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Original article

# Insights from a thermography-based method suggesting higher carotid inflammation in patients with diabetes mellitus and coronary artery disease

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**Abstract**

*Aim.* – Diabetes mellitus (DM) is an independent risk factor for stroke. In a DM population, carotid atheromatosis is a major cause of stroke. The role of carotid plaque inflammation remains conflicting. Microwave radiometry (MWR) is a new non-invasive method allowing in vivo measurement of the temperature of tissues, so reflecting inflammation. The aim of this prospective study was to evaluate the impact of DM on carotid artery inflammation in patients with documented coronary artery disease (CAD).

*Methods.* – Consecutive patients ($n = 300$) with significant CAD were evaluated by: (1) ultrasound study of both carotid arteries; and (2) the temperature difference ($\Delta T$) along each carotid artery on MWR. $\Delta T \geq 0.90\,^{\circ}C$ was considered high $\Delta T$. Vessel- and patient-based analyses were performed to determine the impact of DM on morphological and functional characteristics of carotid arteries.

*Results.* – Out of 300 patients, 113 (37.7%) had DM. Patients with DM had similar carotid plaque thickness compared with patients without DM in both vessel- and patient-based analyses. In contrast, patients with DM exhibited higher $\Delta T$ values in both vessel- and patient-based analyses. On multivariate logistic regression analysis, DM was an independent predictor of high $\Delta T$ both unilaterally and bilaterally (OR: 1.66, 95% CI: 1.06–2.58, $P = 0.03$ and OR: 1.96, 95% CI: 1.01–3.81, $P = 0.05$, respectively).

*Conclusion.* – In patients with CAD, DM was an independent predictor of local carotid plaque inflammatory activation. Whether or not the assessment of functional plaque characteristics by MWR can be an additional prognostic tool independent of structural factors now needs to be further investigated.


*Keywords:* Carotid ultrasound; Inflammation; Coronary artery disease; Microwave radiometry; Diabetes mellitus

## 1. Introduction

Diabetes mellitus (DM) is independently associated with a two- to six-fold increased rate of stroke after adjusting for all other known risk factors [1,2]. Carotid atherosclerosis is a major cause of stroke [3]. Inflammation has been suggested to play a pivotal mechanistic role in the atherogenesis in DM [4]. Nevertheless, data regarding the role of systemic inflammatory status remain conflicting. While several studies have shown that levels of high-sensitivity C-reactive protein (CRP) is a prognostic biomarker for stroke along with cardiovascular events [5], other studies have failed to show such a relationship [6–8].

Ultrasonography constitutes an invaluable tool for the assessment of carotid atherosclerosis in DM. Intima–media thickness (IMT) and plaque score are independent predictors of stroke in patients with DM [9,10]. However, ultrasonography provides no information on the inflammatory status of the carotid arteries, whereas differences in their morphological and functional characteristics have already been demonstrated in patients with DM [11]. New methods have shown that local inflammatory activation, as quantified by 18-fluorodeoxyglucose positron emission

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tomography ($^{18}$FDG-PET), is increased in patients with DM and has prognostic implications [12–14]. Although $^{18}$FDG-PET is the most accurate non-invasive method for detection of local inflammation, its wider application is still not feasible, especially for serial evaluations. Thus, new non-invasive methods are required for assessment of inflammatory activation to stratify patients with carotid atheromatosis [15,16]. Microwave radiometry (MWR) allows in vivo non-invasive measurement of the temperature of carotid atherosclerotic plaques, thereby reflecting their inflammatory status, although, in fact, there is no evidence of a direct etiological relationship between inflammation and heat generation in atherosclerosis [17–20].

The aim of the present study was to investigate the inflammatory status of carotid atherosclerotic plaques in patients with both DM and coronary artery disease (CAD), as assessed non-invasively by MWR.

## 2. Methods

### 2.1. Study population

Consecutive patients undergoing coronary angiography for evaluation of either stable angina (SA) or acute coronary syndrome (ACS) were prospectively enrolled in the study. Patients with CAD, as documented by coronary angiography ($\geq 50\%$ stenosis in one major epicardial vessel), underwent standard carotid ultrasound examination followed by MWR measurement carried out by different blinded specialists.

The study population was divided into two groups: patients with type 2 diabetes mellitus (DM group) and patients without diabetes mellitus (non-DM group). The definition of DM was based on American Diabetes Association (ADA) diagnostic criteria [21].

Conventional risk factors for CAD, current medical therapy and laboratory data were recorded for all patients. Exclusion criteria for MWR were previous stroke or transient ischemic attacks, vasculitis, non-atherosclerotic carotid artery disease and/or intermittent inflammatory, infectious or neoplastic conditions. All participants gave their informed consent, and our institution's ethics committee approved the study.

### 2.2. Ultrasound imaging

Carotid artery ultrasound imaging was performed as previously described [17,19,20]. More specifically, extracranial (common, internal, external) carotid arteries were examined with a high-resolution B-mode ultrasound unit (iE33 xMATRIX, Philips Healthcare, Bothell, WA, USA), using a 7.5 MHz transducer. All data were collected and interpreted by two experienced ultrasonographers (D.T., C.A.).

The ultrasound protocol included scanning of both carotid arteries from their point of origin throughout their whole length. Both the internal and external carotid arteries were investigated in transverse and longitudinal sections. The vertebral arteries were also examined and evaluated with color and power Doppler imaging.

IMT measurements were performed as previously described [22]. In particular, IMT was measured at the far wall of the distal 10 mm of the common carotid segment of each carotid artery and designated "ccIMT". The highest value for both carotid arteries was termed "$ccIMT_{max}$".

Carotid plaques were identified as focal structures encroaching at least 0.5 mm into the arterial lumen, with focal wall thickening $\geq 50\%$ than the surrounding vessel wall or a thickness > 1.5 mm, as measured from the intima–lumen interface to the media–adventitia interface [22]. The following parameters were evaluated in all carotid plaques: thickness; echogenicity; texture; and surface contour.

Plaque thickness measurements were performed in three 20 mm segments along each carotid artery. In each case, the middle segment was the region of common carotid bifurcation (bifurcation segment) and served as a marker. The regions 20 mm proximal and 20 mm distal to the bifurcation region defined the two other segments—namely, the common carotid artery segment and the internal carotid artery segment, respectively. Maximum plaque thickness for each segment was calculated from three preselected images. The segment of each carotid artery with the highest plaque thickness was designated the "target segment" for the following MWR measurements. The greatest plaque thickness in the target segment was also used in the vessel-based analysis. For the carotids in which no plaques were identified, the bifurcation segment was the "target segment". The greatest plaque thickness of both carotid arteries was defined as the "max plaque thickness".

For plaque echogenicity assessment, the Gray–Weale classification was used as previously described (Types I–V) [19,20,23–25].Type I and II plaques were considered fatty, Type III and IV as mixed, and Type V as calcified. According to the classification previously described, fatty plaques were considered heterogeneous and mixed, and calcified plaques were homogeneous. The plaque surface was defined as regular if smooth or irregular if a variation $\geq 0.3$ mm was observed on the surface of any plaque with a thickness of 1 mm [26].

### 2.3. Microwave radiometry measurements

RTM-01-RES, a microwave computer-based system (Bolton, UK), was used for the MWR measurements. The system measures the temperature of internal tissues at microwave frequencies. To avoid any influence on temperature from palpation or ultrasonography, MWR measurements were obtained at least 10 min after ultrasound examination. The basic principles of MWR have been previously described [17–20]. In brief, the MWR system has an antenna with two sensors: one for microwaves and the other for infrared. The microwave sensor filters all possible microwaves or radiofrequency waves that may be present in the room vicinity and cause interference with the sensor. The antenna is 3.9 cm in diameter and detects microwave radiation at 2–5 GHz with an accuracy of 0.20 °C. The "volume under investigation" is a rectangular area 3 cm wide, 2 cm long and 3–7 cm in depth, depending on the water content of the body. The second sensor takes infrared measurements from the skin for calibrating the microwave sensor readings.