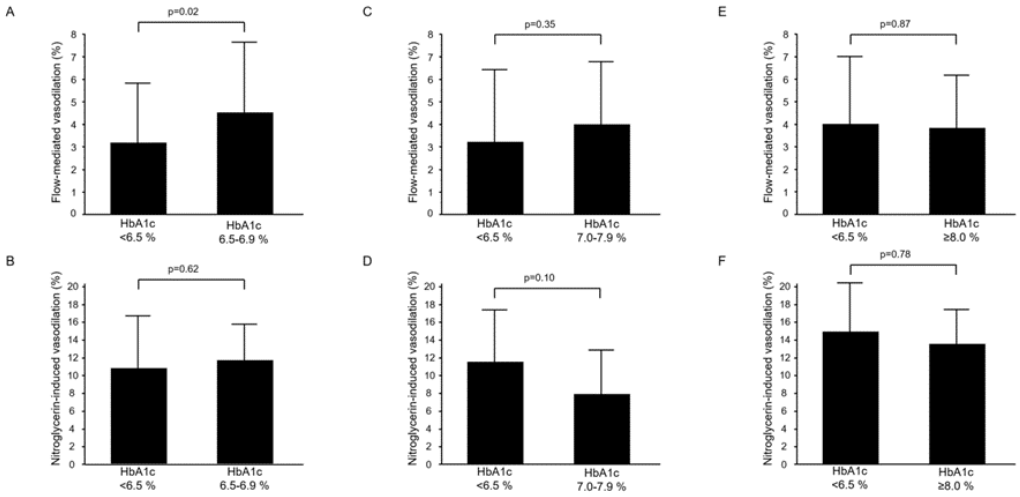

Figure 7. Bar graphs show flow-mediated vasodilation (A) and nitroglycerine-induced vasodilation (B) in patients with HbA1c of <6.5% and patients with HbA1c of 6.5%-6.9% not receiving antidiabetic drug treatment, flow-mediated vasodilation (C) and nitroglycerine-induced vasodilation (D) in patients with HbA1c of <6.5% and patients with HbA1c of 7.0%-7.9% not receiving antidiabetic drug treatment, and flow-mediated vasodilation (E) and nitroglycerine-induced vasodilation (F) in patients with HbA1c of <6.5% and patients with HbA1c of ≥8.0% not receiving antidiabetic drug treatment antidiabetic drugs treatment in a propensity score-matched population.