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Poor glycemic control impairs recovery from central retinal vein occlusion

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Purpose: To evaluate the association between suboptimal glycemic control and central macular thickness in central retinal vein occlusion patients over a 1-year follow-up period.
Methods: This retrospective cohort study included adult patients with central retinal vein occlusion diagnosed at the Helsinki University Hospital, Finland, with HbA1c levels measured within 6 months before or at diagnosis. Patients were divided into two groups: those with good (≤42 mmol/mol) and poor glycemic control (>42 mmol/mol). Central macular thickness and best-corrected visual acuity were assessed at baseline, 3 months, and 1 year.
Results: Among 40 patients, 10 had suboptimal glycemic control. At 3 months and 1 year, central macular thickness was significantly higher in the poor glycemic control group compared with the good glycemic control group (367.0 ± 43.3 µm vs. 288.2 ± 36.6 µm, $p = 0.016$ and 380.8 ± 44.8 µm vs. 302.0 ± 71.3 µm, $p = 0.035$, respectively). HbA1c levels correlated with central macular thickness at 3 months ($R^2 = 0.514$, $p = 0.045$) but did not reach statistical significance at 1 year ($R^2 = 0.246$, $p = 0.071$).
Conclusions: Poor glycemic control in patients with central retinal vein occlusion is associated with greater central macular thickness at both 3 months and 1 year. These findings emphasize the importance of optimal glycemic control to improve retinal outcomes in central retinal vein occlusion.

Central retinal vein occlusion (CRVO) is a common, sight-threatening retinal vascular disease with a reported global prevalence of 0.8% [1]. Poor vision associated with CRVO is mainly caused by chronic macular edema. Diabetes mellitus is a significant risk factor for CRVO [2-4], with the prevalence of retinal vein occlusion in diabetic patients being almost double that of nondiabetics [5].

In patients with diabetes mellitus who have CRVO, poor glycemic control is linked to various anatomic complications, such as retinal neovascularization and the absence of optic nerve head collaterals [6]. A recent study found that HbA1c levels were correlated with both central macular thickness (CMT) and the presence of cystoid macular edema at presentation of CRVO [7]. However, the long-term impact of glycemic control on CMT in diabetic patients with CRVO remains inadequately studied. This gap is concerning, given that CMT is known to predict visual acuity outcomes in CRVO [8]. This study aimed to determine whether suboptimal glycemic control itself in CRVO correlates with greater CMT over a 1-year follow-up.

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METHODS

This retrospective cohort study encompassed adult patients in the Helsinki and Uusimaa Hospital District, Finland. We conducted a comprehensive review of electronic medical records belonging to patients diagnosed with CRVO. The study adhered to the ethical principles outlined in the Declaration of Helsinki. The ethics committee approved this noninterventional study (CRVOrisk HUS/53/2023).

Study population: The study inclusion criteria necessitated a diagnosis of CRVO at the Helsinki University Hospital, Department of Ophthalmology, with a HbA1c measurement within 6 months before or at the time of CRVO diagnosis and a minimum 1-year follow-up. Exclusion criteria comprised patients with diagnosed coronary artery disease, high myopia (≥6 diopters), diabetic retinopathy, neovascular age-related macular degeneration, or a history of retinal detachment, vitritis, or endophthalmitis in their study eye. Furthermore, patients who developed neovascular glaucoma during the 1-year follow-up were also excluded from the study. We categorized the CRVO cohort into two groups: patients with good glycemic control and those with poor glycemic control. The cutoff was set at 42 mmol/mol [9].

Observation procedures: Diagnosis of CRVO was determined from ophthalmologists' reports and International

Classification of Diseases, 10th Revision diagnoses. Reports with CRVO diagnosis and mention of pertinent ophthalmic findings (e.g., tortuosity and dilatation of all branches of the central retinal vein, dot/blot, and flame-shaped hemorrhages throughout all four quadrants and most numerous in the periphery) or central retinal venous occlusion in free text were considered positive for CRVO. All patients with cystoid macular edema received intravitreal anti–vascular endothelial growth factor (VEGF) treatment with the induction phase, followed by the pro re nata protocol. Bevacizumab (Avastin; Genentech, South San Francisco, CA) was the first-line anti-VEGF agent for all patients, whereas aflibercept (Eylea; Bayer AG, Leverkusen, Germany) was the second-line anti-VEGF treatment.

Statistics: Continuous variables were analyzed using the Student *t* test, while proportions underwent the χ^2 test with Yates' correction. To account for repeated testing, only probabilities less than 0.05 were deemed statistically significant. Data analysis was conducted using SPSS version 28.0 (SPSS, Inc., Chicago, IL).

RESULTS

In our cohort of 40 patients diagnosed with CRVO, 30 had good glycemic control (mean HbA1c 37.3 ± 2.9 mmol/mol), while 10 had poor glycemic control (mean HbA1c 58.0 ± 14.7 mmol/mol). Both groups were similar in terms of gender distribution, smoking, glaucoma, systemic medication for hypertension and hypercholesterolemia, acetylsalicylic acid treatment, chronic kidney disease, contralateral eye retinal laser photocoagulation and anti-VEGF status, baseline CMT and best-corrected visual acuity values, and first-line (Avastin) to second-line (Eylea) anti-VEGF distribution at 1 year (Table 1). However, patients with CRVO who had poor glycemic control were significantly younger than those with good glycemic control (72.4 ± 8.2 years vs. 78.0 ± 8.0 years, $p = 0.032$; Table 1).

At 3 months and 1 year, CMT was significantly higher among patients with poor glycemic control (367.0 ± 43.3 µm vs. 288.2 ± 36.6 µm, $p = 0.016$, and 380.8 ± 44.8 µm vs. 302.0 ± 71.3 µm, $p = 0.035$, respectively; Table 2). Best-corrected visual acuity in logarithm of the minimum angle of resolution

Table 1. Baseline clinical characteristics among 40 central retinal vein occlusion patients.

Variable	Glycemic control		P value
	Good (n=30)	Poor (n=10)	
Age (years)	78.0±8.0	72.4±8.2	**0.032**
Females (%/n)	53% (16)	50% (5)	0.855
HbA1c (mmol/mol)	37.3±2.9	58.0±14.7	**<0.001**
Smokers (%)*	26% (5 out of 19)	33% (2 out of 6)	0.739
Glaucoma (%/n)	23% (7)	30% (3)	0.673
Antihypertensives (%/n)	87% (26)	50% (5)	0.162
Statin (n/%)	83% (25)	60% (6)	0.274
ASA (%/n)	37% (11)	30% (3)	0.702
Chronic kidney disease (%/n)	10% (3)	0% (-)	0.560
Contralateral eye retinal laser (n/%)	0% (-)	10% (1)	0.250
Contralateral eye anti-VEGF (n/%)	0% (-)	10% (1)	0.250
CMT (µm)	469.6±284.2	490.9±261.0	0.434
BCVA (LogMAR)	0.78±0.86	1.20±0.87	0.409
Second-line intravitreal treatments at 1-year (%/n)			
Aflibercept	10% (3)	10% (1)	0.543
Dexamethasone implant	3% (1)	-	0.559

Good glycemic control; mean HbA1c <42 mmol/mol. Poor glycemic control; mean HbA1c ≥42mmol/mol. Antihypertensives; blood pressure medication, ASA; acetylsalicylic acid treatment, BCVA; best-corrected visual acuity, CMT; central macular thickness (mean thickness in the central 1000-m diameter area), HbA1c; hemoglobin A1c, LogMAR; logarithm of the minimum angle of resolution, statin; HMG-CoA reductase inhibitor treatment. *Smoking status was confirmed for 25 patients. Bold=p<0.05.

Table 2. Outcomes in central macular thickness among 40 central retinal vein occlusion patients in regards of glycemic control.

CSMT (µm)	Glycemic control		p-value
	Good (N=30)	Poor (N=10)	
Onset	469.6±284.2	490.9±261.0	0.434
3-months	288.2±36.6	367.0±43.3	**0.016**
12-months	302.0±71.3	380.8±44.8	**0.035**

Good glycemic control; mean HbA1c < 42 mmol/mol. Poor glycemic control; mean HbA1c ≥ 42 mmol/mol. Bold for p < 0.05.

units tended to be worse among those with poor versus good glycemic control at both follow-up time points (Table 2).

At baseline, HbA1c levels did not correlate with CMT levels (univariate R^2 = 0.004, p = 0.770 and age and sex-adjusted B = –0.768; 95% confidence interval [CI], −11.37 to 9.834, p = 0.881; Table 3). HbA1c levels correlated with CMT at 3 months (R^2 = 0.514, p = 0.045; Table 3) but did not reach statistical significance at 1 year (R^2 = 0.246, p = 0.071; Table 3). After age and sex adjustment, HbA1c levels correlated with CMT at 1 year (B = 4.841; 95% CI, 1.454-8.228, p = 0.010; Table 3).

Next, we included potential confounders in the multivariable analysis. In multivariable linear regression analysis after adjustments for age and sex, glaucoma, and systemic medication for hypertension and hypercholesterolemia, HbA1c levels tended to correlate with CMT levels at 3 months (B = 7.810; 95% CI, −1.845 to 17.464, p = 0.074; Table 4) and significantly correlated with CMT levels at 1 year (B = 6.334; 95% CI, 2.003 to 10.665, p = 0.010; Table 4).

DISCUSSION

In our cohort of patients with CRVO, those with poor glycemic control exhibited significantly higher CMT than those with good glycemic control. This observation aligns with prior studies showing a positive correlation between HbA1c levels and macular thickness in diabetic patients both with [10,11] and without [12] macular edema.

Macular edema in CRVO is associated with elevated levels of angiopoietin 2 [13], an angiogenic regulator known to increase vascular permeability [14]. A similar mechanism has been observed in patients with diabetic retinopathy, in whom poor glycemic control is associated with high intravitreal angiopoietin 2 levels [15]. These findings emphasize

Table 3. Correlation of HbA1c levels with central macular thickness (CMT) among 40 patients with central retinal vein occlusion.

Outcome: CMT (µm)	HbA1c (mmol/mol)	Regression Coefficient (B)	95% Confidence Interval	P value
At baseline	per 1 mmol/mol	–0.768	–11.37 to 9.834	0.881
3 months	per 1 mmol/mol	3.11	–1.101 to 7.321	0.11
1 year	per 1 mmol/mol	4.841	1.454 to 8.228	0.01

Baseline clinical characteristics and outcomes among central retinal vein occlusion patients in regard glycemic control. CMT; central macular thickness, HbA1c; hemoglobin A1c. Bold = p<0.05.

Table 4. Multivariable linear regression analyses for the association between HbA1c levels and central macular thickness (CMT) among 40 patients with central retinal vein occlusion.

Outcome: CMT (µm)	HbA1c (mmol/mol)	Regression Coefficient (B)	95% Confidence Interval	P value
3 months	per 1 mmol/mol	7.81	–1.845 to 17.464	0.074
1 year	per 1 mmol/mol	6.334	2.003 to 10.665	0.01

Adjusted for age, sex, glaucoma, and systemic medication for hypertension and hypercholesterolemia. CMT: central macular thickness; HbA1c: hemoglobin A1c. Bold = p < 0.05.

potential molecular mechanisms and therapeutic targets to optimize long-term outcomes in patients with CRVO who have suboptimal glycemic control [16,17].

There are some limitations in the study. Due to follow-up and glycemic control requirements for the study inclusion and exclusion for major retinal confounders, the number of patients in the study is relatively small. We were unable to retrieve and compare the exact cumulative number of anti-VEGFs given in the 1-year follow-up. Moreover, despite multivariable analyses, residual confounders may exist. In conclusion, poor glycemic control among patients with CRVO is associated with significantly higher CMT at both 3 months and 1 year. These findings highlight the importance of maintaining optimal glycemic control to improve retinal long-term outcomes in this population. Future studies are warranted to further explore the role of glycemic management and corresponding molecular mechanisms and targets behind CRVO recovery.

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