Ocular and Systemic Risk Markers for Development of Macular Edema and Proliferative Retinopathy in Type 2 Diabetes: A 5-Year Longitudinal Study

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Diabetic retinopathy (DR) is a common complication of diabetes and may lead to blindness through vision-threatening complications, such as diabetic macular edema and proliferative DR (PDR). Several studies have established that certain systemic factors have associations with incidence and progression of DR, namely, glycemic control, arterial hypertension, high cholesterol and hyperlipidemia obesity, inflammatory markers, sleep-disordered breathing, and exercise (1,2). In addition to systemic factors, there are ocular factors that should be considered, since they may identify the eyes at risk (2).

We here report a 5-year prospective longitudinal observational cohort study that investigates the risk of both systemic and ocular factors that may play a role in the development of diabetic macular edema and PDR, the vision-threatening complications of DR.

This observational cohort study included eyes/patients with mild nonproliferative PDR, Early Treatment Diabetic Retinopathy Study (ETDRS) classification grades 20 and 35 (3), who were followed for a period of 5 years or until the time of development of center-involved macular edema (CIME), clinically significant macular edema (CSME), or PDR. A total of 212 patients were included: men and women with diagnosed adult-onset type 2 diabetes, aged 42–82 years, with a maximum baseline HbA_{1c} value of 10% (86 mmol/mol). Exclusion criteria included any laser treatment or intravitreal injections or any other comorbidity that could affect the retina. Also excluded were subjects with uncontrolled systemic hypertension >210 mmHg and history of ischemic heart disease.

A complete eye examination, which included best corrected visual acuity, slit-lamp examination, intraocular pressure measurement, digital seven-field color fundus photography, and optical coherence tomography, was performed annually. Additionally, 45°/50° field-2 images were obtained for microaneurysm turnover (MAT) analyses using RetmarkerDR (Retmarker SA, Coimbra, Portugal). Of the 212 eyes included in the study, 172 individuals with type 2 diabetes, one eye per person, completed the study. Fourteen eyes developed CSME (8%) and 10 developed CIME (6%), whereas 4 eyes developed PDR (2%), with 1 of these eyes showing both CSME and PDR (3).

Univariate analysis of demographic and systemic characteristics determined that patients who developed CSME or PDR had lower age ($P < 0.001$), lower BMI ($P = 0.040$), and higher HbA_{1c} values ($P = 0.030$) and higher LDL ($P = 0.041$) and patients who developed CIME had lower systolic blood pressure ($P = 0.044$).

Regarding ocular characteristics and their relationship with vision-threatening outcomes, it was possible to identify statistically higher values of MAT in patients who developed CSME ($P = 0.001$) or PDR ($P = 0.007$) and higher central retinal thickness (CRT) values in patients who developed CIME or CSME (both $P < 0.001$).

The Cox hazards regression confirmed the importance of the ocular markers in the risk of development of CSME (Table 1). After adjustment for systemic characteristics, MAT presented a hazard ratio (HR) of 1.03 (95% CI 1.01–1.06; $P = 0.018$). CRT presented an HR of 1.08 (95% CI 1.03–1.14; $P = 0.003$) and ganglion cell layer + inner plexiform layer (GCL+IPL) thickness an HR of 1.13 (95% CI 1.04–1.22; $P = 0.002$). Among the systemic factors used for adjustment of

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Table 1—Univariate and multivariate Cox proportional hazards regression of progression to CSME and CIME by different types of ocular markers

	Univariate		Multivariate*		
Ocular markers	HR (95% CI)	*P*	HR (95% CI)	*P*	Significant confounders, HR (95% CI, *P*)
CSME					
MA turnover	1.04 (1.02–1.05)	**<0.001***	1.03 (1.01–1.06)	**0.018***	Age, 0.88 (0.79–0.97, 0.015); BMI, 0.84 (0.73–0.97, 0.015)
MA formation rate	1.08 (1.05–1.11)	**<0.001***	1.06 (1.01–1.12)	**0.018***	Age, 0.87 (0.79–0.97, 0.009); BMI, 0.84 (0.73–0.97, 0.015)
MA disappearance rate	1.07 (1.04–1.11)	**<0.001***	1.06 (1.01–1.12)	**0.027***	Age, 0.88 (0.79–0.97, 0.014); BMI, 0.85 (0.74–0.97, 0.017)
CRT	1.06 (1.03–1.10)	**0.001***	1.08 (1.03–1.14)	**0.003***	Age, 0.89 (0.80–0.98, 0.023)
ΔCRT V1_Vlast	1.03 (1.02–1.04)	**<0.001***	1.08 (1.04–1.11)	**<0.001***	Age, 0.83 (0.73–0.94, 0.004); HDL, 0.83 (0.73–0.94, 0.003)
GCL+IPL CSF thickness	1.12 (1.05–1.11)	**<0.001***	1.13 (1.04–1.22)	**0.002***	Age, 0.88 (0.79–0.98, 0.022); BMI, 0.85 (0.74–0.98, 0.028)
ΔGCL+IPL CSF V1_Vlast	0.99 (0.90–1.09)	0.864	1.01 (0.91–1.12)	0.886	Age, 0.85 (0.77–0.94, 0.001); HDL, 0.88 (0.79–0.97, 0.013); BMI, 0.86 (0.76–0.98, 0.024)
GCL+IPL InRing	1.11 (1.04–1.18)	**0.001***	1.05 (0.97–1.12)	0.230	Age, 0.86 (0.78–0.95, 0.003); HDL, 0.89 (0.80–0.99, 0.029; BMI, 0.85 (0.76–0.96, 0.006)
ΔGCL+IPL InRing V1_Vlast	1.05 (0.92–1.19)	0.483	1.07 (0.93–1.24)	0.340	Age, 0.85 (0.77–0.94, 0.001); HDL, 0.87 (0.79–0.97, 0.015); BMI, 0.86 (0.75–0.98, 0.025)
CIME					
MA turnover	0.96 (0.85–1.08)	0.529	0.99 (0.87–1.12)	0.827	
MA formation rate	0.71 (0.43–1.17)	0.177	0.82 (0.52–1.30)	0.398	
MA disappearance rate	1.01 (0.88–1.15)	0.934	1.07 (0.87–1.19)	0.844	
CRT	1.17 (1.08–1.27)	**<0.001***	1.04 (1.02–1.07)	**<0.001***	
ΔRT V1_Vlast	1.02 (1.00–1.04)	**0.047***	1.03 (1.01–1.07)	0.020*	
GCL+IPL CSF thickness	1.18 (1.09–1.28)	**<0.001***	1.27 (1.11–1.46)	**<0.001***	Systolic BP, 0.95 (0.91–1.00, 0.038)
ΔGCL+IPL CSF V1_Vlast	0.97 (0.87–1.07)	0.525	0.96 (0.85–1.09)	0.511	
GCL+IPL InRing	1.05 (0.97–1.14)	0.257	1.03 (0.96–1.12)	0.393	
ΔGCL+IPL InRing V1_Vlast	1.05 (1.02–1.08)	**0.002***	1.05 (1.01–1.10)	**0.018***	

Boldface type indicates statistical significance where $P < 0.005$. BP, blood pressure; CSF, central subfield; MA, microaneurysm; RT, retinal thickness; V1_Vlast, visit 1_last visit. *Multivariate analysis adjusted for age, duration of diabetes, sex, HbA_{1c}, total cholesterol, HDL, LDL, triglycerides, systolic blood pressure, and BMI.

the risk of each ocular marker, age was consistently a significant confounder, with risk reduction of 11–17% per unit increase (HRs 0.83–0.89). BMI was also associated with risk reduction in association with MAT and GCL+IPL thickness. For CIME, only the baseline CRT and GCL+IPL thickness were associated with risk increase (Table 1).

Receiver operating characteristic curves show that MAT, CRT, GCL+IPL thickness, and GCL+IPL inner ring (InRing) are good predictors of the development of CSME (area under the curve [AUC] 0.87, sensitivity 85.7%, and specificity 83.4%). For CIME, the predictive value of these markers is higher (AUC 0.97, sensitivity 90.0%, and specificity 91.7%).

Our results show that development of macular edema, either CSME or CIME, and PDR is associated with ocular risk markers such as baseline MAT, CRT, and GCL+IPL thickness metrics. They can help better predict the development of complications than systemic markers of metabolic control.

Eyes with mild retinopathy in individuals with type 2 diabetes with MAT <6 and with HbA_{1c} measurements <8% (64 mmol/mol) showed a very low likelihood of developing CSME or PDR (3 of 88 [3%]) in a period of 5 years. On the other hand, an eye with mild retinopathy in a patient with type 2 diabetes, with MAT ≥6, and with HbA1c ≥8% (64 mmol/mol), showed high likelihood of developing CSME and PDR (9 of 25 [36%]).

In summary, ocular risk markers (MAT, CRT, and GCL+IPL thickness) are good predictors of the development of CSME with an AUC of 0.87. For CIME, the predictive value of the ocular markers is even higher with an AUC of 0.97. When considering CIME, CSME, and PDR, the ocular risk markers remain determinant.

Limitations of this study include the fact that the study population is relatively small and with a small number of eyes that developed the end points of interest, possibly because it was a group with well-controlled diabetes that was selected based on exclusion criteria such as excessive HbA_{1c} levels and uncontrolled blood pressure.

In conclusion, ocular risk markers are more informative than systemic risk markers for prediction in eyes of patients with well-controlled diabetes with mild retinopathy which ones are at risk for developing vision-threatening complications.

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