International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Thermal heterogeneity of carotid arteries as a novel biomarker in patients with diabetes mellitus assessed for coronary artery disease

G. Tzanis [a,*], M. Bonou [a], G. Benetos [a,c], S. Biliou [a], S. Liatis [b], C. Kapelios [a], K. Toutouzas [c], D. Tousoulis [c], J. Barbetseas [a]

[a] Cardiology Department, Laiko General Hospital, Athens, Greece
[b] First Department of Propaedeutic Internal Medicine, Diabetes Center, Laiko General Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece
[c] First Department of Cardiology, Hippokration Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece

ARTICLE INFO

Article history:
Received 9 July 2017
Received in revised form 10 March 2018
Accepted 21 March 2018
Available online xxxx

Keywords:
Thermal heterogeneity
Vulnerable plaque
Carotid
Coronary artery disease
Microwave radiometry
Diabetes mellitus

ABSTRACT

Background: Vulnerable plaque plays crucial role in prognosis of diabetes mellitus (DM). Microwave radiometry (MWR) allows measurement of the temperature of tissues, thus indirectly reflecting inflammation, a characteristic of atherosclerotic plaque stability. Aim of the study was to evaluate the relation of carotid artery inflammation with glycemic control and presence of coronary artery disease (CAD).
Methods: We included 112 patients (65 ± 9 years, 30 ± 5 kg/m^2, 74 DM and 38 non-DM, with a 2:1 ratio) that were referred for scheduled coronary angiography (CA) for evaluation of their clinical condition. We measured thermal heterogeneity, expressed as temperature difference (ΔT) along each carotid artery, with MWR and maximum temperature difference between the 2 carotid arteries (ΔTmax).
Results: Patients with DM presented higher ΔTmax comparing to patients without DM (0.91 ± 0.29 vs 0.71 ± 0.25 °C, $p < 0.001$). Glycaemia over time was associated with thermal heterogeneity of carotids (HbA1c: <*6.5*: 0.78 ± 0.23, HbA1c: *6.5–7*: 0.87 ± 0.24, HbA1c: *7–8*: 0.99 ± 0.30, HbA1c: >*8*: 1.15 ± 0.35 °C, $p = 0.003$). Patients with CAD presented higher ΔTmax comparing to patients with normal CA (0.93 ± 0.24 vs 0.68 ± 0.25 °C, $p < 0.001$) and patients that underwent coronary revascularization presented higher ΔTmax (0.95 ± 0.25 vs 0.76 ± 0.26 °C, $p < 0.001$). A ΔTmax ≥ 0.9 (received by ROC analysis) was an independent predictor for revascularization in DM patients (odds ratio 3.29, 95% CI: 1.07–10.16; $p = 0.039$) when adjusted for sex, age and the established risk factors of CAD.
Conclusion: Local inflammatory activation of carotid arteries is more pronounced in patients with DM and is associated with the glycemic control. Carotids' thermal heterogeneity is associated with need for revascularization supporting its predictive value in DM patients assessed for CAD.

1. Introduction

Diabetes mellitus (DM) is established as one of the significant risk factors of coronary artery disease (CAD) that affects cardiovascular events and mortality [1]. Vulnerable plaques seem to play a crucial role in cardiovascular outcomes [2], while glycemic status and presence of DM is associated with more pronounced vulnerable plaque characteristics [3,4], probably linked to the unfavorable outcomes. Early identification of vulnerable atherosclerotic plaques in order to intervene in level of primary and secondary prevention could dramatically change outcomes of cardiovascular disease.

Microwave radiometry (MWR) is a new non-invasive method allowing measurement of the temperature of tissues, thus indirectly reflecting inflammation, a characteristic of vulnerable plaques [5]. This method can designate thermal heterogeneity (TH) of carotid arteries [6,7], which, unlike structural characteristics and degree of luminal stenosis, assesses the inflammatory activation within the plaque [8]. TH of carotids has been found to be predictive of the presence and extend of CAD [9], and is significantly attenuated in patients with CAD and DM [10]. However, the relationship of TH with glycemic control and its impact on the need for coronary revascularization has not been investigated so far.

We aimed to assess the relation of carotid artery inflammation with: a) glycemic control and b) coronary revascularization, in patients with DM undergoing coronary angiography for CAD assessment.

2. Methods

2.1. Study population

We prospectively evaluated 112 patients that were referred to our department for scheduled diagnostic coronary angiography (CA) for evaluation of their clinical status, without including patients with myocardial infraction. Patients were enrolled with a 2:1

* Corresponding author at: Cardiology Department, Laiko General Hospital, 17, Agiou Thoma str, Athens 11527, Greece.
E-mail address: gs.tzanis@gmail.com (G. Tzanis).

https://doi.org/10.1016/j.ijcard.2018.03.102
0167-5273/

ratio (DM: non-DM) in order to better investigate the effects of glycemic control in DM patients.

All patients were evaluated for temperature difference (ΔT) along each carotid artery with MWR. Patients' baseline, clinical characteristics and medications are presented in Table 1. All participants gave informed consent to participate in the study, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study was approved by the ethics committee of the institution.

2.2. Microwave radiometry measurements

The MWR measurements were performed with the RTM 01 RES microwave computer-based system (Bolton, UK). The system measures the temperature of internal tissues at microwave frequencies. The basic principles of MWR have been previously described [7,9]. 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 detects microwave radiation at 2–5 GHz. The volume under investigation is a rectangular area 3 cm wide, 2 cm long and 3–7 cm in depth. The second sensor takes infrared measurements from the skin for calibrating the microwave sensor reading.

The segments analyzed were about 20 mm in length, starting from the proximal common carotid artery and moving distally, thus avoiding overlapping or missing areas by MWR. The microwave antenna of the device was placed at a 90° angle to the skin. After setting vertically the transducer, carotid temperature measurements were performed three times on each segment (overall, 9 measurements). The temperature of each segment used for further analysis was the mean of the 3 temperatures. This method has been validated as previously described [6,7]. The temperature difference (ΔT) for each carotid artery was defined as the temperature of the segment with the highest temperature minus the lowest temperature for each carotid (reference temperature), as previously described [7,9]. In the statistical analysis, "ΔTmax" was defined as the maximum ΔT value of both carotid arteries.

2.3. Laboratory tests

The laboratory tests included an evaluation of glycemic control based on fasting glucose and glycated haemoglobin (HbA1c) and other tests measuring total cholesterol and fractions, triglycerides, urea, creatinine, transaminases, and blood count. High-sensitivity troponin T (TnT-hs) was analyzed only in 37 patients, because only during the last period of the study the high sensitivity assay was available. HbA1c values were obtained from all patients (DM and non DM).

Table 1
Baseline characteristics and medication.

	Total (n = 112)	DM (n = 74)	Non-DM (n = 38)	p Value
Clinical characteristics				
Age, years	65 ± 9	66 ± 9	63 ± 9	0.08
Body mass index, kg/m^2	30 ± 5	30 ± 5	30 ± 5	0.89
Gender, m/f	70/42	44/30	26/12	0.57
Hypertension	85 (76)	59 (80)	26 (68)	0.19
Dyslipidaemia	71 (63)	51 (69)	22 (58)	0.25
Family history	14 (13)	7 (10)	7 (18)	0.18
Smoking (current)	38 (34)	23 (31)	15 (40)	0.64
CAD history	28 (25)	19 (26)	9 (24)	0.82
DM duration, years	–	11 ± 9	–	
Coronary angiography				0.26
1-vessel CAD (%)	25	26	24	
2-vessel CAD (%)	17	16	17	
3-vessel CAD (%)	18	23	11	
Medication				
ASA	42 (38)	28 (38)	14 (37)	0.94
ADP receptor inhibitor	27 (24)	19 (25)	8 (20)	0.55
ACE-i/ARB	73 (65)	49 (66)	24 (63)	0.75
Calcium antagonist	22 (20)	16 (22)	6 (17)	0.57
b-blocker	68 (61)	45 (61)	23 (60)	0.92
Diuretics	48 (43)	33 (44)	15 (40)	0.70
Statins	72 (64)	55 (74)	17 (46)	**0.01**
Laboratory tests				
Glucose, mg/dl	142 ± 59	161 ± 66	102 ± 16	<**0.001**
Haemoglobin A1c, %	6.6 ± 1.4	7.1 ± 1.5	5.5 ± 0.4	<**0.001**
Haemoglobin, g/dl	13.6 ± 1.8	13.4 ± 1.7	14.1 ± 1.8	**0.05**
Creatinine, mg/dl	1.0 ± 0.6	1.1 ± 0.8	0.9 ± 0.2	0.13
AST, U/L	24 ± 15	25 ± 18	21 ± 7	0.29
ALT, U/L	23 ± 16	24 ± 18	21 ± 10	0.33
Total cholesterol, mg/dL	167 ± 37	163 ± 38	178 ± 30	0.12
LDL cholesterol, mg/dL	91 ± 31	88 ± 30	98 ± 36	0.30
HDL cholesterol, mg/dL	44 ± 13	42 ± 11	51 ± 16	**0.01**
Triglyceride, mg/dL	146 ± 73	151 ± 80	130 ± 47	0.28

DM: Diabetes mellitus; CAD: Coronary artery disease; ASA: Acetylsalicylic acid; ADP: Adenosine diphosphate; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blockers; AST/ALT: Aspartate/alanine transaminase; LDL/HDL: low-density/high-density lipoprotein; Values are mean ± SD.
Bold indicates significance of p < 0.05.

2.4. Coronary angiography

Angiograms were assessed independently by 2 experienced interventional cardiologists. CAD was defined as angiographic atherosclerotic involvement of >50% in at least 1 major coronary artery or its major branches. The severity of CAD was assessed from the number of involved coronary vessels with significant luminal obstructions.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation. Before analysis, all continuous variables were tested by Kolmogorov-Smirnov test showing normal distribution. Group means of continuous variables were compared by unpaired Student's *t*-test. ΔTmax values between HbA1c and CAD categories (known without progression, known with disease progression and first diagnosis) were compared using one-way analysis of variance (ANOVA).

Correlations between variables were obtained and tested by Pearson's correlation coefficient after tested for normality curves. The cut-off value for ΔTmax to predict presence of CAD was based on receiver operating characteristic (ROC) curve analysis. Multiple logistic regression analysis was used to determine independent predictors for coronary revascularization in presence of CAD. The lowest level for statistical significance was set at p < 0.05.

3. Results

We included a total of 112 patients, 74 DM patients (44 males, 66 ± 9 years, 30 ± 5 kg/m^2) and 38 patients without DM (26 males, 63 ± 9 years, 30 ± 5 kg/m^2, Table 1).

Patients with DM presented significantly higher TH comparing to patients without DM (0.91 ± 0.29 vs 0.71 ± 0.25 °C, p < 0.001). Glycaemia control over time was associated with TH of carotid arteries in DM patients (*HbA1c < 6.5%*: 0.78 ± 0.23, *HbA1c 6.5–7%*: 0.87 ± 0.24, *HbA1c 7–8%*: 0.99 ± 0.30, *HbA1c > 8%*: 1.15 ± 0.35 °C, p = 0.003 ANOVA, Fig. 1). A significant correlation between HbA1c and ΔTmax was found in patients with DM (r = 0.50, p < 0.001), while in non-DM patients HbA1c was not found to be correlated with ΔTmax (r = 0.09, p = 0.63).

Patients with CAD presented higher ΔTmax comparing to patients with normal CA (0.93 ± 0.24 vs 0.68 ± 0.25 °C, p < 0.001, Fig. 2). This finding was confirmed also for both patient subgroups: a) DM patients with CAD presented higher ΔTmax than DM without CAD (0.96 ± 0.25 vs 0.77 ± 0.26 °C, p = 0.005), b) non-DM patients with CAD presented higher ΔTmax than non-DM patients without CAD (0.85 ± 0.23 vs 0.54 ± 0.18 °C, p < 0.001). Another notable finding is that

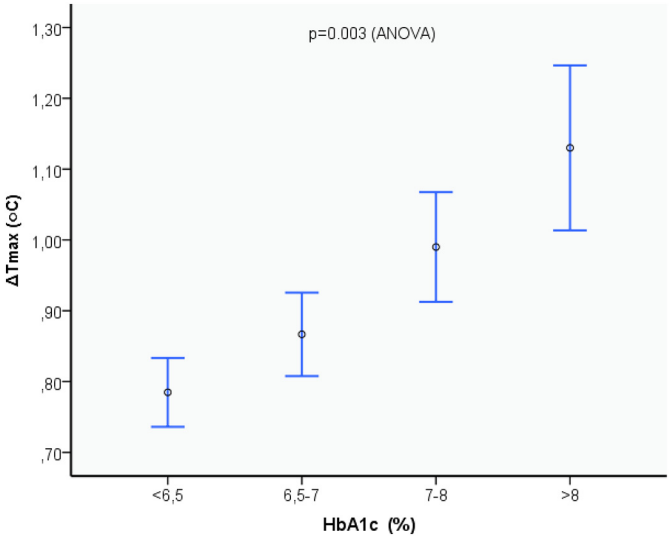

Fig. 1. Hba1c levels and thermal heterogeneity of carotid arteries. (Bars are mean ± SE).

Please cite this article as: G. Tzanis, et al., Thermal heterogeneity of carotid arteries as a novel biomarker in patients with diabetes mellitus assessed for coronary artery dis..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.03.102

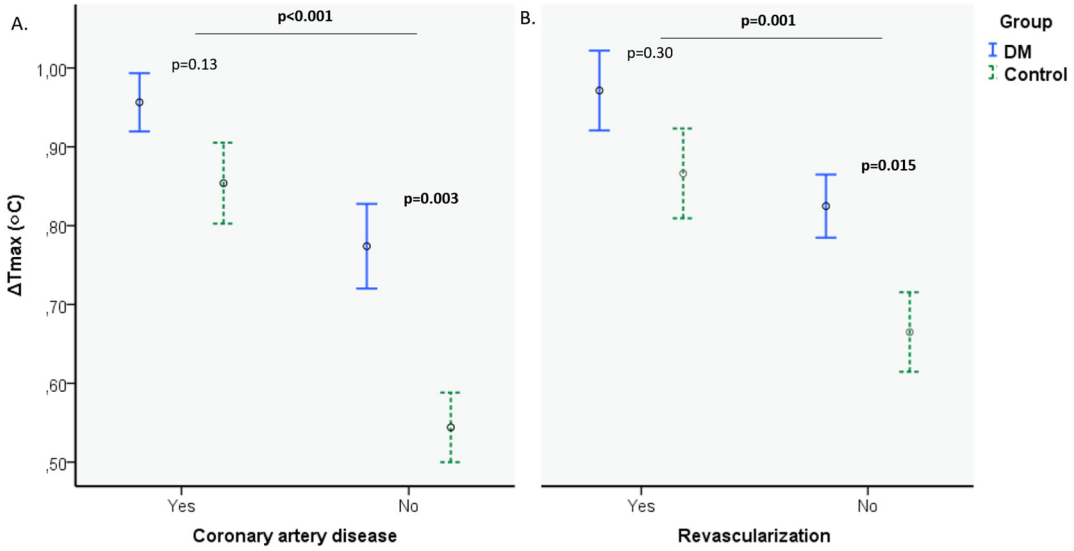

Fig. 2. A) Thermal heterogeneity of carotid arteries in patients with and without CAD, **B)** Thermal heterogeneity of carotid arteries in patients that underwent or not coronary revascularization. (Bars are mean ± SE).

among patients without CAD: DM patients had higher ΔTmax when compared to non-DM (0.77 ± 0.26 vs 0.54 ± 0.18 °C, p = 0.003, Fig. 2). Among patients with CAD there was no significant temperature difference between patients with and without DM (Fig. 2).

Forty patients finally underwent coronary revascularization (27 males, 66 ± 9 years, 29 ± 5 kg/m^2) with percutaneous coronary intervention (n = 28) or coronary artery bypass grafting (n = 12). Patients that underwent revascularization also presented higher ΔTmax values comparing to patients with no need for revascularization, either because of absence of CAD or because of CAD without indications for coronary revascularization (0.95 ± 0.25 vs 0.75 ± 0.26 °C, p = 0.001, Fig. 2). This finding was also confirmed for each of the patient subgroups: a) DM patients with need for revascularization presented higher ΔTmax than DM without revascularization (0.97 ± 0.27 vs 0.82 ± 0.25 °C, p = 0.025), b) non-DM patients with need for revascularization presented higher ΔTmax than non-DM patients without revascularization (0.87 ± 0.16 vs 0.66 ± 0.26 °C, p = 0.036). There was a trend for higher ΔTmax for DM patients comparing to patients without DM, that underwent revascularization although not statistically significant (0.97 ± 0.27 vs 0.87 ± 0.16 °C, p = 0.30, Fig. 2). Patients with 3-vessel disease had higher ΔTmax (1.02 ± 0.25 vs 0.87 ± 0.22 °C, p = 0.02).

From patients with CAD, patients with disease progression (comparing to their previous CA) presented significantly higher TH of carotids when compared to patients with known CAD but without disease progression from previous CA (1.03 ± 0.25 vs 0.79 ± 0.20 °C, p = 0.03, Fig. 3), while there was noted a trend for statistical significance for the differences of ΔTmax values between all 3 groups (p = 0.056, ANOVA). An interesting correlation was found between TnT-hs and ΔTmax, in the sub-group of 37 patients that where analyzed for TnT-hs (r = 0.41, p = 0.01).

By receiver-operating characteristic (ROC) curve analysis, we obtained a good predictive capacity of ΔTmax for CAD [AUC (area under the curve) = 0.79, 95% CI: 0.69–0.88; p < 0.001] with a ΔTmax value of 0.8 °C having sensitivity 61% and specificity 83% for presence of CAD. We also obtained a good predictive capacity of ΔTmax for CAD in DM patients [AUC = 0.73, 95% CI: 0.60–0.86; p = 0.002].

In multivariate logistic regression analysis, ΔTmax≥ 0.8 was an independent predictor for revascularization (odds ratio 3.48, 95% CI: 1.32–9.18; p = 0.01), when adjusted for gender, age and the established risk factors of CAD (DM, hypertension, smoking, dyslipidemia, family history of CAD). For patients with DM a ΔTmax≥ 0.9 (received by ROC analysis) was an independent predictor for revascularization (odds ratio 3.29, 95% CI: 1.07–10.16; p = 0.039) when adjusted for the same factors.

4. Discussion

Our findings highlight the role of thermal heterogeneity of carotid arteries estimation in DM patients assessed for CAD. We showed that in patients undergoing scheduled coronary angiography for CAD assessment: a) TH is a significant independent predictor of coronary revascularization and is associated with the presence of CAD, b) TH is more pronounced in patients with DM and it is associated with glycaemia over time.

4.1. Thermal heterogeneity and glycemic control

Inflammatory activation, a marker of vulnerable atherosclerotic plaque, within carotid arteries has been previously shown to be

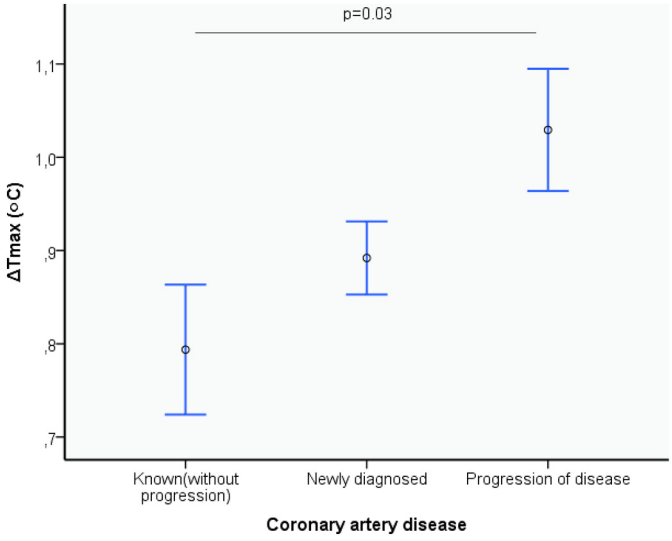

Fig. 3. Thermal heterogeneity of carotid arteries according to the status of CAD: Presence of CAD without disease progression comparing to previous coronary angiogram; newly diagnosed CAD; disease progression comparing to previous coronary angiogram. (Bars are mean ± SE).

Please cite this article as: G. Tzanis, et al., Thermal heterogeneity of carotid arteries as a novel biomarker in patients with diabetes mellitus assessed for coronary artery dis..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.03.102

associated with heat formation by activated macrophages and thermal heterogeneity [11]. In our study, local carotid artery inflammation was assessed by MWR, which has been found to provide accurate temperature measurements to assess TH, reflecting the local inflammatory activation [12].

We found that patients with DM presented higher carotid arteries inflammation comparing to patients evaluated for CAD without DM. Our finding is in agreement with the previous study by Toutouzas et al., which showed that DM in patients with CAD is an independent predictor of TH while morphological characteristics (i.e. atherosclerotic plaque thickness) were similar between patients with and without DM [10]. However, a remarkable finding of our study is that DM patients without CAD also presented significantly higher carotid arteries inflammation, possibly indicating that DM might interfere early in the cardiovascular disease progression with vulnerable atherosclerotic plaque formation.

It is already known that there is a correlation between glycaemia and microvascular complications of DM without an obvious threshold [13,14], while the association with macrovascular disorders is less clear. It has been previously shown that HbA1c was a predictor of CAD with critical lesions [15]. Tavares et al. investigated the role of glycemic control in DM with presence of CAD and characteristics of atherosclerotic plaques, more specifically they demonstrated that DM patients with poorest glycemic control were prone to higher frequency of CAD, increased CAD severity, and plaque characteristics (associated with detection of vulnerable plaques) compared to those with adequate control [16], providing evidence that CAD and vulnerable plaques are associated with poorest glycemic control. We have shown, for the first time (to our knowledge), that TH a marker of vulnerable plaque was associated with the glycaemia status over time as assessed by HbA1c levels. This finding supports the evidence from the previous study by Tavares et al. [16] linking glycemic control with presence of vulnerable plaque characteristics.

4.2. Thermal heterogeneity and revascularization

Another finding arose from our study is that patients with CAD and patients that finally underwent coronary revascularization had significantly higher carotid arteries inflammation. This is in agreement with the previous study by Toutouzas et al. demonstrating an increased local inflammation of carotid arteries in patients with CAD [9]. In that study, TH was increased proportionally to the extent of CAD as detected by CA [9]. Similarly, we presented higher TH in presence of 3-vessel disease. For first time we showed a more unfavorable profile for patients with progression of CAD; patients with angiographic evidence of disease progression had more pronounced carotid arteries inflammation, in concordance with the more unfavorable outcomes of this group of patients [17].

There are also previous studies correlating carotid arteries stenosis [18] and characteristics, i.e. intima-media thickness, with the presence of CAD [9,19], while one step further Fujihara et al. showed that intima-media thickness was predictive of vulnerable coronary plaque [20]. Also, in patients with acute ischemic stroke culprit arteries present high TH and TH offers incremental predictive value in the identification of culprit carotid artery [21]. The same research team showed that carotid inflammation was predictive for the presence of CAD [9]. Toutouzas et al. in recent elegant study found that carotid inflammation was independently associated with one-year major adverse cardiovascular events rate and had an incremental prognostic value for patients with CAD [22]. Our findings are in line with these studies. We confirmed the predictive ability of TH for presence of CAD.

Finally, our study showed for first time that carotid artery inflammation was an independent predictor of coronary revascularization for all patients referred for diagnostic CA and additionally for patients with DM. The impact of these observations on prognosis and diagnostic quiver of CAD remains to be clarified.

4.3. Study limitations

This is a cross-sectional study, therefore the predictivity of the TH for long term outcomes, such as stoke or acute coronary syndromes, could not be assessed. Moreover, the physician who performed the MWR measurements was not blinded for the presence of DM or CAD, but he was blinded for the HbA1c values. Another limitation of our study is that patients were enrolled with a 2:1 ratio (DM: non-DM) in order to better evaluate the glycemic control in DM patients, and thus DM patients are overexpressed in our results.

Finally, we did not assess carotid arteries with ultrasound imaging, so we could not correlate thermal heterogeneity with presence, extend and characteristics of atherosclerotic plaques. However, the predictive value of carotid arteries heterogeneity was significant irrespectively of the existence or extend of atherosclerotic burden, emphasizing its role as a possible biomarker. This is also supported by a recent study that has not found any correlation between lumen stenosis and TH of carotids [8].

5. Conclusions

In patients with DM local carotid plaque inflammation, as evaluated by MWR, is associated with glycemic control. Thermal heterogeneity of carotid arteries was predictive of coronary revascularization in patients evaluated for CAD.

Disclosures

Dr. Tzanis was funded with a grant by Hellenic Heart Foundation (ELIKAR) for this study.

Acknowledgements

We wish to express our gratitude to Dr. Vasileios Votteas for his contribution and support.

References

[1] W.B. Kannel, D.L. McGee, Diabetes and cardiovascular disease. The Framingham study, JAMA 241 (1979) 2035–2038.
[2] R. Virmani, F.D. Kolodgie, A.P. Burke, A. Farb, S.M. Schwartz, Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 1262–1275.
[3] R. De Rosa, M. Vasa-Nicotera, D.M. Leistner, et al., Coronary atherosclerotic plaque characteristics and cardiovascular risk factors - insights from an optical coherence tomography study, Circ. J. 81 (2017) 1165–1173.
[4] K. Suzuki, H. Takano, Y. Kubota, et al., Plaque characteristics in coronary artery disease patients with impaired glucose tolerance, PLoS One 11 (2016), e0167645.
[5] K. Toutouzas, G. Benetos, A. Karanasos, Y.S. Chatzizisis, A.A. Giannopoulos, D. Tousoulis, Vulnerable plaque imaging: updates on new pathobiological mechanisms, Eur. Heart J. 36 (2015) 3147–3154.
[6] K. Toutouzas, C. Grassos, M. Drakopoulou, et al., First in vivo application of microwave radiometry in human carotids: a new noninvasive method for detection of local inflammatory activation, J. Am. Coll. Cardiol. 59 (2012) 1645–1653.
[7] K. Toutouzas, M. Drakopoulou, C. Aggeli, et al., In vivo measurement of plaque neovascularisation and thermal heterogeneity in intermediate lesions of human carotid arteries, Heart 98 (2012) 1716–1721.
[8] K. Toutouzas, I. Koutagiar, G. Benetos, et al., Inflamed human carotid plaques evaluated by PET/CT exhibit increased temperature: insights from an in vivo study, Eur. Heart J. Cardiovasc. Imaging 18 (2016) 1236–1244.
[9] K. Toutouzas, G. Benetos, M. Drakopoulou, et al., Morphological and functional assessment of carotid plaques have similar predictive accuracy for coronary artery disease, Stroke 44 (9) (2013) 2607.
[10] K. Toutouzas, G. Benetos, M. Drakopoulou, et al., Insights from a thermography-based method suggesting higher carotid inflammation in patients with diabetes mellitus and coronary artery disease, Diabete Metab. 40 (2014) 431–438.
[11] W. Casscells, B. Hathorn, M. David, et al., Thermal detection of cellular infiltrates in living atherosclerotic plaques: possible implications for plaque rupture and thrombosis, Lancet 347 (1996) 1447–1451.
[12] K. Toutouzas, H. Grassos, A. Synetos, et al., A new non-invasive method for detection of local inflammation in atherosclerotic plaques: experimental application of microwave radiometry, Atherosclerosis 215 (2011) 82–89.
[13] I.M. Stratton, A.I. Adler, H.A. Neil, et al., Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study, BMJ 321 (2000) 405–412.

[14] Anon, The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial, Diabetes 45 (1996) 1289–1298.
[15] M. Shimabukuro, T. Saito, T. Higa, et al., Risk stratification of coronary artery disease in asymptomatic diabetic subjects using multidetector computed tomography, Circ. J. 79 (2015) 2422–2429.
[16] C.A. Tavares, C.H. Rassi, M.G. Fahel, B.L. Wajchenberg, C.E. Rochitte, A.C. Lerario, Relationship between glycemic control and coronary artery disease severity, prevalence and plaque characteristics by computed tomography coronary angiography in asymptomatic type 2 diabetic patients, Int. J. Card. Imaging 32 (2016) 1577–1585.
[17] G. Ndrepepa, R. Iijima, S. Kufner, et al., Association of progression or regression of coronary artery atherosclerosis with long-term prognosis, Am. Heart J. 177 (2016) 9–16.
[18] I. Kallikazaros, C. Tsioufis, S. Sideris, C. Stefanadis, P. Toutouzas, Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain, Stroke 30 (1999) 1002–1007.
[19] Y. Irie, N. Katakami, H. Kaneto, et al., Maximum carotid intima-media thickness improves the prediction ability of coronary artery stenosis in type 2 diabetic patients without history of coronary artery disease, Atherosclerosis 221 (2012) 438–444.
[20] K. Fujihara, H. Suzuki, A. Sato, et al., Carotid artery plaque and LDL-to-HDL cholesterol ratio predict atherosclerotic status in coronary arteries in asymptomatic patients with type 2 diabetes mellitus, J. Atheroscler. Thromb. 20 (2013) 452–464.
[21] K. Toutouzas, G. Benetos, M. Drakopoulou, et al., Incremental predictive value of carotid inflammation in acute ischemic stroke, Stroke 46 (2015) 272–274.
[22] K. Toutouzas, G. Benetos, I. Koutagiar, et al., Noninvasive detection of increased carotid artery temperature in patients with coronary artery disease predicts major cardiovascular events at one year: results from a prospective multicenter study, Atherosclerosis 262 (2017) 25–30.

Please cite this article as: G. Tzanis, et al., Thermal heterogeneity of carotid arteries as a novel biomarker in patients with diabetes mellitus assessed for coronary artery dis..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.03.102