• Clinical Research •

Renal function and choroidal thickness using swept-source optical coherence tomography in diabetic patients

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Abstract

• AIM: To assess the relationship between choroidal thickness and renal function in diabetic patients.

• METHODS: Cross-sectional retrospective clinical study of 42 eyes of 21 ocular treatment-naïve diabetic patients. Demographic data included: age, sex, type and course of diabetes. Ocular data included: severity of diabetic retinopathy; retinal thickness at the central macular region, as well as choroidal thickness at the central and paracentral quadrants, using automatically generated maps by swept-source optical coherence tomography; presence of cystic macular edema; and ocular axial length (AXL). Lab-test parameters included: glycated hemoglobin (HbA1c), albuminuria, albumin/creatinine ratio in urine, and glomerular filtration rate.

• RESULTS: A significant negative correlation was mainly observed between several choroidal thicknesses, age (*P*<0.020) and ocular AXL (*P*<0.030). On the contrary, a significant positive correlation was found between all choroidal thicknesses, HbA1c (*P*<0.035) and albuminuria (*P*<0.040).

• CONCLUSION: Choroidal thickness can represent an additional tool to help clinicians predicting the renal status in ocular treatment-naïve diabetic patients.

• KEYWORDS: choroidal thickness; renal function; swept-source optical coherence tomography; spectral-domain optical coherence tomography; diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is a complex progressive disease associated with multiple physiopathological alterations that ultimately cause macro- and microvascular complications (nephropathy, retinopathy and/or neuropathy)[1]. The prevalence of DM has increased in the last decades and has become a major clinical and social concern due to its economic burden and associated premature mortality. The overall prevalence of DM in Spain (types 1 and 2) in subjects >18 years of age is 13.8%[2], with a remarkably higher prevalence of DM2, which accounts for 90% of DM[3].

DM is the main cause of chronic kidney disease (CKD) in developed countries[4]. Diabetic patients are three times more likely to develop CKD as compared to non-diabetic subjects. The natural course of diabetic nephropathy is characterized by changes in urinary excretion of albumin, which are divided into three phases: normoalbuminuria, microalbuminuria (MA) and proteinuria. The proportion of patients with DM2 who develop MA at 10y after diagnosis is approximately 25%. The presence of MA is known to increase overall mortality, cardiovascular morbimortality, the risk for end-stage renal disease (ESRD) and the risk for proliferative diabetic retinopathy. However, the correlation of MA with early-stage retinopathy is still unclear[5].

There is scant literature assessing the relationship between retinal structural changes and renal function in subjects with DM. It has long been known that diabetic patients with chronic retinopathy and nephropathy experience a thickening of glomerular and retinal capillary vessels. This is suggestive that DM and renal function may share microvascular pathogenic mechanisms related to abnormalities in glucose metabolism, inflammatory alterations and endothelial dysfunction[6]. A recent study revealed that renal dysfunction might be associated with a reduced retinal blood flow in early-stage diabetic retinopathy[7].

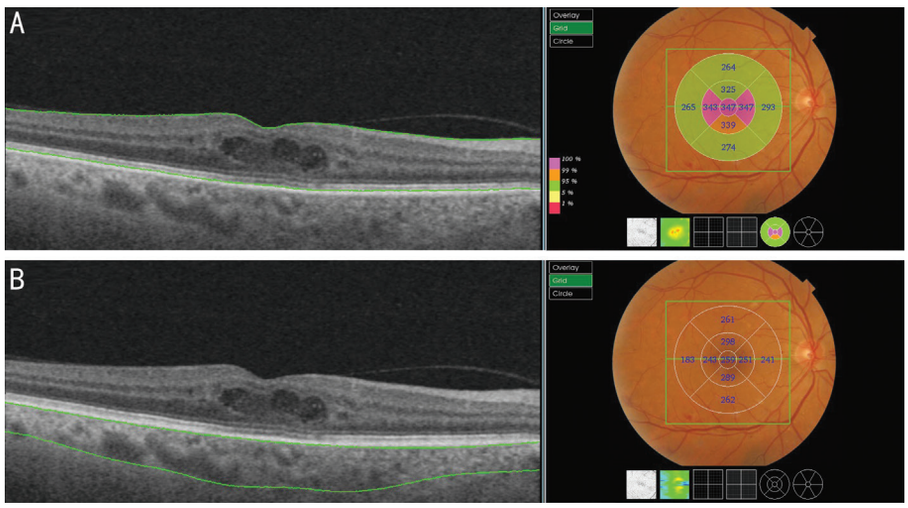

Figure 1 SS-OCT scans showing retinal (A) and choroidal (B) thickness maps generated by automatic layer segmentation Intraretinal cysts can be seen in the macular region.

The development of swept-source optical coherence tomography (SS-OCT) has allowed to detect diagnostic alterations related to chorioretinopathies including diabetic chorioretinopathy. The use of a longer laser wavelength (1050 nm) in SS-OCT scans has helped minimize dispersion caused by the retinal pigment epithelium. Thus, SS-OCT provides a clear picture of the outer retinal layers, primarily the choroid. Ultrahigh speed imaging (100 000 A-scans/s) provides faster and more detailed B-scans (maximum resolution: 1 μm), as compared to spectral-domain optical coherence tomography (SD-OCT).

Previous studies based on electronic microscopy have already recorded the presence of vascular abnormalities in diabetic choriodopathy similar to those found in retinopathy (microaneurysms, tortuous vessels, non-perfused quadrants, *etc.*)[8]. New high-resolution devices will help better understand the choroid, the vascular layer of the eye which provides oxygen and nourishment to the outer layers of the retina. Choroidal alterations may precede findings related to the presence of retinopathy in fundoscopy.

The primary goal of this study was to investigate the relationship between choroidal thickness in diabetic patients and their demographic, ocular and lab-test characteristics, with special focus on renal function parameters.

SUBJECTS AND METHODS

Ethical Approval This study protocol has been approved by the Ethics Committee of the Virgen Macarena and Virgen del Rocío University Hospitals and adheres to the tenets of the Declaration of Helsinki. All recruited patients provided informed consent ahead of participation.

A cross-sectional study of 42 eyes of 21 diabetic patients referred from the Department of Endocrinology to the Department of Ophthalmology for regular fundus examination during the first semester of 2016.

Inclusion criteria were: 1) diabetic patients without any previous treatment based on argon-laser retinal photocoagulation, intravitreal injection of antiangiogenic drugs or pars plana vitrectomy; 2) myopic or hypermetropic refractive error <6 diopters; 3) ocular axial length (AXL) between 21 and 26 mm; 4) transparent ocular media to obtain acceptable quality scans; 5) normal eye fixation; 6) absence of chorioretinal pathology other than diabetic retinopathy (age-related macular degeneration, retinal vein occlusion, *etc.*).

Based on these criteria, only 1 of the 42 eyes selected was excluded, as the patient had a severe amblyopia in her left eye that hindered eye fixation during scanning. The right eye did meet inclusion criteria.

Study variables included: 1) demographic variables: age; sex; type and course of diabetes. 2) Ocular parameters: severity of diabetic retinopathy based on 7-standard field fundus photography performed using Visucam 500 (Carl Zeiss Meditec AG, Jena, Germany); retinal thickness (Figure 1A) at the central macular region (CMT), as well as choroidal thickness (Figure 1B) at the central (C-CT), inner nasal (IN-CT), inner superior (IS-CT), inner temporal (IT-CT) and inner inferior (II-CT) quadrants (expressed in μm), using automatically generated maps based on the standard Early Treatment Diabetic Retinopathy Study (ETDRS) grid of the SS-OCT Triton (Topcon Corporation Ltd., Tokyo, Japan); presence of cystic macular edema (CME) in the horizontal 7×7-mm foveal tomography scan (Figure 1); and ocular AXL (expressed in mm) measured using the ophthalmic ultrasound system OcuScan RxP (Alcon Laboratories Inc., Fort Worth, Texas, USA). 3) Lab-test parameters (data were collected from recent routine endocrinology consultations within a maximum interval of 1mo): glycated hemoglobin HbA1c (expressed as percentages); albuminuria (mg/L); albumin/creatinine ratio

(ACR) in urine (mg/g); and glomerular filtration rate (GFR) estimated by the formulas CKD-EPI and MDRD-4 (mL/min/1.73 m^2).

Statistical analysis was performed using IBM SPSS version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and Excel 2013 spreadsheets (Microsoft Corporation, Redmond, Washington, USA).

Quantitative variables were expressed as means and standard deviations, whereas qualitative variables were expressed as percentages. Linear associations between quantitative variables were determined by Spearman's rank correlation coefficients. The absence of autocorrelation between adjacent observations was confirmed by the Durbin-Watson test. Thus, analysis was performed in 41 eyes.

For bivariate analysis of normally distributed quantitative and qualitative variables (Shapiro-Wilk test), Student's *t*-test was used to compare two independent samples, and ANOVA was used for more than two independent samples. In case of abnormal distribution, Mann-Whitney *U* and Kruskal-Wallis non-parametric tests were performed, respectively. A *P* value <0.05 was considered statistically significant.

RESULTS

Descriptive Analysis

Demographic variables Mean age was 49.76±17.61y (ranging from 18 to 74y) and 52.4% of study subjects were male. Most patients had type 2 DM (66.7%) and the mean duration of disease was 12.14±10.08y.

Ocular variables The mean ocular AXL was 23.14±1.14 mm. The 51.2% did not have retinopathy, whereas 34.2% had mild non-proliferative diabetic retinopathy (NPDR) and 14.6% had moderate NPDR. SS-OCT revealed the presence of CME in five eyes (12.2%). The mean CMT was 246.4±30.39 μm. At choroidal level, the mean C-CT was 262.90±77.25 μm, while the mean thickness of inner paracentral regions was distributed in ascending order as follows: IN-CT (245.56±77.95 μm), II-CT (255.00±80.99 μm), IT-CT (256.40±74.96 μm), and IS-CT (273.00±76.15 μm).

Lab-test parameters The mean HbA1c was 8.19±1.37%. As to renal function parameters, the mean albuminuria was 36.85±67.76 mg/L, the mean ACR was 37.92±74.27 mg/g and the mean GFR as calculated by the CKD-EPI and MDRD-4 formulas was 98.43±22.33 and 101.90±28.75 mL/min/1.73 m^2, respectively.

Bivariate Analysis of Choroidal Thickness

Demographic variables A statistically significant negative correlation was observed between age and C-CT (*P*=0.010), IS-CT (*P*=0.016), IT-CT (*P*=0.007), and II-CT (*P*=0.006). In contrast, years of evolution of diabetes were not observed to be significantly correlated to choroidal thickness. Statistically significant differences were also observed in CMT (*P*=0.0005) and IN-CT (*P*=0.048) between men and women, as well as in C-CT (*P*=0.040) and IT-CT (*P*=0.025) by type of diabetes.

Ocular variables Ocular AXL was found to be negatively correlated to C-CT (*P*=0.029), IN-CT (*P*=0.006), and II-CT (*P*=0.012). There were no significant differences between the right and the left eye in any choroidal thickness. In relation to the grade of diabetic retinopathy, differences were only observed in IT-CT (*P*=0.016). Nevertheless, a non-significant inverse trend was observed in choroidal thickness as the severity of NPDR increased. Patients with CME showed a statistically significant increase of CMT (*P*=0.048) accompanied by a general non-significant choroidal thinning.

Quantitative lab-test parameters Among renal function parameters, albuminuria was found to have a statistically significant positive correlation with chorioretinal thicknesses, occurring the same with glycosylated hemoglobin (Table 1).

DISCUSSION

The distribution of choroidal thicknesses in diabetic patients has been proven to be similar to that in non-diabetic patients, with the superior quadrant thicker than the inferior, and the temporal thicker than the nasal quadrant[9]. Likewise, evidence has been obtained that HbA1c, but not blood glucose, is directly correlated to choroidal thickness[10]. The results from our study coincide with these findings.

Comparative studies of choroidal thickness in diabetic patients with retinopathy and/or macular edema reveal a tendency to thinning[11], although statistically significant results have not been obtained in our investigation. In contrast, some studies have reported choroidal thickening in diabetic patients without retinopathy[12], or independently of disease stage[13]. Other studies have uncovered choroidal thinning in diabetic patients treated with argon laser or intravitreal injections of antiangiogenic drugs, as they reduce vascular permeability[14]. In addition, the thinning of the choroid with age and ocular AXL, reported in previous publications[11], is supported by the results of our study. The advantage of the SS-OCT device used for chorioretinal measurements is that it provides automatically generated maps based on the standard ETDRS grid, versus manual measurements with substantial intra- and inter-observer differences of up to 32 μm[15]. Circadian variations in choroidal thickness should be taken into account as well. It has been observed that choroidal thickness progressively decreases between 9 a.m. and 5 p.m., with diurnal amplitudes of up to 67 μm[16-17]. In our study, measurements were always performed at the same hour interval, *i.e.* from 10 a.m. to 1 p.m., by the same ophthalmologist who manually re-adjusted the segmentation slabs in the infrequent case the automated process produced errors, trying to minimize bias.

Regarding the renal function, considering the growing incidence of DM and diabetic nephropathy worldwide, early

Table 1 Correlations between chorioretinal thicknesses, renal function parameters and HbA1c

Parameters	A	ACR	GFR CKD-EPI	GFR MDRD-4	HbA1c
CMT					
Correlation coefficient	0.428	0.226	-0.139	-0.148	0.336
P	0.005	0.156	0.385	0.357	0.031
C-CT					
Correlation coefficient	0.394	0.181	0.104	0.018	0.412
P	0.011	0.258	0.517	0.912	0.007
IN-CT					
Correlation coefficient	0.324	0.145	0.091	0.031	0.374
P	0.039	0.364	0.570	0.846	0.016
IS-CT					
Correlation coefficient	0.389	0.231	0.024	-0.092	0.432
P	0.012	0.147	0.884	0.567	0.005
IT-CT					
Correlation coefficient	0.359	0.145	0.131	0.013	0.441
P	0.021	0.365	0.415	0.937	0.004
II-CT					
Correlation coefficient	0.351	0.114	0.276	0.194	0.359
P	0.025	0.477	0.081	0.224	0.021

A: Albuminuria; ACR: Albumin/creatinine ratio in urine; GFR CKD-EPI: Glomerular filtration rate based on the CKD-EPI formula; GFR MDRD-4: Glomerular filtration rate based on the MDRD-4 formula; HbA1c: Glycated hemoglobin A1c; CMT: Central macular thickness; CT: Choroidal thickness; C-CT: Central CT; IN-CT: Inner nasal CT; IS-CT: Inner superior CT; IT-CT: Inner temporal CT; II-CT: Inner inferior CT.

detection of the disease is crucial, as it allows to administer timely therapies and prevent progression to ESRD. Urine markers, especially MA, play a major role in early detection. MA is also a marker of generalized endothelial dysfunction associated with DM, thus linking renal impairment to cardiovascular and brain compromise. It has been demonstrated that MA is not only a marker of glomerular injury, but also of renal tubular lesions. Ongoing studies are analyzing other urine markers (transferrin, ceruloplasmin), which could precede the establishment of MA in some patients[18].

The reduction of GFR generally occurs secondary to MA, although it may also occur in patients with normoalbuminuria[19]. For this reason, we quantified albuminuria levels in all patients, not only in patients with MA (30-300 mg/L). MA has a variable course. It can return to normal levels, progress to macroalbuminuria, or remain stable without any changes. Even so, MA has been proven to be a predictor of cardiovascular risk and ESRD in diabetic patients[20].

A recent paper assessed the relationship between MA and choroidal thickness[21]. The authors documented a significant thinning of the choroid in the group of patients with DM2 and MA, especially at the subfoveal and temporal to the fovea regions. In that study, where SD-OCT scanning was used, choroidal thicknesses were measured manually by an experienced operator at several points of a horizontal section through the fovea. Additionally, confounding factors such as ocular AXL, refractive errors or capture time were not considered, at least initially, as a replica study was performed later[22]. In contrast, our study included patients with DM1 and 2, with non-excluding refractory defects and ocular AXL. Albuminuria levels were correlated with choroidal thicknesses automatically mapped on ETDRS grids by SS-OCT. Scans were performed within the same hour range. We found a statistically significant positive correlation between albuminuria levels and all choroidal thicknesses measured. These results are in agreement with those of previous studies reporting a thickening of the choroid in diabetic patients without retinopathy[12], or independently of disease stage[13], probably associated with a vascular hyperpermeability status.

Another study performed in 2013 documented a thinning of the choroid following hemodialysis in non-diabetic patients[23]. The authors theorized that ultrafiltration may induce hypovolemia and increase plasma oncotic pressure, which would reduce intraocular pressure and choroidal thickness. Therefore, the opposite would occur when albuminuria increases. Subsequent studies demonstrated greater reduction in choroidal thickness after hemodialysis in diabetic patients with ESRD[24-25]. The authors speculated that it might be due to diabetes-related vascular changes in the choroid, including alterations in its autonomic regulation.

In conclusion, choroidal thickness could represent an additional tool to help clinicians predicting the renal status in ocular treatment-naïve diabetic patients. Nevertheless, the preliminary retrospective cross-sectional design without a control group and the limited sample size of this study require that larger, prospective, long-term studies are conducted to confirm the results obtained and elucidate the role of choroidopathy in the prognosis of diabetic retinopathy.

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