Impact of type 2 diabetes mellitus on diffuse inflammatory activation of de novo atheromatous lesions: Implications for systemic inflammation

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Original article

Abstract

Aims. – Local coronary and systemic inflammation is pronounced in patients with diabetes mellitus (DM). Intracoronary thermography detects local inflammation and C-reactive protein (CRP) is a marker of systemic inflammation. We investigated whether or not, in patients with DM, thermal heterogeneity of culprit lesions (CLs) correlates with that of non-culprit lesions (NCLs) and with systemic inflammation.

Methods. – We included DM patients who had two angiographically significant lesions and were undergoing percutaneous coronary intervention. We measured the temperature difference (ΔT) between the lesion and proximal vessel wall.

Results. – We included 104 (n = 208 lesions) patients: 32 (n = 64 lesions) had DM and 72 (n = 144 lesions) were non-DM (control group). ΔT was increased in DM in both CLs and NCLs (CLs: DM = 0.12 ± 0.06 °C; no DM = 0.06 ± 0.04 °C; P < 0.01 versus NCLs: DM = 0.13 ± 0.08 °C versus no DM = 0.06 ± 0.05 °C; P < 0.01). Patients with DM had similar ΔT in CLs and NCLs (P = 0.49). A linear correlation was detected between heat production in all lesions and CRP (R = 0.45; P < 0.01), which was attributed to the correlation of ΔT in lesions of patients with DM and CRP (R = 0.32; P < 0.01). In lesions of patients with low CRP, a greater rate of discrepancy was found, as 100% of lesions in patients with DM versus 66.1% of lesions of patients without DM had a high ΔT in one or both lesions (P < 0.01).

Conclusion. – In patients with DM, local inflammatory activation is diffuse and correlates with systemic inflammation. However, low systemic inflammatory activation does not always predict an increase in local thermal heterogeneity.

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Keywords: Diabetes mellitus; Inflammation; Atherosclerosis; Intracoronary thermography; CRP

Résumé

Impact du diabète de type 2 sur l’activation systémique liée aux lésions coronaires athéromateuses.

Objectifs. – Il existe chez les diabétiques une inflammation importante, localement au niveau coronarien et systémique. La thermographie endocoronaire permet d’évaluer l’inflammation locale, la protéine C réactive (CRP) est un marqueur de l’inflammation systémique. Nous avons cherché à établir si, chez les diabétiques, l’élévation de température des sténoses sévères (SS) était en corrélation avec celle des lésions non sévères (SNS) et avec l’inflammation systémique.

Méthodes. – On a étudié 32 patients diabétiques, 72 non diabétiques (soit 208 lésions) ont été inclus. Une élévation de ΔT a été trouvée dans la population diabétique aussi bien pour les SS que SNS (SS : diabétiques ΔT : 0.12 ± 0.06 °C versus non diabétiques 0.06 ± 0.04 °C ; P < 0.01 ; SNS : diabétiques ΔT : 0.13 ± 0.08 °C versus non diabétiques : 0.06 ± 0.05 °C ; P < 0.01). Dans la population diabétique, ΔT était comparable pour les deux types de lésions (P = 0.49). Une corrélation linéaire a été mise en évidence entre le ΔT de toutes les lésions et la CRP (R = 0.45 ; P < 0.01), en relation avec la corrélation de ΔT avec la CRP dans la population diabétique (R = 0.32 ; P < 0.01). Un plus fort pourcentage de discordance a été observé pour les lésions des patients avec CRP basse, car 100 % des lésions des patients diabétiques versus 66.1 % des lésions des non-diabétiques présentaient un ΔT élevé pour l’une ou les deux lésions (P < 0.01).

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Conclusion. – Chez les diabétiques, il existe une inflammation vasculaire, en corrélation avec l’inflammation systémique. Cependant, un faible taux d’activation de l’inflammation ne permet pas toujours de prédire une augmentation de la différence de température locale.

Mots clés : Diabète sucré ; Inflammation ; Athérosclérose ; Thermographie endocoronaire ; CRP

1. Abbreviations

ACS acute coronary syndrome
CRP C-reactive protein
DM diabetes mellitus
CL culprit lesion
NCL non-culprit lesion
SA stable angina
ΔT temperature difference

2. Introduction

Inflammation, known to play a key role in the destabilization of coronary lesions, appears to have relevance to local diabetic vascular complications [1–7]. Coronary atherectomy specimens from patients with type 2 DM exhibited a greater content of lipid-rich atheroma and macrophage infiltration than specimens from non-DM patients [7,8]. Also, increased local inflammatory involvement is found in the CLs of patients with DM, as evaluated by intracoronary thermography [9].

Systemic inflammation has also been closely associated with DM. Higher levels of inflammatory indices and adhesion molecules are detected in patients with DM and coronary artery disease compared with controls [6]. Among the numerous circulating inflammatory markers of the atherosclerotic process, CRP has received the greatest attention and is also a mediator of cardiovascular disease [6,10].

Other studies, however, suggest that there are no significant differences in the number of diffuse lesions among patients with and without DM [1,2,7]. In addition, it has been confirmed that the incidence of vascular events is strongly affected by angiographic status, but not the diabetic status [5].

There are, nevertheless, limited data as to whether or not patients with DM have diffusely inflamed coronary lesions and whether or not local inflammatory activation is correlated with systemic inflammation. For this reason, we investigated whether or not there is a correlation between local plaque temperature in CLs and NCLs with systemic inflammation. We also analyzed the effect of statin treatment on the local inflammatory activation of both CLs and NCLs.

3. Methods

3.1. Study population

Patients with DM and de novo CLs and NCLs who had undergone percutaneous coronary intervention were enrolled into the study. Angiographic inclusion criteria were a CL and at least one angiographic NCL, both less than 20 mm in length and producing an intermediate stenosis in vessels with a reference diameter of greater or equals to 2.25 mm. The NCL had to be clearly identifiable from the CL through the combination of precrisis and intercrisis ECG findings, left ventricular wall motion abnormalities, scintigraphic defects and angiographic lesion morphology. Two experienced cardiologists (E.T., M.V.) independently reviewed all clinical and angiographic data to assign angina status and CLs prior to the procedure.

Patients who had concomitant inflammatory or neoplastic conditions and those taking corticosteroids or any nonsteroidal anti-inflammatory drugs (NSAIDs) except aspirin were excluded. Patients with chronic total occlusion, more than one lesion in the culprit vessel or in whom no NCLs could be detected were also excluded. The institutional ethics committee approved the study protocol and all participating patients gave their written informed consent.

3.2. Clinical data

DM was defined as a fasting blood glucose level greater than 140 mg/dL in more than two different values. Study patients were known to have DM for 8.7 ± 3.9 years at the time of the intervention and had been treated with insulin or an oral hypoglycaemic agent for at least 1 month. Risk factors included hypertension, hypercholesterolaemia and current smoking.

3.3. Angiographic analysis

Coronary angiograms were analyzed, using a computer-assisted, automated edge-detection algorithm (Medcon Telemedicine Technology, Tel-Aviv, Israel), by a core laboratory according to the standard qualitative and quantitative definitions and measurements.

3.4. Temperature measurements

Temperature was recorded using a coronary thermography catheter (Epiphany, MEDISPES SW A.G., Zug, Switzerland) as described elsewhere [11]. The ΔT between the atherosclerotic plaque and proximal vessel wall was calculated by subtracting the temperature at the proximal vessel wall from the maximum plaque temperature.

3.5. Inflammatory index measurements

Peripheral blood samples were taken before the procedure for measurement of CRP levels, using a validated assay (Denka Seiken UK Limited, Coventry, UK).
3.6. Statistical analysis

Continuous variables are presented as means ± 1 standard deviation (S.D.) as well as medians, while qualitative variables are presented as absolute and relative frequencies. The specific \( P \) values arise from non-parametric comparisons and have a significance level of 5%. Also, parametric comparisons with the unpaired \( t \) test were used to confirm the findings of the non-parametric statistical analyses.

The associations between various patients’ characteristics and the presence of a high \( \Delta T \) (>0.05 °C) were evaluated using multiple logistic-regression analysis. Results are presented as odds ratios (OR) with their corresponding 95% confidence intervals (CI). Deviance residuals were calculated to evaluate the model goodness of fit. Stata 6 software was used for the calculations (StataCorp LP, College Station, TX, USA).

4. Results

4.1. Study population

A total of 353 consecutive patients were included in the study. Patients in whom NCLs could not be identified and those who declined to participate in the study were excluded. A total of 104 (\( n = 208 \) lesions) patients were included: 32 (\( n = 64 \) lesions) had DM and 72 (\( n = 144 \) lesions) did not (non-DM controls). In the group with ACS (\( n = 53 \), 60.3% (\( n = 32 \)) of patients had unstable angina and 39.6% (\( n = 21 \)) had post-thrombolytic STEMI (ST-segment elevated myocardial infarction). The study patients’ demographic characteristics are presented in Table 1. Most of the NCLs were identified by ECG and ultrasound findings. Complex coronary lesions were identified according to criteria described elsewhere [12]. A single complex lesion was identified in 35.6% (\( n = 37 \)) and multiple complex lesions in 27.9% (\( n = 29 \)) of the study patients. The angiographic characteristics of the CLs and NCLs are shown in Table 2. The study population was also categorized according to clinical syndrome.

### Table 1

Demographic characteristics of patients with diabetes mellitus (DM) and without (non-DM) DM.

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 32)</th>
<th>Non-DM (n = 72)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.00 ± 10.65</td>
<td>63.27 ± 10.55</td>
<td>0.54</td>
</tr>
<tr>
<td>Male</td>
<td>17 (53.1%)</td>
<td>40 (55.5%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (65.6%)</td>
<td>45 (62.5%)</td>
<td>0.82</td>
</tr>
<tr>
<td>ACS</td>
<td>21 (65.6%)</td>
<td>32 (44.4%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>22 (68.7%)</td>
<td>55 (76.4%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Taking statins</td>
<td>8 (25.0%)</td>
<td>44 (61.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Taking aspirin</td>
<td>29 (90.6%)</td>
<td>61 (84.7%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Taking ACE inhibitors</td>
<td>13 (40.6%)</td>
<td>29 (40.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Taking beta-blockers</td>
<td>21 (65.6%)</td>
<td>48 (66.6%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Family history</td>
<td>11 (34.3%)</td>
<td>17 (23.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Current smoker</td>
<td>16 (50.0%)</td>
<td>37 (51.4%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; SA: stable angina.

### Table 2

Angiographic characteristics based on the presence or not of diabetes mellitus (DM).

<table>
<thead>
<tr>
<th></th>
<th>Culprit lesions (( n = 104 ))</th>
<th>Non-culprit lesions (( n = 104 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM (( n = 32 ))</td>
<td>Non-DM (( n = 72 ))</td>
<td>DM (( n = 32 ))</td>
</tr>
<tr>
<td>Vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>10 (31.2%)</td>
<td>25 (34.7%)</td>
<td>9 (28.1%)</td>
</tr>
<tr>
<td>LCX</td>
<td>9 (28.1%)</td>
<td>24 (33.3%)</td>
<td>13 (40.6%)</td>
</tr>
<tr>
<td>RCA</td>
<td>13 (40.6%)</td>
<td>23 (31.9%)</td>
<td>10 (31.5%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>16 (50%)</td>
<td>23 (31.9%)</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>Middle</td>
<td>10 (31.2%)</td>
<td>36 (50%)</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Distal</td>
<td>6 (18.7%)</td>
<td>13 (18.0%)</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.55 ± 0.53</td>
<td>2.61 ± 0.51</td>
<td>2.61 ± 0.49</td>
</tr>
<tr>
<td>Pre-MLD (mm)</td>
<td>0.66 ± 0.33</td>
<td>0.68 ± 0.30</td>
<td>0.75 ± 0.38</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>13.27 ± 5.79</td>
<td>13.27 ± 4.80</td>
<td>13.26 ± 5.74</td>
</tr>
<tr>
<td>Stenosis (%)</td>
<td>73.20 ± 12.30</td>
<td>72.86 ± 11.95</td>
<td>71.50 ± 12.14</td>
</tr>
</tbody>
</table>

LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; RD: reference diameter; MLD: minimal lumen diameter.
In the DM group, patients taking statins had lower treatment for greater or equals to 4 weeks and 52 were not.

4.5. Impact of statins

Statins decreased temperature (\(\Delta T\)) in culprit (grey boxes) and non-culprit (black boxes) lesions compared with non-treated patients (CLs: statins = 0.05 ± 0.04 °C; no statins = 0.08 ± 0.04 °C; \(P<0.01\) versus NCLs: statins = 0.04 ± 0.04 °C; no statins = 0.08 ± 0.04 °C; \(P<0.01\)). Patients using statins with DM compared with non-DM patients had similar \(\Delta T\) in both CLs and NCLs (CLs: DM = 0.06 ± 0.03 °C; non-DM = 0.05 ± 0.04 °C; \(P = 0.70\); NCLs: DM = 0.06 ± 0.05 °C; no-DM = 0.04 ± 0.04 °C; \(P = 0.35\)). DM patients not receiving statins had higher \(\Delta T\) compared with the non-DM in both CLs and NCLs (CLs: DM = 0.13 ± 0.05 °C; no-DM = 0.08 ± 0.04 °C; \(P<0.01\); NCLs: DM = 0.15 ± 0.07 °C; no-DM = 0.08 ± 0.04 °C; \(P<0.01\)).

4.6. CRP measurements

CRP was higher in patients with DM compared with non-DM (1.71 ± 0.86 mg/L versus 0.44 ± 0.39 mg/L respectively; \(P<0.01\)). Linear correlation was detected between heat production in all lesions and CRP (\(R = 0.45\); \(P<0.01\)). In the subgroup analyses, patients with DM had a positive correlation between \(\Delta T\) and CRP (\(R = 0.32\); \(P<0.01\); Fig. 1B). However, in the non-DM patients, no correlation between \(\Delta T\) and CRP was detected (DM: \(R = 0.04\); \(P = 0.59\); NCLs: DM = 0.06 ± 0.05 °C; no-DM = 0.04 ± 0.04 °C; \(P = 0.35\)). DM patients not receiving statins had higher \(\Delta T\) compared with the non-DM in both CLs and NCLs (CLs: DM = 0.13 ± 0.05 °C; non-DM = 0.08 ± 0.04 °C; \(P<0.01\); NCLs: DM = 0.15 ± 0.07 °C; no-DM = 0.08 ± 0.04 °C; \(P<0.01\)).

4.7. Multivariate analysis

Multiple logistic-regression analyses showed that the presence of DM was positively associated with high \(\Delta T\) (OR = 3.88; 95% CI: 1.36–11.01), after adjusting for age, and presence of hypertension and hypercholesterolaemia, as well as type of clinical syndrome. In addition, patients with ACS were 7.6 times lower \(\Delta T\) in both CLs and NCLs compared with non-treated patients (CLs: statins = 0.05 ± 0.04 °C; no statins = 0.08 ± 0.04 °C; \(P<0.01\) versus NCLs: statins = 0.04 ± 0.04 °C; no statins = 0.08 ± 0.04 °C; \(P<0.01\)). Patients using statins with DM compared with non-DM patients had similar \(\Delta T\) in both CLs and NCLs (CLs: DM = 0.06 ± 0.03 °C; non-DM = 0.05 ± 0.04 °C; \(P = 0.70\); NCLs: DM = 0.06 ± 0.05 °C; non-DM = 0.04 ± 0.04 °C; \(P = 0.35\)). DM patients not receiving statins had higher \(\Delta T\) compared with the non-DM in both CLs and NCLs (CLs: DM = 0.13 ± 0.05 °C; non-DM = 0.08 ± 0.04 °C; \(P<0.01\); NCLs: DM = 0.15 ± 0.07 °C; no-DM = 0.08 ± 0.04 °C; \(P<0.01\)).

4.5. Impact of statins

Of the total study population, 52 patients were taking statin treatment for greater or equals to 4 weeks and 52 were not. In the DM group, patients taking statins had lower \(\Delta T\) in both CLs and NCLs compared with non-treated patients (CLs: statins = 0.06 ± 0.03 °C; no statins = 0.13 ± 0.05 °C; \(P<0.01\) versus NCLs: statins = 0.06 ± 0.05 °C; no statins = 0.15 ± 0.07 °C; \(P<0.01\)). Similarly, non-DM patients taking statins had lower \(\Delta T\) in both CLs and NCLs compared with non-treated patients (CLs: statins = 0.05 ± 0.04 °C; no statins = 0.08 ± 0.04 °C; \(P<0.01\) versus NCLs: statins = 0.04 ± 0.04 °C; no statins = 0.08 ± 0.04 °C; \(P<0.01\)). Patients using statins with DM compared with non-DM patients had similar \(\Delta T\) in both CLs and NCLs (CLs: DM = 0.06 ± 0.03 °C; non-DM = 0.05 ± 0.04 °C; \(P = 0.70\); NCLs: DM = 0.06 ± 0.05 °C; non-DM = 0.04 ± 0.04 °C; \(P = 0.35\)). DM patients not receiving statins had higher \(\Delta T\) compared with the non-DM in both CLs and NCLs (CLs: DM = 0.13 ± 0.05 °C; non-DM = 0.08 ± 0.04 °C; \(P<0.01\); NCLs: DM = 0.15 ± 0.07 °C; no-DM = 0.08 ± 0.04 °C; \(P<0.01\)).

Table 3: Temperature measurements based on diabetes mellitus (DM) and clinical syndrome.

<table>
<thead>
<tr>
<th></th>
<th>DM (n = 32)</th>
<th>Non-DM (n = 72)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS (n = 53)</td>
<td>0.13 ± 0.06</td>
<td>0.08 ± 0.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SA (n = 51)</td>
<td>0.08 ± 0.02</td>
<td>0.05 ± 0.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(P)</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Non-culprit lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS (n = 53)</td>
<td>0.15 ± 0.08</td>
<td>0.07 ± 0.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SA (n = 51)</td>
<td>0.08 ± 0.06</td>
<td>0.05 ± 0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; SA: stable angina.
more likely to have high $\Delta T$ compared with those who had SA, after adjusting for the above-mentioned confounders ($OR = 7.6; 95\% CI: 2.96–19.54$). Furthermore, CRP levels were positively associated with high $\Delta T$ ($OR per 1 \text{mg/dL increase} = 1.75; 95\% \text{CI: 0.99–3.08}$) after adjusting for the patients’ age and presence of hypertension and hypercholesterolaemia. DM and type of syndrome were excluded from the latter model because of high colinearity.

5. Discussion

The principal findings for DM patients in this study were:

- there is widespread coronary inflammation, as the $\Delta T$ of CLs and NCLs was similar;
- in patients with ACS, there is profound thermal heterogeneity in both CLs and NCLs compared with those in patients with SA;
- low levels of CRP are not predictive of increased local inflammatory activation;
- patients taking statins have lower thermal heterogeneity in both CLs and NCLs compared with non-treated patients.

Patients with DM may have more diffuse coronary artery disease than non-DM patients. Histological examination of coronary tissue from DM patients exhibited more lipid-rich atheroma and macrophage infiltration, and an increased incidence of ulcerated plaque morphology compared with non-DM patients [8,13]. The concentration of systemic inflammatory markers is also greater in DM patients with or without overt coronary artery disease. However, other studies have found no significant differences in the risk of diffuse lesions between DM and non-DM [1,7]. In particular, DM patients more often had multivessel disease, although the disease was not necessarily more diffuse than in non-DM patients [14]. It appears that the mere presence of DM does not affect the patient’s prognosis; however, if coronary atherosclerosis is already present, then DM adds a further risk to that of coronary artery disease [5].

Nevertheless, in this study, we demonstrated that local inflammatory involvement is found simultaneously in both CLs and NCLs compared with those in patients with SA [17–20]. An interesting finding was the discrepancy observed in 21% of patients with SA, but also for NCLs using a strategy that combines pharmaceutical and interventional approaches.

Whether the evaluation of CRP would serve as an additional criterion for the assessment of a stenosis that requires intervention needs to be clarified in future studies. The discrepancy between CRP levels and local inflammatory involvement in patients with DM may be important in those who have low levels of systemic inflammatory indices.

5.1. Clinical implications

The findings of the present study support the idea that, in DM patients, NCLs and the increased thermal heterogeneity in CLs need to be further evaluated, as they may have an increased risk. Several new invasive methods, such as optical coherence tomography, intravascular ultrasound, virtual histology and elastography may help in the identification of patients with high-risk plaques [21–24]. In such patients, a more aggressive therapeutic strategy is required not only in the mechanical treatment of CLs but also for NCLs using a strategy that combines pharmaceutical and interventional approaches.

Both CLs and NCLs were angiographically intermediate and, therefore, no conclusions can be extrapolated to apply to stenoses less than 50% or in significant lesions. However, the treatment of CLs that provoke significant stenosis is not a major problem in clinical practice, as an intervention is usually performed. Intermediate stenoses, however, need to be further morphologically and functionally evaluated to determine a therapeutic strategy, especially in patients with ACS. It is also important to evaluate stenoses less than 50% to prevent future ACS. However, the coronary thermography catheter used in the present study cannot exclude the ‘cooling effect’ of blood flow [25]. Nevertheless, our study population, the rates of stenosis, which were similar in CLs and NCLs, did not influence our findings, as demonstrated by multivariate analyses. Thus, the conclusions of the present study could be stronger as thermal heterogeneity may be underestimated in both CLs and NCLs.

6. Conclusion

In patients with DM, local inflammatory activation is diffuse and correlates with systemic inflammation that, in turn, supports the idea of global coronary instability and widespread systemic inflammation. However, low systemic inflammation cannot predict the increase of local inflammatory activation in
coronary atheromatous lesions. Thus, extensive investigation of atheromatous lesions is required in patients with DM.

7. Conflict of interests

The authors have no conflict of interests to declare.

References


