Journal of the American Heart Association

ORIGINAL RESEARCH

Coronary Plaque Characteristics and Underlying Mechanism of Acute Coronary Syndromes in Different Age Groups of Patients With Diabetes

Keishi Suzuki, MD, PhD; Takayuki Niida, MD, PhD; Haruhito Yuki, MD; Daisuke Kinoshita, MD, PhD; Daichi Fujimoto, MD, PhD; Hang Lee, PhD; Iris McNulty, RN; Masamichi Takano, MD, PhD; Sunao Nakamura, MD, PhD; Tsunekazu Kakuta, MD, PhD; Kyoichi Mizuno, MD, PhD; Ik-Kyung Jang, MD, PhD

BACKGROUND: High cardiovascular mortality has been reported in young patients with diabetes. However, the underlying pathology in different age groups of patients with diabetes has not been studied.

METHODS AND RESULTS: The aim of this study was to investigate the plaque characteristics and underlying pathology of acute coronary syndrome in different age groups of patients with or without diabetes in a large cohort. Patients who presented with acute coronary syndrome and underwent preintervention optical coherence tomography imaging were included. Culprit plaque was classified as plaque rupture, plaque erosion, or calcified plaque and stratified into 5 age groups. Plaque characteristics including features of vulnerability were examined by optical coherence tomography. Among 1394 patients, 482 (34.6%) had diabetes. Patients with diabetes, compared with patients without diabetes, had a higher prevalence of lipid-rich plaque (71.2% versus 64.8%, P=0.016), macrophage (72.0% versus 62.6%, P<0.001), and cholesterol crystal (27.6% versus 19.7%, P<0.001). Both diabetes and nondiabetes groups showed a decreasing trend in plaque erosion with age (patients with diabetes, P=0.020; patients without diabetes, P<0.001). Patients without diabetes showed an increasing trend with age in plaque rupture (P=0.004) and lipid-rich plaque (P=0.018), whereas patients with diabetes had a high prevalence of these vulnerable features at an early age that remained high across age groups.

CONCLUSIONS: Patients without diabetes showed an increasing trend with age in plaque rupture and lipid-rich plaque, whereas patients with diabetes had a high prevalence of these vulnerable features at an early age. These results suggest that atherosclerotic vascular changes with increased vulnerability start at a younger age in patients with diabetes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT04523194, NCT03479723. URL: https://www.umin.ac.jp/ctr/. Unique identifier: UMIN000041692.

Key Words: acute coronary syndrome ■ age ■ diabetes ■ optical coherence tomography

Diabetes is an important independent risk factor for developing cardiovascular events.[1] In a recent large cohort study of >2 500 000 individuals, mortality was 2- to 3-fold higher among young or middle-aged patients with diabetes compared with patients without diabetes, and cardiovascular disease was a major contributing factor for mortality.[2] Pathology studies have demonstrated that patients

Correspondence to: Ik-Kyung Jang, MD, PhD, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, GRB 800, Boston, MA 02114. Email: ijang@mgh.harvard.edu

This article was sent to Hani Jneid, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.031474

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The present study represents the largest series so far among the optical coherence tomography studies in patients with diabetes.
- Our results demonstrate that patients with diabetes have a high prevalence of vulnerable features in coronary plaques from an early age.

What Are the Clinical Implications?

- Our results suggest that atherosclerotic vascular changes with increased vulnerability start at a young age in patients with diabetes.
- More aggressive risk management is particularly important in young patients with diabetes.

with diabetes have coronary plaques with larger necrotic cores and advanced coronary artery calcification.[3] However, plaque characteristics among different age groups in living patients with diabetes have not been systematically investigated. Optical coherence tomography (OCT) offers a direct assessment of plaque characteristics, including features of vulnerability in living patients. Recently, several studies have reported plaque characteristics in patients with diabetes using OCT; however, the number of patients in those reports was small.[4–9] The aim of the current study was to investigate the plaque characteristics and underlying pathology among different age groups of patients with acute coronary syndrome (ACS) with or without diabetes in a large cohort.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Patients with ACS who underwent preintervention OCT imaging of the culprit lesion were identified from the Predictor (Identification of Predictors for Coronary Plaque Erosion in Patients With Acute Coronary Syndrome) study (NCT03479723), Tsuchiura Kyodo General Hospital Coronary Imaging Collaboration (NCT04523194), and New Tokyo Hospital study (Optical Coherence Tomography for In Vivo Detection of Layered Plaque: A Prospective Study) (UMIN000041692). The Predictor study is an international, multicenter registry study that included patients with ACS undergoing OCT at 12 institutions in 7 countries (Japan, China, Italy, Belgium, United States, India, and Germany) from October 2008 to August 2019. The Tsuchiura Kyodo General Hospital Coronary Imaging Collaboration is a single-center study that included patients with ACS undergoing OCT from January 2011 to July 2020. The New Tokyo Hospital study is a single-center study that included patients with ACS undergoing OCT from October 2020 to April 2021. Exclusion criteria included incomplete data, stent thrombosis/in-stent restenosis, graft failure, indeterminate culprit lesion, poor image quality, postpercutaneous coronary intervention OCT imaging only, and rare pathology other than plaque rupture, plaque erosion, or calcified plaque (Figure S1). In the final analysis, 1394 patients were included. The diagnosis of ACS was made according to the American Heart Association/American College of Cardiology guidelines[10,11] defined as ST-segment–elevation myocardial infarction (MI) or non–ST-segment–elevation ACS. Non–ST-segment–elevation ACS was defined as non–ST-segment–elevation MI or unstable angina pectoris. Culprit lesions and laboratory parameters were analyzed. In multivessel disease, the culprit lesion was defined as the one with the most severe stenosis or evidence of recent plaque disruption. Diabetes was defined by baseline medical history, glycohemoglobin ≥6.5%, or reported use of glucose-lowering medication. All registries were approved by each site's institutional review board and conducted according to the Helsinki Declaration. Waivers of consent were granted by each site's local institutional review board for the Predictor study and the Tsuchiura Kyodo General Hospital Coronary Imaging Collaboration, but written informed consent was obtained from subjects for the New Tokyo Hospital study.

OCT Analysis

OCT images were obtained using a frequency domain (C7/C8; OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN) or a time domain (M2/M3; Cardiology Imaging Systems, LightLab Imaging, Westford, MA) OCT system. OCT imaging was performed before coronary interventional procedures, except in cases of aspiration thrombectomy for occlusive thrombus precluding visualization of underlying plaque. All OCT images were submitted to the Cardiology Laboratory for Integrative Physiology and Imaging at Massachusetts General Hospital and were analyzed by investigators blinded to patient data. Plaque rupture was defined by fibrous cap discontinuity with cavity formation.[12] Plaque erosion was identified as a culprit plaque with an intact fibrous cap with or without attached thrombus.[12] Calcified plaque was defined by the identification of superficial substantive calcium at the culprit site without signs of ruptured lipid plaque.[12] Detailed descriptions of further OCT analysis are in Data S1. Plaque characteristics were compared between patients with and without diabetes. Plaque characteristics were also compared among different

age groups separately in patients with and without diabetes.

Statistical Analysis

Continuous data are expressed as mean with SD or median with interquartile range. Continuous variables were compared using the Student *t* test or, if not normally distributed, using the Mann–Whitney *U* test. Categorical data were expressed as absolute frequencies and percentages and compared using the χ^2 test. Patients were placed into 5 groups based on their age (years): <45, 45 to 54, 55 to 64, 65 to 74, and ≥75.[13] The Cochran–Armitage trend test was applied for trend analyses of categorical variables along the age groups, and the Jonckheere–Terpstra trend test was applied for continuous variables. A 2-sided *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 28.0 (SPSS, Inc, Chicago, IL) and R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The baseline characteristics of patients are summarized in Table 1. Among 1394 patients, 34.6% (n=482) had diabetes. The mean age was 64±13 years, and patients with diabetes were older than patients without diabetes. Patients with diabetes had a higher prevalence of prior MI, prior percutaneous coronary intervention, hypertension, dyslipidemia, and chronic kidney disease. Although patients with diabetes were more frequently on statins and had lower levels of low-density lipoprotein cholesterol, the level of hs-CRP (high-sensitivity C-reactive protein) was significantly higher in this group.

Table 1. Baseline Characteristics

	With diabetes (n=482)	Without diabetes (n=912)	*P* value
Age, y	65.2±11.4	63.5±13.0	0.011
Age subgroups, y			
<45, n (%)	22 (4.6)	76 (8.3)	
45–54, n (%)	67 (13.9)	161 (17.7)	
55–64, n (%)	129 (26.8)	216 (23.7)	
65–74, n (%)	155 (32.2)	267 (23.7)	
≥75, n (%)	109 (22.6)	192 (21.1)	
Male sex, n (%)	385 (79.9)	731 (80.2)	0.933
Clinical presentation			0.206
ST-segment–elevation myocardial infarction, n (%)	227 (47.1)	462 (50.7)	
Non–ST-segment–elevation acute coronary syndromes, n (%)	255 (52.9)	450 (49.3)	
Prior myocardial infarction, n (%)	55 (11.4)	57 (6.3)	<0.001
Prior percutaneous coronary intervention, n (%)	60 (12.4)	69 (7.6)	0.003
Hypertension, n (%)	327 (67.8)	542 (59.4)	0.002
Dyslipidemia, n (%)	334 (69.3)	576 (63.2)	0.022
Chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), n (%)	85 (18.1)	99 (11.1)	<0.001
Current smoking, n (%)	156 (32.4)	365 (40.2)	0.004
Laboratory data			
Total cholesterol, mg/dL	181.0 (154.0–211.0)	191.0 (163.0–219.0)	0.002
Low-density lipoprotein cholesterol, mg/dL	114.0 (90.0–145.0)	120.0 (97.5–147.4)	0.007
High-density lipoprotein cholesterol, mg/dL	42.0 (37.0–49.0)	45.0 (38.6–55.0)	<0.001
Triglyceride, mg/dL	108.0 (69.0–167.9)	94.0 (57.0–145.5)	<0.001
Hemoglobin A1c, %	7.0 (6.5–7.9)	5.6 (5.4–5.9)	<0.001
High-sensitivity C-reactive protein, mg/dL	0.19 (0.07–0.60)	0.11 (0.06–0.41)	0.021
Medication at admission			
Aspirin, n (%)	93 (22.9)	145 (19.6)	0.193
Statin, n (%)	124 (30.6)	158 (21.4)	<0.001
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, n (%)	164 (34.0)	166 (18.2)	<0.001

Values are n (%), mean±SD, or median (interquartile range).

OCT Findings in Patients With and Without Diabetes

Quantitative and qualitative OCT characteristics are shown in Table 2. Patients with diabetes, compared with patients without diabetes, had a lower prevalence of plaque erosion and a higher prevalence of lipid-rich plaque, macrophage, cholesterol crystal, and calcification.

Plaque Phenotype Among Different Age Groups in Patients With and Without Diabetes

Plaque phenotype among different age groups is shown in Figure 1 and Tables 3 and 4. Both patients with and without diabetes showed a decreasing trend in plaque erosion and an increasing trend in calcified plaque with age. Patients without diabetes showed an increasing trend with age in plaque rupture (from 30.3% in age <45 years to 58.3% in age ≥75 years [*P*=0.004]), whereas patients with diabetes had a high prevalence of plaque rupture at an early age that plateaued across age groups (from 50.0% in age <45 years to 47.7% in age ≥75 years [*P*=0.907]).

Plaque Characteristics Among Different Age Groups in Patients With and Without Diabetes

Plaque characteristics found in the age-sorted groups are shown in Tables 3 and 4. Patients without diabetes showed an increasing trend with age in lipid-rich plaque (from 50.0% in age <45 years to 70.8% in age ≥75 years [*P*=0.018]), whereas patients with diabetes had a high prevalence of lipid-rich plaque at an early age that plateaued across age groups (from 77.3% in age <45 years to 72.5% in age ≥75 years [*P*=0.497]) (Figure 2 and 3). Patients without diabetes had a decreasing trend in minimum lumen area, whereas patients with diabetes had a small lumen area throughout different age groups starting at an early age. Patients with diabetes showed a decreasing trend with age for the presence of macrophage. In both patients with and without diabetes, the prevalence of calcification increased with age.

DISCUSSION

The collection of a large number of ACS cases provided an opportunity to study detailed OCT features of coronary plaques among different age groups in patients with and without diabetes. The current study demonstrated that (1) patients with diabetes had a higher prevalence of OCT features of plaque vulnerability than patients without diabetes; (2) both patients with and without diabetes showed a decreasing trend in plaque erosion with age; (3) patients without diabetes had an increasing trend with age in plaque rupture and lipid-rich plaque, whereas patients with diabetes had a high prevalence of these vulnerable features at early age that plateaued across all age groups (Figure 3).

Table 2. OCT Findings Between Patients With and Without Diabetes

	With diabetes (n=482)	Without diabetes (n=912)	*P* value
Phenotype			
Plaque rupture, n (%)	251 (52.1)	432 (47.4)	0.095
Plaque erosion, n (%)	168 (34.9)	392 (43.0)	0.003
Calcified plaque, n (%)	63 (13.1)	88 (9.6)	0.051
Qualitative			
Lipid-rich plaque, n (%)	343 (71.2)	591 (64.8)	0.016
Thin-cap fibroatheroma, n (%)	187 (38.8)	316 (34.6)	0.125
Macrophage, n (%)	347 (72.0)	571 (62.6)	<0.001
Cholesterol crystal, n (%)	133 (27.6)	180 (19.7)	<0.001
Calcification, n (%)	251 (52.1)	373 (40.9)	<0.001
Quantitative			
Minimum lumen area, mm^2	1.00 (0.79–1.49)	1.08 (0.80–1.73)	0.066
Reference lumen area mm^2	6.59 (4.80–8.20)	6.77 (5.19–8.71)	0.005
Fibrous cap thickness, μm	63.0 (53.0–97.0)	63.0 (50.0–100.0)	0.783
Mean lipid arc	176.0 (147.0–212.0)	173.0 (144.0–209.0)	0.219
Lipid length, mm	9.9 (7.5–12.7)	9.2 (7.0–12.8)	0.235
Lipid index	1791.4 (1203.3–2548.0)	1659.0 (1060.8–2405.7)	0.147

Values are n (%), or median (interquartile range). OCT indicates optical coherence tomography.

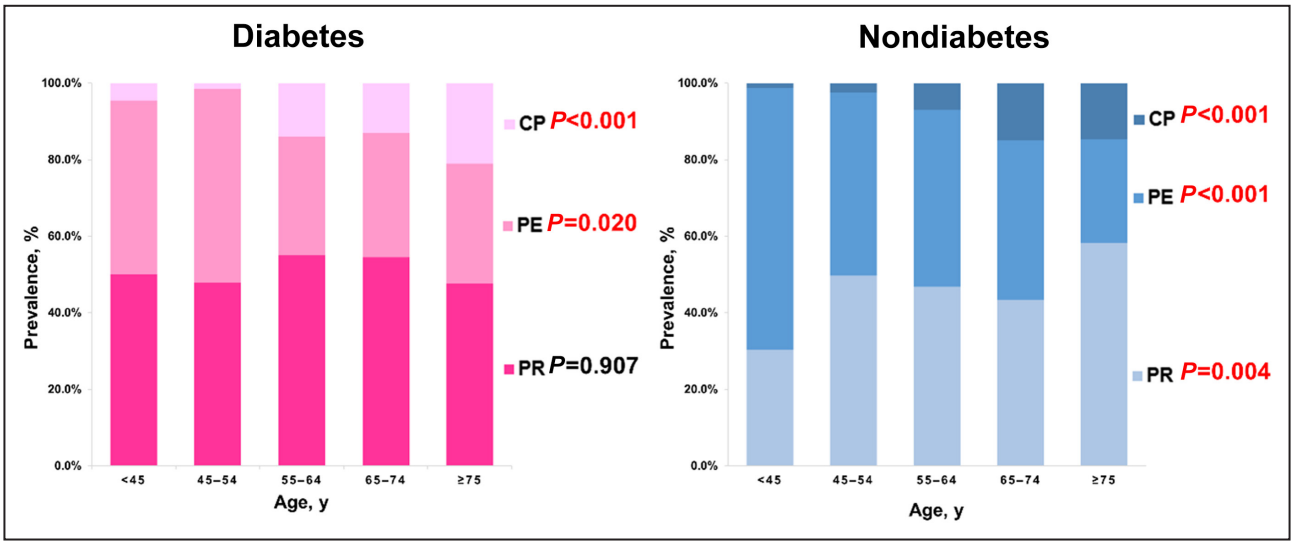

Figure 1. Plaque phenotype among different age groups in patients with and without diabetes.
Both patients with and without diabetes showed a decreasing trend in plaque erosion and increasing trend in calcified plaque with age. Patients without diabetes showed an increasing trend with age in plaque rupture, whereas patients with diabetes had a high prevalence of plaque rupture at an early age, which plateaued across age groups. *P* values are for the Cochran–Armitage trend test for categorical data. CP indicates calcified plaque; PE, plaque erosion; and PR, plaque rupture.

Plaque Characteristics in Patients With Diabetes

Lipid-rich plaque is considered a precursor of rupture, and, when disrupted, exposes thrombogenic substrate to circulation.[14] A previous OCT study demonstrated that lipid-rich plaque was an independent predictor of cardiac events.[15] In pathology studies, atherosclerotic plaques in patients with diabetes had larger necrotic cores and higher levels of inflammation characterized

Table 3. OCT Findings in Different Age Groups of Patients With Diabetes

Age, y	<45 (n=22)	45–54 (n=67)	55–64 (n=129)	65–74 (n=155)	≥75 (n=109)	*P* value
Phenotype						
Plaque rupture	11 (50.0)	32 (47.8)	71 (55.0)	85 (54.8)	52 (47.7)	0.907
Plaque erosion	10 (45.5)	34 (50.7)	40 (31.0)	50 (32.3)	34 (31.2)	0.020
Calcified plaque	1 (4.5)	1 (1.5)	18 (14.0)	20 (12.9)	23 (21.1)	<0.001
Qualitative						
Lipid-rich plaque	17 (77.3)	45 (67.2)	87 (67.4)	115 (74.2)	79 (72.5)	0.497
Thin-cap fibroatheroma	12 (54.5)	24 (35.8)	44 (34.1)	67 (43.2)	40 (36.7)	0.825
Macrophage	18 (81.8)	52 (77.6)	100 (77.5)	105 (67.7)	72 (66.1)	0.012
Cholesterol crystal	5 (22.7)	19 (28.4)	41 (31.8)	41 (26.5)	27 (24.8)	0.567
Calcification	5 (22.7)	24 (35.8)	66 (51.2)	84 (54.2)	72 (66.1)	<0.001
Quantitative						
Minimum lumen area, mm^2	1.18 (0.80–2.19)	1.00 (0.71–1.66)	1.03 (0.80–1.50)	0.90 (0.80–1.39)	1.01 (0.80–1.50)	0.822
Reference lumen area mm^2	7.59 (5.20–8.75)	6.97 (4.70–7.99)	6.51 (5.00–8.10)	6.74 (4.80–8.55)	6.08 (4.65–7.94)	0.230
Fibrous cap thickness, μm	60.0 (53.0–80.0)	63.0 (50.0–100.0)	65.0 (55.0–90.0)	60.0 (52.0–97.0)	63.0 (57.0–99.0)	0.510
Mean lipid arc	190.0 (153.0–216.0)	183.0 (158.6–209.0)	175.5 (148.0–209.4)	168.0 (146.0–212.0)	174.0 (148.5–218.5)	0.628
Lipid length, mm	10.0 (6.9–13.8)	9.4 (5.5–11.5)	9.5 (7.1–11.9)	9.8 (7.5–12.2)	10.4 (8.2–13.9)	0.051
Lipid index	2160.0 (1252.8–2899.8)	1687.6 (823.5–2548.0)	1763.0 (1207.6–2290.9)	1798.2 (1237.7–2384.0)	1855.0 (1303.8–2725.6)	0.288

Values are n (%), or median (interquartile range). *P* values are for the Jonckheere–Terpstra trend test for continuous variables or the Cochran–Armitage trend test for categorical data. OCT indicates optical coherence tomography.

Table 4. OCT Findings in Different Age Groups of Patients Without Diabetes

Age, y	<45 (n=76)	45–54 (n=161)	55–64 (n=216)	65–74 (n=267)	≥75 (n=192)	*P* value
Phenotype						
Plaque rupture	23 (30.3)	80 (49.7)	101 (46.8)	116 (43.4)	112 (58.3)	0.004
Plaque erosion	52 (68.4)	77 (47.8)	100 (46.3)	111 (41.6)	52 (27.1)	<0.001
Calcified plaque	1 (1.3)	4 (2.5)	15 (6.9)	40 (15.0)	28 (14.6)	<0.001
Qualitative						
Lipid-rich plaque	38 (50.0)	108 (67.1)	136 (63.0)	173 (64.8)	136 (70.8)	0.018
Thin-cap fibroatheroma	22 (28.9)	69 (42.9)	68 (31.5)	82 (30.7)	75 (39.1)	0.915
Macrophage	37 (48.7)	111 (68.9)	138 (63.9)	166 (62.2)	119 (62.0)	0.681
Cholesterol crystal	11 (14.5)	31 (19.3)	45 (20.8)	49 (18.4)	44 (22.9)	0.241
Calcification	13 (17.1)	60 (37.3)	70 (32.4)	121 (45.3)	109 (56.8)	<0.001
Quantitative						
Minimum lumen area, mm^2	1.60 (0.95–3.4)	1.10 (0.76–1.88)	1.08 (0.77–1.84)	1.00 (0.80–1.57)	1.10 (0.80–1.46)	0.002
Reference lumen area mm^2	8.26 (6.82–10.42)	7.42 (5.43–8.62)	6.61 (5.34–8.62)	6.43 (5.00–8.50)	6.40 (4.91–8.33)	<0.001
Fibrous cap thickness, μm	60.0 (47.0–87.0)	63.0 (53.0–90.0)	67.0 (50.0–99.0)	73.0 (59.0–110.0)	63.0 (50.0–100.0)	0.142
Mean lipid arc	172.9 (138.0–196.0)	181.5 (147.0–222.0)	175.0 (145.0–209.0)	161.0 (137.0–195.5)	181.5 (153.0–213.4)	0.958
Lipid length, mm	9.3 (7.5–13.2)	7.9 (6.7–12.5)	9.1 (6.9–12.2)	9.3 (6.7–12.3)	10.0 (8.0–13.4)	0.010
Lipid index	1584.4 (926.6–2367.4)	1487.9 (986.1–2502.6)	1607.2 (1084.1–2394.7)	1628.0 (1022.5–2206.6)	1878.4 (1258.4–2639.5)	0.056

Values are n (%), or median (interquartile range). *P* values are for the Jonckheere–Terpstra trend test for continuous variables or the Cochran–Armitage trend test for categorical data. OCT indicates optical coherence tomography.

as T lymphocytes.[16,17] Intravascular ultrasound study also showed that patients with diabetes had a larger necrotic core volume than patients without diabetes.[18]

Several OCT studies compared culprit plaques between patients with and without diabetes.[4–9] However, those studies reported only a small number of patients

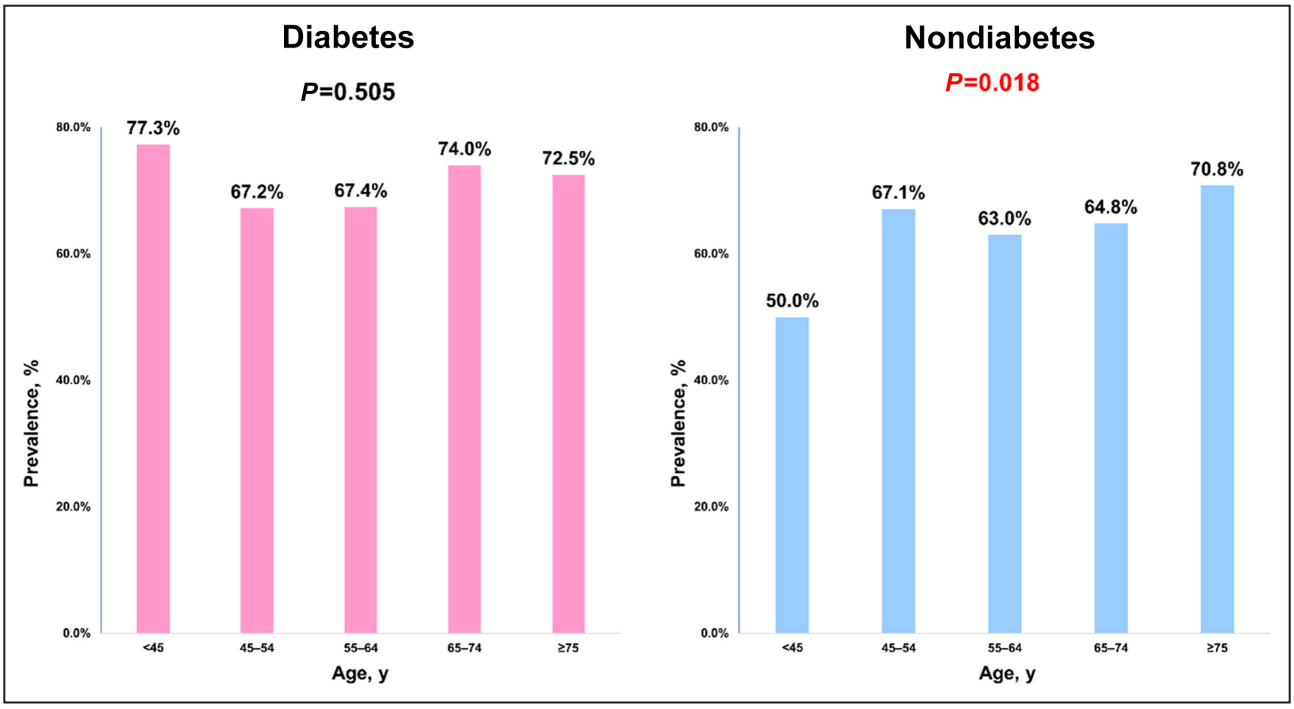

Figure 2. The prevalence of lipid-rich plaque in different age groups.
Patients without diabetes showed an increasing trend with age in lipid-rich plaque, whereas patients with diabetes had a high prevalence of lipid-rich plaque at an early age, which plateaued across age groups. *P* values are for the Cochran–Armitage trend test for the prevalence of lipid-rich plaque.

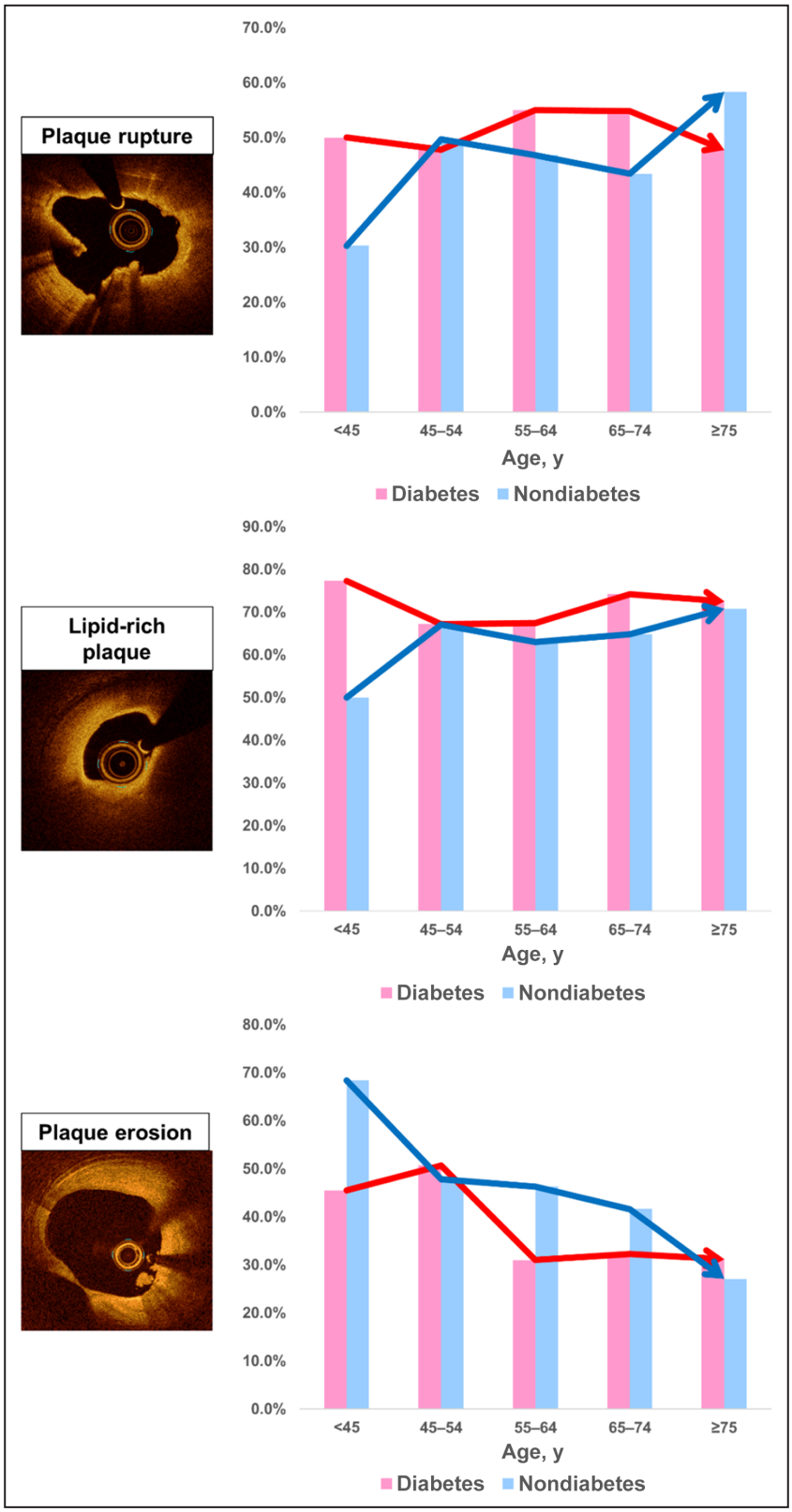

Figure 3. Age and plaque characteristics in patients with and without diabetes. Patients without diabetes had an increasing trend with age in plaque rupture and lipid-rich plaque, whereas patients with diabetes had a high prevalence of these vulnerable features at an early age that plateaued across age groups. Both patients with and without diabetes showed a decreasing trend in plaque erosion with age.

with diabetes (n<100), and findings were inconsistent regarding the prevalence of lipid-rich plaque. To the best of our knowledge, the current report is the largest study (n=1394) comparing plaque characteristics between patients with and without diabetes. Our study demonstrated that patients with diabetes had a higher prevalence of lipid-rich plaque than patients without diabetes. This finding is in line with the study of Sheng et al that reported the higher prevalence of lipid-rich plaque among patients with diabetes compared with patients without diabetes.[9]

The potential biological mechanisms through which diabetes aggravates cardiovascular disease include the low-grade inflammation related to the metabolic changes.[19] Previous pathology studies have reported that coronary plaques from patients with diabetes had a larger area occupied by macrophages than those from patients without diabetes.[16,17] An increased number of macrophages was reported to be related to necrotic core expansion and plaque instability.[16] Our study also demonstrated that patients with diabetes had a higher prevalence of macrophages than patients without diabetes.

The current study demonstrated for the first time that patients with diabetes had a higher prevalence of cholesterol crystal than patients without diabetes. Cholesterol crystals have a proinflammatory role in plaque progression and macrophage activation by triggering macrophage to interleukin-1β secretion.[20] The crystallization could cause plaque rupture by mechanically piercing the fibrous cap.[21]

In our study, despite the fact that patients with diabetes had lower levels of low-density lipoprotein cholesterol and were more frequently on statins, hs-CRP levels and the prevalence of OCT features of plaque vulnerability were higher in patients with diabetes than in patients without diabetes. One previous study showed that hs-CRP was a predictor for risk of future cardiovascular events and death among patients receiving contemporary statins,[22] whereas several studies reported that colchicine, with its broad anti-inflammatory action, reduced cardiovascular risk.[23–25] Therefore, an anti-inflammatory agent such as colchicine may provide additional benefit to improve the prognosis of patients with diabetes with elevated hs-CRP.

Age and Plaque Characteristics in Patients With and Without Diabetes

Previous pathology and OCT studies have reported that patients with ACS and plaque erosion tended to be younger than those with plaque rupture.[26–30] In the present study, both patients with and without diabetes showed a decreasing trend in plaque erosion with age. A “2-hit scheme” has been proposed for the pathogenesis of plaque erosion.[31] The “first hit” is local flow perturbation leading to activation of endothelial Toll-like receptor 2 and subsequent damage of the endothelium. The “second hit” is the formation of a neutrophil extracellular trap resulting in occlusive thrombosis. This process is independent of chronic inflammation. This mechanism may explain the lack of difference in the trend of plaque erosion between patients with and without diabetes.

Vascular aging changes the function of the endothelium. Endothelial dysfunction includes reduced vasodilatory and antithrombotic properties, with an increase in oxidative stress and inflammatory cytokines[32,33] favoring atherogenesis and thrombosis predisposing to coronary artery disease.[34] A previous intravascular ultrasound study showed that plaque burden and necrotic core increased with age.[35] A previous OCT study demonstrated that the older group had a higher prevalence of plaque rupture and lipid-rich plaque than the younger group among patients with ST-segment–elevation MI.[27] The current study demonstrated for the first time that patients without diabetes showed an increasing trend with age in plaque rupture and lipid-rich plaque among 5 age groups.

There is increasing evidence of a high risk of cardiovascular events in young patients with diabetes.[2,36–40] A recent study compared mortality after MI between patients with and without diabetes, divided into 2 age groups. The relative risk of 3-year mortality was significantly higher in young patients than in their older counterparts.[41] However, no study has evaluated plaque characteristics within different age groups in patients with diabetes. The current study demonstrated for the first time that patients with diabetes had a high prevalence of plaque rupture and lipid-rich plaque at an early age that plateaued across age groups. Supporting these results, a previous study reported that young onset diabetes was associated with a high risk for glycemic progression.[42] Rapid decline in β-cell function in young onset diabetes explains the rapidly worsening progression of diabetic status and cardiovascular disease. In a previous study, β-cell function decreased by 20% to 35% per year in young onset diabetes, whereas it declined by roughly 7% per year in older onset diabetes.[43] Some evidence suggests the second phase of nutrient-induced insulin secretion might be compromised earlier in the pathogenic process in young patients with diabetes.[44,45] Our findings indicate that young patients with diabetes have a high level of plaque vulnerability. When plaque becomes disrupted, resulting in occlusive thrombosis, it may result in more extensive myocardial damage in the absence of preconditioning. These findings highlight the importance of even more aggressive risk modification in young patients with diabetes.

Limitations

Several limitations should be acknowledged. First, this study included a retrospective analysis of multicenter databases. Therefore, selection bias cannot be excluded. However, most patients were enrolled at institutions where OCT is routinely used. Second, OCT analysis can be compromised by massive thrombus. Therefore, if needed, thrombus aspiration was performed before OCT imaging, which could have altered the underlying plaque morphology. However, extreme care was exercised to not damage the underlying plaque. Third, 2 different OCT systems (frequency-domain and time-domain OCT) were used in the current study. Finally, we had limited information on diabetes-related characteristics, such as the type of diabetes, diabetic duration, and treatment.

CONCLUSIONS

Patients without diabetes showed an increasing trend with age in plaque rupture and lipid-rich plaque, whereas patients with diabetes had a high prevalence of these vulnerable features at an early age, and the level of vulnerability persisted across all age groups. These results suggest that atherosclerotic vascular changes with increased vulnerability start at young age in patients with diabetes.

ARTICLE INFORMATION

Received June 20, 2023; accepted October 17, 2023.

Affiliations

Cardiology Division, Massachusetts General Hospital (K.S., T.N., H.Y., D.K., D.F., I.M., I.-K.J.) and Biostatistics Center, Massachusetts General Hospital (H.L.), Harvard Medical School, Boston, MACardiovascular Center, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Chiba, Japan (M.T.); Interventional Cardiology Unit, New Tokyo Hospital, Chiba, Japan (S.N.); Department of Cardiology, Tsuchiura Kyodo General Hospital, Tsuchiura, Ibaraki, Japan (T.K.); and Mitsukoshi Health and Welfare Foundation, Tokyo, Japan (K.M.).

Sources of Funding

I.-K.J's research has been supported by Mrs Gillian Gray through the Allan Gray Fellowship Fund in Cardiology and by Mukesh and Priti Chatter through the Chatter Foundation.

Disclosures

Dr Jang received educational grants from Abbott Vascular and consulting fees from Svelte Medical Systems, Inc.

Supplemental Material

Data S1
Figure S1

REFERENCES

1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9
2. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720–1732. doi: 10.1056/NEJMoa1504347
3. Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV, Virmani R. Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2017;37:191–204. doi: 10.1161/ATVBAHA.116.306256
4. Chia S, Raffel OC, Takano M, Tearney GJ, Bouma BE, Jang IK. Comparison of coronary plaque characteristics between diabetic and non-diabetic subjects: an in vivo optical coherence tomography study. *Diabetes Res Clin Pract*. 2008;81:155–160. doi: 10.1016/j.diabres.2008.03.014
5. Feng T, Yundai C, Lian C, Zhijun S, Changfu L, Jun G, Hongbin L. Assessment of coronary plaque characteristics by optical coherence tomography in patients with diabetes mellitus complicated with unstable angina pectoris. *Atherosclerosis*. 2010;213:482–485. doi: 10.1016/j.atherosclerosis.2010.09.019
6. Fukunaga M, Fujii K, Nakata T, Shibuya M, Miki K, Kawasaki D, Masutani M, Kawabata-Lee M, Ohyanagi M, Masuyama T. Multiple complex coronary atherosclerosis in diabetic patients with acute myocardial infarction: a three-vessel optical coherence tomography study. *EuroIntervention*. 2012;8:955–961. doi: 10.4244/EIJV8I8A145
7. Niccoli G, Giubilato S, Di Vito L, Leo A, Cosentino N, Pitocco D, Marco V, Ghirlanda G, Prati F, Crea F. Severity of coronary atherosclerosis in patients with a first acute coronary event: a diabetes paradox. *Eur Heart J*. 2013;34:729–741. doi: 10.1093/eurheartj/ehs393
8. Sugiyama T, Yamamoto E, Bryniarski K, Xing L, Fracassi F, Lee H, Jang IK. Coronary plaque characteristics in patients with diabetes mellitus who presented with acute coronary syndromes. *J Am Heart Assoc*. 2018;7:e009245. doi: 10.1161/JAHA.118.009245
9. Sheng Z, Zhou P, Liu C, Li J, Chen R, Zhou J, Song L, Zhao H, Yan H. Relationships of coronary culprit-plaque characteristics with duration of diabetes mellitus in acute myocardial infarction: an intravascular optical coherence tomography study. *Cardiovasc Diabetol*. 2019;18:136. doi: 10.1186/s12933-019-0944-8
10. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;127:e362–e425. doi: 10.1161/CIR.0b013e3182742cf6
11. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014;130:2354–2394. doi: 10.1161/CIR.0000000000000133
12. Araki M, Park SJ, Dauerman HL, Uemura S, Kim JS, Di Mario C, Johnson TW, Guagliumi G, Kastrati A, Joner M, et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. *Nat Rev Cardiol*. 2022;19:684–703. doi: 10.1038/s41569-022-00687-9
13. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G, Zheng ZJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307:813–822. doi: 10.1001/jama.2012.199
14. Fernandez-Ortiz A, Badimon JJ, Falk E, Fuster V, Meyer B, Mailhac A, Weng D, Shah PK, Badimon L. Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J Am Coll Cardiol*. 1994;23:1562–1569. doi: 10.1016/0735-1097(94)90657-2
15. Xing L, Higuma T, Wang Z, Aguirre AD, Mizuno K, Takano M, Dauerman HL, Park SJ, Jang Y, Kim CJ, et al. Clinical significance of lipid-rich plaque detected by optical coherence tomography: a 4-year follow-up study. *J Am Coll Cardiol*. 2017;69:2502–2513. doi: 10.1016/j.jacc.2017.03.556
16. Burke AP, Kolodgie FD, Zieske A, Fowler DR, Weber DK, Varghese PJ, Farb A, Virmani R. Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study. *Arterioscler Thromb Vasc Biol*. 2004;24:1266–1271. doi: 10.1161/01.ATV.0000131783.74034.97
17. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, Fuster V, Fallon JT. Coronary composition and macrophage infiltration in

atherectomy specimens from patients with diabetes mellitus. *Circulation*. 2000;102:2180–2184. doi: 10.1161/01.cir.102.18.2180
18. Zheng M, Choi SY, Tahk SJ, Lim HS, Yang HM, Choi BJ, Yoon MH, Park JS, Hwang GS, Shin JH. The relationship between volumetric plaque components and classical cardiovascular risk factors and the metabolic syndrome a 3-vessel coronary artery virtual histology-intravascular ultrasound analysis. *JACC Cardiovasc Interv*. 2011;4:503–510. doi: 10.1016/j.jcin.2010.12.015
19. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287:2570–2581. doi: 10.1001/jama.287.19.2570
20. Rajamaki K, Lappalainen J, Oorni K, Valimaki E, Matikainen S, Kovanen PT, Eklund KK. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One*. 2010;5:e11765. doi: 10.1371/journal.pone.0011765
21. Abela GS, Aziz K, Vedre A, Pathak DR, Talbott JD, Dejong J. Effect of cholesterol crystals on plaques and intima in arteries of patients with acute coronary and cerebrovascular syndromes. *Am J Cardiol*. 2009;103:959–968. doi: 10.1016/j.amjcard.2008.12.019
22. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE, Prominent R-I; Investigators S. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet*. 2023;401:1293–1301. doi: 10.1016/S0140-6736(23)00215-5
23. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2013;61:404–410. doi: 10.1016/j.jacc.2012.10.027
24. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383:1838–1847. doi: 10.1056/NEJMoa2021372
25. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497–2505. doi: 10.1056/NEJMoa1912388
26. Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. *Atherosclerosis*. 2015;239:260–267. doi: 10.1016/j.atherosclerosis.2015.01.017
27. Fang C, Dai J, Zhang S, Wang Y, Wang J, Li L, Wang Y, Yu H, Wei G, Zhang X, et al. Culprit lesion morphology in young patients with ST-segment elevated myocardial infarction: a clinical, angiographic and optical coherence tomography study. *Atherosclerosis*. 2019;289:94–100. doi: 10.1016/j.atherosclerosis.2019.08.011
28. Higuma T, Soeda T, Abe N, Yamada M, Yokoyama H, Shibutani S, Vergallo R, Minami Y, Ong DS, Lee H, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2015;8:1166–1176. doi: 10.1016/j.jcin.2015.02.026
29. Yamamoto E, Yonetsu T, Kakuta T, Soeda T, Saito Y, Yan BP, Kurihara O, Takano M, Niccoli G, Higuma T, et al. Clinical and laboratory predictors for plaque erosion in patients with acute coronary syndromes. *J Am Heart Assoc*. 2019;8:e012322. doi: 10.1161/JAHA.119.012322
30. Kim HO, Kim CJ, Kim W, Cho JM, Soeda T, Takano M, Yan BP, Crea F, Niccoli G, Vergallo R, et al. Relative risk of plaque erosion among different age and sex groups in patients with acute coronary syndrome. *J Thromb Thrombolysis*. 2020;49:352–359. doi: 10.1007/s11239-019-01969-9
31. Franck G, Mawson T, Sausen G, Salinas M, Masson GS, Cole A, Beltrami-Moreira M, Chatzizisis Y, Quillard T, Tesmenitsky Y, et al. Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in mice: implications for superficial erosion. *Circ Res*. 2017;121:31–42. doi: 10.1161/CIRCRESAHA.117.310694
32. Delp MD, Behnke BJ, Spier SA, Wu G, Muller-Delp JM. Ageing diminishes endothelium-dependent vasodilatation and tetrahydrobiopterin content in rat skeletal muscle arterioles. *J Physiol*. 2008;586:1161–1168. doi: 10.1113/jphysiol.2007.147686
33. Donato AJ, Eskurza I, Silver AE, Levy AS, Pierce GL, Gates PE, Seals DR. Direct evidence of endothelial oxidative stress with aging in humans: relation to impaired endothelium-dependent dilation and upregulation of nuclear factor-kappaB. *Circ Res*. 2007;100:1659–1666. doi: 10.1161/01.RES.0000269183.13937.e8
34. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107:139–146. doi: 10.1161/01.cir.0000048892.83521.58
35. Ruiz-Garcia J, Lerman A, Weisz G, Maehara A, Mintz GS, Fahy M, Xu K, Lansky AJ, Cristea E, Farah TG, et al. Age- and gender-related changes in plaque composition in patients with acute coronary syndrome: the PROSPECT study. *EuroIntervention*. 2012;8:929–938. doi: 10.4244/EIJV8I8A142
36. Sattar N, Rawshani A, Franzen S, Rawshani A, Svensson AM, Rosengren A, McGuire DK, Eliasson B, Gudbjornsdottir S. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation*. 2019;139:2228–2237. doi: 10.1161/CIRCULATIONAHA.118.037885
37. Svane J, Lynge TH, Pedersen-Bjergaard U, Jespersen T, Gislason GH, Risgaard B, Winkel BG, Tfelt-Hansen J. Cause-specific mortality in children and young adults with diabetes mellitus: a Danish nationwide cohort study. *Eur J Prev Cardiol*. 2021;28:159–165. doi: 10.1177/2047487319836550
38. Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. *Diabetes Care*. 2003;26:2999–3005. doi: 10.2337/diacare.26.11.2999
39. Chan JC, Lau ES, Luk AO, Cheung KK, Kong AP, Yu LW, Choi KC, Chow FC, Ozaki R, Brown N, et al. Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. *Am J Med*. 2014;127:616–624. doi: 10.1016/j.amjmed.2014.03.018
40. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, Twigg SM, Yue DK, Wong J. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care*. 2013;36:3863–3869. doi: 10.2337/dc12-2455
41. Song PS, Ahn KT, Kim MJ, Seong SW, Choi SW, Gwon HC, Hur SH, Rha SW, Yoon CH, Jeong MH, et al. Age-related difference in the impact of diabetes mellitus on all-cause mortality after acute myocardial infarction. *Diabetes Metab*. 2022;48:101349. doi: 10.1016/j.diabet.2022.101349
42. Liu JJ, Gurung RL, Liu S, Yiamunaa M, Lee J, Ang K, Tavintharan S, Tang WE, Sum CF, Lim SC. Associations of young onset age and genetic risk of beta cell dysfunction with glycaemic progression in individuals with type 2 diabetes. *Diabetes Metab*. 2021;47:101238. doi: 10.1016/j.diabet.2021.101238
43. Group TS. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and beta-cell function in TODAY. *Diabetes Care*. 2013;36:1749–1757. doi: 10.2337/dc12-2393
44. Druet C, Tubiana-Rufi N, Chevenne D, Rigal O, Polak M, Levy-Marchal C. Characterization of insulin secretion and resistance in type 2 diabetes of adolescents. *J Clin Endocrinol Metab*. 2006;91:401–404. doi: 10.1210/jc.2005-1672
45. Gungor N, Bacha F, Saad R, Janosky J, Arslanian S. Youth type 2 diabetes: insulin resistance, beta-cell failure, or both? *Diabetes Care*. 2005;28:638–644. doi: 10.2337/diacare.28.3.638