Clinical Research

Patients with Type Two Diabetes Mellitus: Increased Local Inflammatory Activation in Culprit Atheromatous Plaques

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Introduction: Diabetes mellitus (DM) predisposes to coronary artery disease (CAD). The progression of CAD has recently come to be regarded as an inflammatory activation. Thermography detects local inflammatory involvement as heat generation. The aim of this study was to investigate whether patients with CAD and DM have increased local heat generation compared to non-diabetic patients.

Methods: We enrolled 45 patients with DM and 63 non-diabetic patients who were undergoing percutaneous coronary interventions. The two groups were matched for age, type of clinical syndrome, statin and aspirin intake and angiographic stenosis (%). Coronary thermography was performed and the temperature difference (ΔT) between the atherosclerotic plaque and the proximal vessel wall was measured.

Results: Patients with DM had increased ΔT compared to non-diabetic patients (ΔT: 0.17 ± 0.18˚C vs. 0.09 ± 0.02˚C, p=0.01). Patients with DM and acute coronary syndromes (ACS)(n= 21) had increased ΔT compared to non-diabetic patients (n=22) (ΔT: 0.29 ± 0.31˚C vs. 0.15 ± 0.21˚C, p=0.02). Similarly, patients with DM and stable angina (SA) had a higher ΔT than non-diabetics with SA (ΔT: 0.09 ± 0.08 ˚C vs. 0.05 ± 0.04 ˚C, p=0.006).

Conclusion: Patients with DM have increased ΔT compared to non-diabetic patients.

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It is well known that inflammatory activation plays a significant role in the pathogenesis of coronary artery disease. This activation is more profound in the presence of diabetes mellitus (DM). This has been shown by several methods including peripheral indexes of inflammation, which are higher in patients with DM and coronary artery disease compared to non-diabetics.[1,2]

Local inflammatory activation, however, can only be detected by invasive methods. Functional assessment of atherosclerotic plaques can be performed by coronary thermography. Previous studies have demonstrated that local inflammatory activation is well correlated with systemic indexes of inflammation. Therefore, the local inflammation is an expression of widespread inflammatory activation. Thus, heat production from atherosclerotic plaques is positively correlated with the levels of C-reactive protein, the most widely used inflammatory index.[3-7] Moreover, the concentration of macrophages is higher in culprit coronary atherosclerotic plaques, with increased temperature as detected by coronary thermography.[6,8]

It is unknown whether the presence of DM has an impact on coronary thermography. We therefore investigated whether patients with coronary artery disease and DM have increased local heat production from culprit atherosclerotic lesions compared to patients suffering from coronary artery disease without DM.

Methods

Study population

We included prospectively patients undergoing percutaneous coronary intervention. We divided the patients into two groups: Patients with type 2 DM and patients without DM, serving as a control group.

The inclusion criteria were as follows: one significant de novo angiographic lesion (≥50%) <20 mm in length with reference vessel diameter ≥2.5 mm. The culprit lesion needed to be clearly identified by noninvasive methods or angiographic lesion appearance. A committee had to review all clinical and angiographic characteristics and agree on the identification of culprit lesions.

The exclusion criteria were: cardiogenic shock, allergy to aspirin, heparin, or clopidogrel, inflammatory or neoplastic condition, treatment with an immune suppressive agent, corticosteroids or nonsteroidal anti-inflammatory drugs, except for aspirin, or treatment with a glycoprotein IIb/IIIa inhibitor within the previous 30 days.

Informed consent was obtained from all patients. The institutional ethics committee approved the protocol. The investigation was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Risk factors included hypertension (medication-treated), hypercholesterolaemia (treated or ≥200 mg/dl), and current smoking. The definition of DM was fasting glucose level >140 mg/dL measured on ≥2 different occasions. The first group including patients with DM known for 8.2 ± 4.3 years at the time of the intervention. All of them had to be treated with insulin or an oral hypoglycaemic agent for >1 month before coronary intervention.

Stable angina was defined as no change in frequency, duration, or intensity of symptoms within the last six weeks. Acute coronary syndrome included patients with unstable angina or acute myocardial infarction. Unstable angina was defined as angina at rest, new onset angina, or an increase in the severity of angina in the previous month (with negative cardiac markers). Previous myocardial infarction (<6 weeks), coronary artery bypass grafting, percutaneous coronary intervention in other lesions, and left ventricular function were tabulated. Statin administration was considered when patients had been treated with statins for over 4 weeks.

Angiographic analysis

Coronary angiograms were analysed with a computer-assisted, automated edge detection algorithm (Medcon, Israel) using standard qualitative and quantitative definitions and measurements. The outer diameter of the contrast-filled catheter was used for calibration, and the minimal lumen diameter was obtained from the single "worst" view.

Temperature measurements

Coronary Thermography Catheter

At the distal part of the thermography catheter (Epiphany, Medispes S.W., Switzerland) a thermistor probe (Microchip NTC Thermistor, model 100K6-MCD368, BetaTHERM), 0.457 mm in diameter, is attached. The technical characteristics of the polyamide thermistor include (1) temperature accuracy, 0.05˚C; (2) time constant, 300 ms; (3) spatial resolution, 0.5 mm; and (4) linear correlation of resistance versus temperature over the range of 33˚C to 43˚C. The gold-plated lead wires of the thermistor pass through the shaft of the catheter and end in a connector at the distal part of the thermography catheter. Through the distal 20 cm the catheter has a second lumen for insertion of a guide wire; thus, the catheter can be inserted into the coronary artery over a standard guide wire (0.014"). Opposite the thermistor is a hydrofoil specially designed to ensure contact of the thermistor with the vessel wall. The catheter is provided in sizes of 3.0-4.5 F.

Procedure

The lesion of interest was well delineated in at least two views, on which the positioning of the catheter was based. The projections in which the lesion was best visualised were frozen for guidance of the thermography catheter advancement. Five minutes after the last injection of contrast medium, the coronary thermography catheter was advanced over the guidewire to the target vessel and blood temperature was measured when the thermistor had just emerged from the tip of the guiding catheter without being in contact with the vessel wall. Thereafter, temperature was recorded at the proximal non-diseased segment and the most frequent temperature was designated the proximal vessel wall temperature. Afterwards, temperature recordings at the atherosclerotic lesion were performed based in the same projections, that had been frozen from the initial angiography. Temperature difference (ΔT) between the atherosclerotic plaque and the proximal vessel wall was calculated by subtracting the temperature at the proximal vessel wall

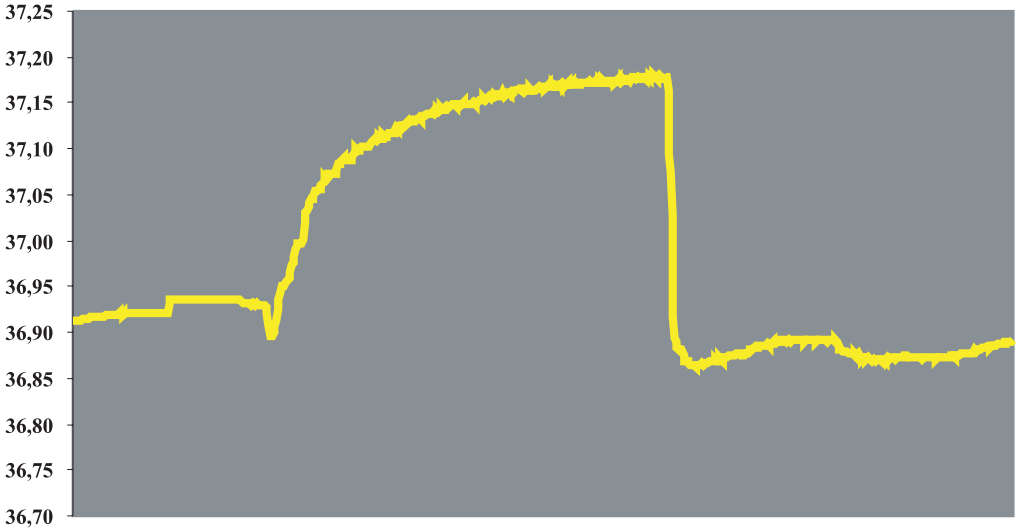

Figure 1. The thermogram shows a temperature difference between the atherosclerotic plaque temperature and the proximal vessel wall temperature (ΔT) of 0.20 °C.

from the maximal temperature at the lesion (Figure 1). After temperature measurements the operator proceeded with the intervention.

Statistical analysis

Continuous variables are presented as mean ± one standard deviation, while qualitative variables are presented as absolute and relative frequencies. The exact p-values presented arise from non-parametric comparison (Wilcoxon test) and were compared to a 5% level of significance. In addition, parametric comparisons were made using the unpaired t-test in order to confirm the findings of non-parametric statistical analysis. STATA 6 software was used for the calculations (STATA Corp, Lakeway Drive, Texas, USA).

Results

Study population

We enrolled 108 patients who met the inclusion criteria: 45 patients with type 2 DM and 63 non-diabetic patients, serving as a control group. Twenty-five patients with type 2 DM were being treated with oral agents (55.6%), 15 of them were under hypoglycaemic diet (33.3%), and 5 patients received a combination of insulin and oral agents (11.1%).

Patients were also categorised according to the clinical syndrome. Among patients with type 2 DM, 21 patients had acute coronary syndrome (ACS) and 24 had chronic stable angina (SA). The control group included 22 patients with ACS and 41 with SA. There were no differences between the two groups in the clinical and angiographic characteristics.

The demographic and angiographic data for the study population are given in tables 1 and 2.

All patients enrolled in the study underwent successful stent implantation without any complication.

Measurements of ΔT

We performed coronary thermography successfully in all patients, without any complication. The measurement obtained for determination of the proximal vessel wall temperature was constant in each patient of the total study group, varying by only 0.03°C, with a standard deviation from 0 to 0.03. The proximal vessel wall temperature and the temperature of the blood did not differ (p=0.7).

Patients with type 2 DM had a higher ΔT compared to non-diabetic patients (mean ΔT: 0.17±0.18°C vs. 0.09±0.02°C, p=0.01) (Figure 2). When stratified according to the presenting syndrome, patients with type 2 DM showed increased thermal heterogeneity compared to non-diabetic patients, both in the ACS group (mean ΔT: 0.29 ± 0.31°C vs. 0.15 ± 0.21°C, p=0.02), and in the SA group (mean ΔT: 0.09 ± 0.08°C vs. 0.05 ± 0.04°C, p=0.006). Among patients with type 2 DM those presenting with ACS showed elevated ΔT compared to those with SA (mean ΔT: 0.29 ± 0.31°C vs. 0.09 ± 0.08°C, p=0.007), and the same was true for non-diabetic patients (mean ΔT: 0.15 ± 0.21°C vs. 0.05 ± 0.04°C, p=0.005).

Table 1. Demographic characteristics stratified by diabetes mellitus (DM) and clinical syndrome.

	Non-DM (n=63)	DM (n=45)	P value	ACS (n=43)	SA (n=65)	P value
Age (years)	60.67 ± 8.96	63.40 ± 9.32	0.13	59.98 ± 8.98	63.02 ± 9.16	0.09
Male	49 (77.8%)	28 (62.2%)	0.08	30 (69.8%)	47 (72.3%)	0.78
Hypertension	37 (58.7%)	32 (71.1%)	0.18	30 (69.8%)	39 (60%)	0.30
Smoking	36 (57.1%)	21 (46.7%)	0.28	27 (62.8%)	30 (46.2%)	0.09
Family history	23 (36.5%)	9 (20%)	0.06	13 (30.2%)	19 (29.2%)	0.91
Statins	30 (47.6%)	23 (51.1%)	0.72	18 (41.9%)	35 (53.8%)	0.22
ACE inhibitors	19 (30.2%)	21 (46.7%)	0.08	17 (39.5%)	23 (35.4%)	0.66
Aspirin	52 (82.5%)	39 (86.7%)	0.56	37 (86%)	54 (83.1%)	0.18
b-blocker	42 (66.7%)	28 (62.2%)	0.63	34 (79.1%)	36 (55.4%)	0.13

ACS – acute coronary syndrome, DM – diabetes mellitus, SA – chronic stable angina

Discussion

In this study we demonstrate that culprit lesions of patients with type 2 DM have increased thermal heterogeneity compared to non-diabetic patients with coronary artery disease. We also show that patients suffering from ACS and DM have profound local thermal heterogeneity within the culprit atherosclerotic plaques.

In the presence of DM there are several pathophysiologic pathways that lead to an increase in inflammatory activation. Interestingly, a chronic inflammation has been recognised in patients with DM, possibly due to the insulin resistance.[9,10]. Moreover, hyperglycaemia has a pro-inflammatory effect in non-diabetic subjects.[11]

Especially in patients with type 2 DM who have coronary artery disease, an increased inflammatory activation is observed compared to non-diabetic patients.[1,12-14] Specific inflammatory markers have been detected in higher concentrations in patients with DM, with or without overt coronary artery disease, than in control subjects.[1] Moreover, histological examination of coronary tissue from patients with DM reveals a larger content of lipid-rich atheroma and macrophage infiltration compared to non-diabetic patients.[13] In agreement with these observations we found an increased local thermal heterogeneity in culprit atherosclerotic plaques of patients with DM. Animal studies,[6] and human[4,8] observations have confirmed that local heat generation is associated with increased macrophage content. Thus,

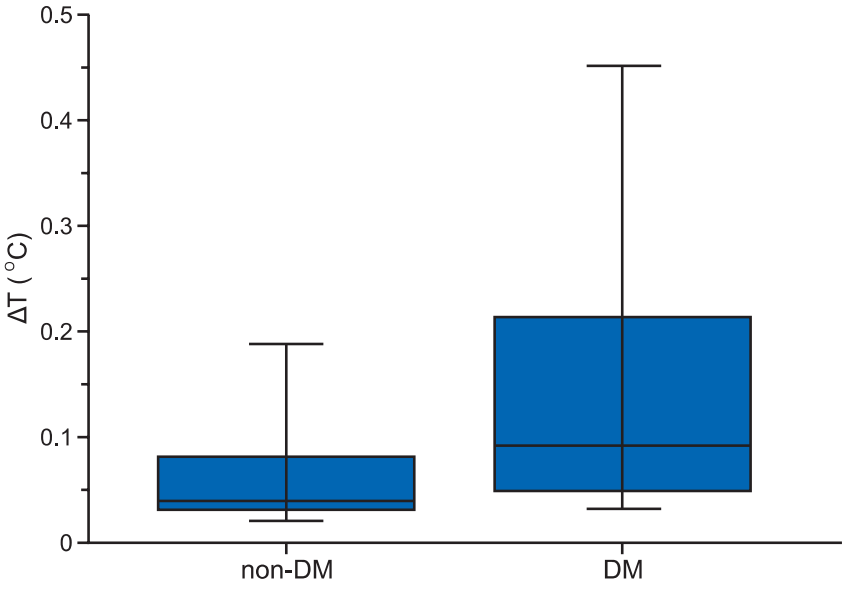

Figure 2. The difference between atherosclerotic plaque temperature and proximal vessel wall temperature (ΔT) in type 2 DM and non-DM. The bottom of the box represents the first quartile; the top of the box represents the third quartile, and the line in the box represents the median value. (DM – diabetes mellitus).

Table 2. Angiographic characteristics stratified by DM and clinical syndrome.

	Non-DM (n=63)	DM (n=45)	P value	ACS (n=43)	SA (n=65)	P value
Vessels						
LAD	21 (33.3%)	14 (31.1%)		15 (34.9%)	20 (30.8%)	
LCX	19 (30.2%)	13 (28.9%)	0.96	8 (18.6%)	23 (35.4%)	0.15
RCA	24 (38.1%)	18 (40.0%)		20 (46.5%)	22 (33.8%)	
Location						
Proximal	19 (30.2%)	16 (35.6%)		9 (20.9%)	26 (40%)	
Middle	36 (57.1%)	19 (42.2%)	0.25	25 (58.2%)	30 (46.2%)	0.10
Distal	8 (12.7%)	10 (22.2%)		9 (20.9%)	9 (13.8%)	
RVD (mm)	2.86 ± 0.41	2.81 ± 0.70	0.72	2.80 ± 0.60	2.86 ± 0.51	0.68
Pre MLD (mm)	0.85 ± 0.45	0.71 ± 0.49	0.23	0.73 ± 0.48	0.83 ± 0.46	0.47
Length (mm)	13.58 ± 5.40	12.09 ± 3.65	0.24	14.79 ± 5.62	12.33 ± 4.37	0.07
Stenosis (%)	69.12 ± 13.15	74.18 ± 15.79	0.17	71.30 ± 16.19	70.91 ± 13.67	0.92

ACS – acute coronary syndrome, DM – diabetes mellitus, LAD – left anterior descending artery, LCX – left circumflex artery, MLD – minimum lumen diameter, RCA – right coronary artery, RVD – reference vessel diameter, SA – chronic stable angina.

our results may be explained by the greater inflammatory cell infiltration within the culprit lesions of patients with DM.

Greater inflammatory infiltration is also observed in patients with ACS,[15,16] accompanied by a higher local atherosclerotic plaque temperature.[3] Angioscopically ulcerated plaques and intracoronary thrombi are more frequently observed in patients with DM suffering from ACS.[17] Moreover, the percentages of total area occupied by lipid-rich atheroma and macro=-phages were larger in atherectomy specimens from coronary atherosclerotic plaques of patients with DM and unstable angina.[13] These observations may explain the findings of the present study, in which patients with ACS and DM had higher temperature of the culprit atherosclerotic plaques compared to patients with SA and DM. The increased local inflammatory activation may have a significant impact on the clinical outcome of diabetic patients suffering from ACS, known to have the highest overall incidence of death or re-infarction at long term follow-up.[18]

Study limitations

In this study we included patients with angiographically significant lesions, and we used different catheters depending on the percentage of stenosis and the size of the vessel, to avoid the 'cooling effect' of coronary blood flow on coronary thermography measurements.[3]

Conclusion

The results of the present study reveal that local heat generation is increased in significant culprit lesions of patients with type 2 DM compared to non-diabetic patients.

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