Choroidal Thickness and Carotid Artery Doppler Ultrasound in Diabetic Patients without Diabetic Retinopathy

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ABSTRACT

Purpose: To correlate choroid thickness (CT) with carotid arteries ultrasound (US) variables in patients with diabetes mellitus without diabetic retinopathy (DR).

Methods: Cross-sectional study of 17 eyes and 17 carotid US of 17 diabetic patients without DR. CT was measured with EDI-OCT. Common and Internal Carotid Arteries (CCA, ICA) US were performed and the variables: Peak Systolic Velocity (PSV), End-Diastolic Velocity, Resistance Index (RI) and Intima-Media Thickness were measured. Systemic Blood Pressure (SBP) and Ocular Pulse Amplitude were also assed.

Results: CT at 1500 μm inferior to the fovea correlated negatively with RI of ICA and CCA (p=0.022 and 0.035, r=-0.55 and -0.52). CT was not correlated with the other variables. The SBP was positively correlated with PSV and RI of ICA (p=0.003 and 0.03, r=0.69 and 0.53).

Conclusions: The lack of correlation between carotid US and CT lead us to infer that the diabetic choroidopathy is a localized microangiopathy.

Keywords: Choroid, Diabetes mellitus, Optical Coherence Tomography, Carotid Ultrasound

INTRODUCTION

Diabetic Retinopathy (DR) is the leading cause of blindness in working age individuals in developed countries. It has been commonly recognized and classified as a microvascular complication of diabetes [1,2]. However, since the availability of Spectral Domain Optical Coherence Tomography (SD-OCT) with high-quality and high-resolution cross-sectional retina imaging, DR is now recognized as a neurovascular complication of Diabetes Mellitus (DM). The alterations of neuroretinal structure and function seem to result from a disruption of the neurovascular unit formed by neurons, vessels and blood-retinal barriers, and precede the observable common lesions associated to DR [3].

The choroid is a highly vascularized layer, interposed between retina and sclera. Its main function is to provide oxygen and nourishment to the outer retina, retinal pigment epithelium and the prelaminar portion of the optic nerve [4,5]. Therefore, a healthy choroid is essential to a normal retinal function, so that changes in choroid may be implicated in retinal diseases.

In 2008, Spaide et al. described a new method called Enhanced Depth Imaging Spectral Domain Optical Coherence Tomography (SD-OCT-EDI) that enabled in vivo reliable cross-sectional choroid imaging. Since then, several clinical studies have been evaluating Choroidal Thickness (CT) changes in diabetic patients [6,7]. Beyond retinal changes, choroidal vasculopathy may also play a role in DR pathogenesis [8,9]. Therefore, a comprehensive understanding of choroid is critically important to the evaluation of diabetic eye disease.

Once choroidal circulation has a high blood flow rate, it may be sensitive to systemic vascular changes seen in DM, such as systemic atherosclerosis [10].

Carotid ultrasound is a noninvasive, sensitive and reproducible technique that is the modality of choice for screening, diagnosis and monitoring systemic atheromatous diseases [11]. It can measure anatomic and hemodynamic variables such as Carotid Intima-media Thickness (CIMT), Resistance Index (RI), Peak Systolic Velocity (PSV) and End-Diastolic Velocity (EDV), which are currently considered biomarkers for systemic atherosclerosis, subclinical vascular disease and for cardiovascular risk [12-18].

The aim of this study is to correlate CT with hemodynamic and anatomic variables obtained by carotid ultrasound (US) in patients with type 2 DM without DR.

MATERIAL AND METHODS

The authors performed a cross-sectional study including 17 eyes of 17 type 2 diabetic patients without DR. The informed consent for the participation in thisstudy was obtained for each patient and the tenets of theDeclaration of Helsinki were accomplished, including the approval from institutional Ethics Committee.

The participants with refractive error equal or superior to ± 5 diopters (D), diabetic retinopathy, previous retinal laser photocoagulation, ocular hypertension or glaucoma, retinal or neurodegenerative disease, history of intraocular surgery and significant media opacities that precluded fundus imaging were excluded.

The diagnosis of type 2 DM was made following the normative of Portuguese General Health direction at a primary health care center, namely fasting blood glucose ≥ 126 mg/dL; or classic symptoms of diabetes plus casual blood glucose ≥ 200 mg/dl; or blood glucose ≥ 200 mg/dL 2 hours after oral glucose tolerance test; or random glycated hemoglobin (HbA1c) ≥ 6.5% [18].

All patients were submitted to a complete ophthalmological evaluation that included best corrected visual acuity assessment, biomicroscopy, fundoscopy, Goldmann applanation tonometry and dynamic contour tonometry with Pascal digital tonometer, ultrasound biometry and choroidal thickness measurement using SD-OCT (Spectralis Heidelberg Engineering®). Randomly, one eye of each subject was included in this study.

All OCT scans were performed in EDI mode to improve the quality of choroidal imaging according to the previously reported method [6]. All OCT examinations were performed at the same time of the day from 2 PM to 4 PM. The OCT images were obtained by a technician (G.A.) and were assessed by two experienced ophthalmologists (J.F., JP.C.), independently of each other. The CT was measured using the caliper function from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium to the hyporeflective line or margin corresponding to the sclerochoroidal interface. These measurements were made in the subfoveal choroid and at intervals of 500µm from the fovea to 1500µm nasal, 1500µm temporal, 1500µm superior and 1500µm inferior, in a total of 13 locations - Figure 1. At each location the obtained values were averaged for analysis.

The Systemic Blood Pressure (SBP) was also assessed in seated position by an automatic sphygmomanometer. The measurement was performed twice at intervals of 1–2 min and the mean value is analyzed.

Carotid artery US was performed by experienced neuro-radiologists. Carotid arteries were evaluated at baseline using high-resolution B-mode ultrasonography (model Logic E9 ultrasound machine; GE, Yokogawa. Medical Systems, Hino, Japan®).

The protocols for recording carotid US and measuring CIMT were the same. Transverse and longitudinal B-Mode scans were made, imaging CCA - Figure 2, ICA and bulb bilaterally.

Pulsed wave Doppler mode was used to sample systolic and diastolic blood flow velocity on CCA and ICA - PSV, EDV and RI. The sample volume was parallel to flow by beam steering and an angle correction of less than 60 degrees.

Quantitative measurements of CIMT were performed on one longitudinal image of the distal segment of CCA, 1 or 2 centimeters before the bulb. The boundaries of lumen-intima and media-adventitia interfaces of arterial wall were traced by manual delineation. The distance between these two lines corresponded to the combined thickness of the intima and media - Figure 3. Only the ipsilateral artery to the eye in study was included.

The data were statistically analysed using *GraphPad version 6.01*. Correlations between CT and hemodynamic carotid US variables were determined using Spearman's correlation test. A *p-value* of less than 0.05 was considered statistically significant. All the results were expressed as mean ± standard deviation, except when indicated.

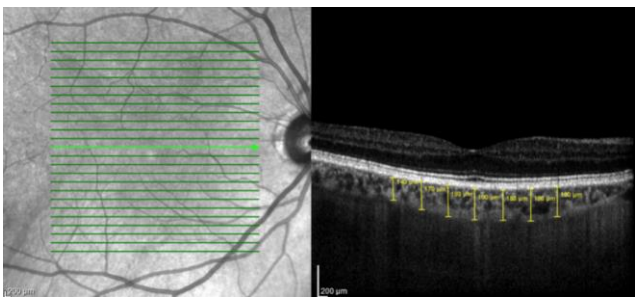


Figure 1 - Choroidal Thickness Measurement with EDI SD-OCT.

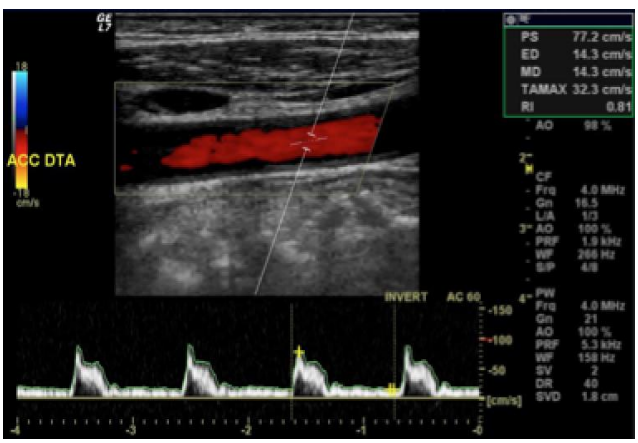


Figure 2 - Pulsed Wave Doppler of Common Carotid Artery- Hemodynamic Variables measurement.

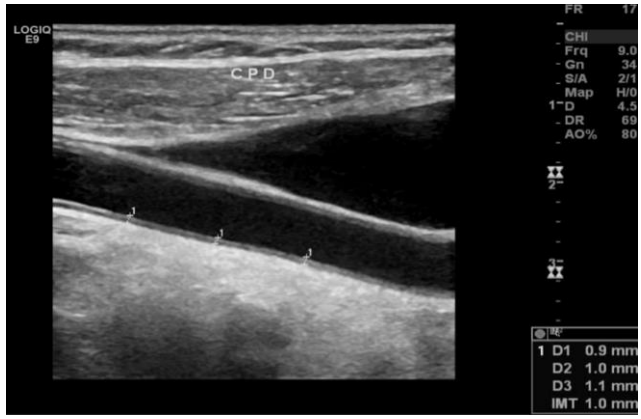


Figure 3 - Manual measurement of intima-media thickness at Common Carotid Artery.

RESULTS

A total of 17 eyes of 17 diabetic patients (13 females and 4 males; mean age, 65.3 ± 10.3 years) were included in this study. All patients did not have clinically visible diabetic retinopathy. The demographic data of this study population are listed in Table 1.

The choroidal thickness measurements of the 13 locations are shown in Table 2.

The mean of anatomic and hemodynamic variables: CIMT, RI, PSV and EDV are displayed in Table 3 and Table 4.

Choroidal Thickness at 1500 µm inferior to the fovea correlated negatively with the RI of both ICA and CCA (p=0.022 and 0.035, r=-0.55 and -0.52, respectively) - Graphic 1-2.

Choroidal Thickness is not correlated with CIMT, PSV, EDV and RI, neither with SBP and OPA in any of the other sites (p > 0.05) - Graphic 3.

The SBP is positively correlated with PSV and RI of ICA (p=0.003 and 0.03, r=0.69 and 0.53, respectively) - Graphic 4.

Table 1 - Demographic Characteristics of the patients. Best Corrected Visual Acuity (BCVA); Intra-Ocular Pressure (IOP); Ocular Pulse Amplitude (OPA).

Demographic Characteristics of the Patients (mean ± standard deviation)	
Patients, number	17
Gender	13 ♀ : 4 ♂
Age (years)	65.3 ± 10.3
BCVA (logMAR)	0.03 ± 0.05
IOP (mmHg)	16.5 ± 2.5
PIO Pascal (mmHg)	19.6 ± 3.9
OPA	3.6 ± 1.6
Spherical equivalent	0.35 ± 1.77
Axial length (mm)	23 ± 0.9
Diabetes Duration (years)	8.4 ± 6.4
Systolic Blood Pressure (mmHg)	147.9 ± 27.4
Diastolic Blood Pressure (mmHg)	78.5 ± 23.4

Table 2 - Choroidal Thickness Measurements.

SD-OCT (mean ± standard deviation) Choroidal Thickness (µm)	
Subfoveal central	271.76 ± 60.77
Temporal 500 µm	265.41 ± 63.96
Temporal 1000 µm	253.82 ± 53.39
Temporal 1500 µm	236.12 ± 53.74
Nasal 500 µm	249.24 ± 55.03
Nasal 1000 µm	226.18 ± 58.39
Nasal 1500 µm	204.65 ± 53.41
Superior 500 µm	269.47 ± 56.37
Superior 1000 µm	263.65 ± 54.55
Superior 1500 µm	269.53 ± 59.29
Inferior 500 µm	250.41 ± 63.75
Inferior 1000 µm	240.00 ± 66.05
Inferior 1500 µm	250.12 ± 72.18

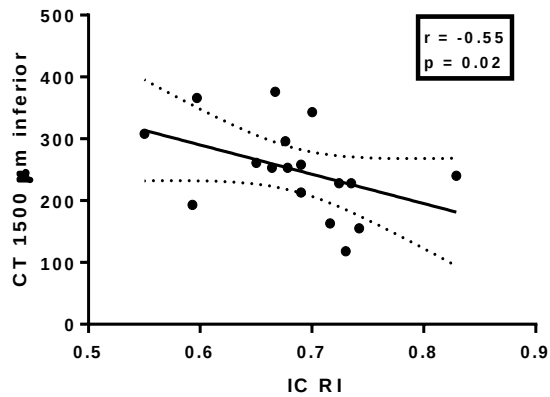
Table 3 - Common Carotid Artery Hemodynamic and Anatomic Variables. Peak-Systolic Velocity (PSV); End-Diastolic Velocity (EDV); Resistance Index (RI); Carotid Intima-Media Thickness (CIMT).

Hemodynamic Variables (cm/s) (mean ± standard deviation)	
PSV	98,89 ± 23,69
EDV	23,81 ± 7,09
RI	0,76 ± 0,08
Anatomic Variables (mean ± standard deviation)	
CIMT	0,87 ± 0,18

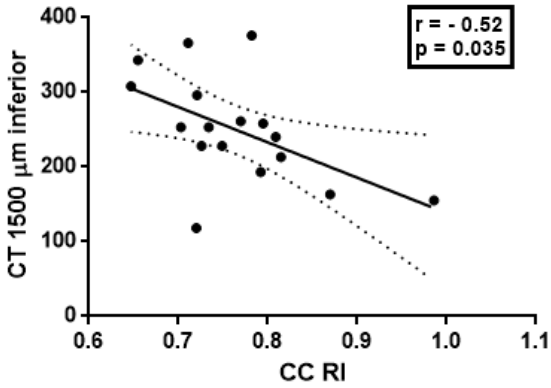
Table 4 - Internal Carotid Artery Hemodynamic Variables. Peak-Systolic Velocity (PSV); End-Diastolic Velocity (EDV); Resistance Index (RI).

Hemodynamic Variables (cm/s) (mean ± standard deviation)	
PSV	91,53 ± 38,13
EDV	28,39 ± 9,81
RI	0,68 ± 0,07

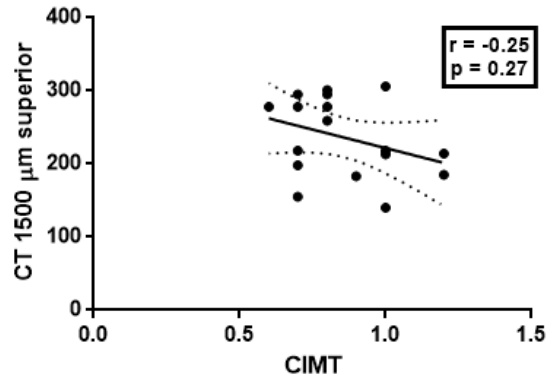
Graph 1 – Negative correlation between Choroidal Thickness (CT) 1500 µm inferior to fovea and Resistance Index of the Internal Carotid Artery (IC RI).



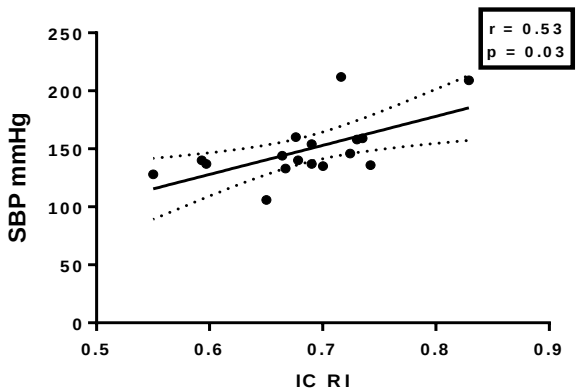
Graph 2 – Negative correlation between Choroidal Thickness (CT) 1500 µm inferior to fovea and Resistance Index of the Common Carotid Artery (CC RI).



Graph 3 – Absence of correlation between Choroidal Thickness and Carotid Intima-Media Thickness (C CIMT).



Graph 4 – Positive Correlation between Systemic Blood Pressure (SBP) and Internal Carotid Resistance Index (IC RI).



DISCUSSION

In this study, our aim was comparing the CT with carotid US, in order to determine if CT is modulated by systemic vascular changes of diabetes, such as systemic artheriosclerosis. To our Knowledge, the present study is the first that correlate choroidal thickness and carotid Doppler ultrasound in diabetic patients without DR.

The CT was not directly correlated with hemodynamic parameters of carotid US, except in the 1500µm inferior to the fovea, where it demonstrated a negative correlation with RI of both ICA and CCA. Additionally, CT was not correlated with PSV, EDV, RI and CMIT, neither with SBP and OPA in any of the other locations. These results may be due to a loss of physiologic regulation at choroidal circulation, which is critical to a normal retinal structure and function [19].

A recent study by Kadir Agladioglu et al., in healthy individuals, demonstrated a negative linear correlation between ICA RI and subfoveal CT, and a positive correlation between subfoveal CT and ICA EDV, showing that in a healthy state, the hemodynamic variables of carotid US reflect the blood flow resistance in choroidal circulation [13].

Before 2008, the in vivo assessment of the choroid structure was only possible with traditional imaging modalities, such as histopathologic evaluation, fluorescein angiography, indocyanine green angiography, laser Doppler flowmetry and high-resolution ultrasonography, with marked imaging resolution restrictions. Nowadays, the use of EDI SD-OCT enabled a more detailed visualization of choroid and since then, the correlation of new anatomical findings with other imaging modalities is increasing the understanding of diabetic eye disease [20,21]. Nevertheless, most of the factors that may alter CT are still not clearly identified. Moreover, diabetic changes in choroid may be modulated by the presence of other concomitant cardiovascular risk factors such as systemic hypertension and arteriosclerosis [22,23].

In this study, CT did not show a correlation with SBP, but SBP was positively correlated with PSV and RI of ICA with statistical significance. These results lead us to infer that changes in choroid of diabetic patients correspond to a localized microangiopathy, independent from systemic vascular regulation.

Except for Jie Xu et al. study, which included 2041 participants of Beijing Eye Study 2011, the majority of the studies about diabetic choroidal changes have only included

a relatively small hospital-based population with DR. They found that DM was associated with an increase in subfoveal CT, but DR was not significantly associated with additional CT changes. However, this study also had some limitations, such as the CT was measured at different times of the day, not respecting CT circadian rhythm; the diagnose of DR was made by fundus photography; and only the right eye of each patient was examined [24].

In the present study, all the CT measurements were made between 2 PM and 4 PM and the eye was randomly chosen, so that circadian and intereye differences were theoretically eliminated [25].

Recently, Ferreira J. et al. found an increase in CT at the 1500 µm superior to fovea in diabetic patients without DR [26], which is consistent with several clinical studies thatdemonstrate the presence of a diabetic choroidopathy before the onset of DR [18], with a predominance of vascular changes in the mid-periphery of choroid [21,22].

There are some limitations to the present methodology that must be mentioned. Firstly, sample size was relatively small. Secondly, only diabetic patients without DR were studied. It would be interesting to include a control group using diabetic patients with DR and compare Doppler parameters of carotid arteries with retina-choroidal vascular structures.

CONCLUSION

Although it was expectable to found a correlation between CT and carotid artery US, due to their anatomic relation and proximity, the absence of correlation between hemodynamic values and CIMT of carotid US and CT lead us to infer that CT variations, already identified in previous studies, result from a localized microangiopathy, which is present even before the development of DR. Choroidal EDI-OCT imaging might be a useful tool to study the contribution of the choroidal circulation to the overall visual dysfunction in diabetic patients, offering a future biomarker for diabetic eye disease.

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