

Factors Associated with Fluctuations in Central Subfield Thickness in Patients with Diabetic Macular Edema Using Diabetic Retinopathy Clinical Research Protocols T and V

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Purpose: To identify baseline ocular and systemic factors associated with central subfield thickness (CST) fluctuations in patients with diabetic macular edema (DME) using data from Diabetic Retinopathy Clinical Research Protocols T and V.

Design: Post hoc analysis of clinical trial databases.

Subjects: Patients in Protocols T and V.

Methods: The standard deviation (SD) of all recorded CSTs for each patient during each Protocol's study period was calculated. The CST SD (corresponding to CST fluctuations) for each patient was analyzed against baseline ocular and systemic factors using linear regression analyses. Each Protocol was analyzed separately.

Main Outcome Measures: Factors associated with CST fluctuations.

Results: A total of 1197 eyes of 1197 subjects were included. In Protocol T (559 eyes, mean CST SD was 56.4 ± 35.1 microns), using multivariate linear regression analysis, baseline urine albumin/creatinine ratio (for every 1000 mg/g, CST point estimate 3.50, 95% confidence interval [CI] 0.58 to 6.43, $P = 0.0190$), and baseline CST (for every 10 microns, 0.87, 95% CI 0.58 to 1.16, $P < 0.0001$) were positively associated with CST fluctuations. Baseline visual acuity (for every 10 ETDRS letters, -9.52 , 95% CI -11.89 to -7.15 , $P < 0.0001$) was negatively associated with CST fluctuations. In Protocol V (638 eyes, mean CST SD 36.6 ± 28.4 microns), gender (female, 2.18, 95% CI 0.30 to 4.06, $P = 0.0227$), baseline CST (for every 10 microns, 2.51, 95% CI 2.21 to 2.82, $P < 0.0001$), systolic blood pressure (for every 1 mm of mercury, 0.11, 95% CI 0.01 to 0.21, $P = 0.0261$), and observation with deferred anti-VEGF injections (5.04, 95% CI 2.51 to 7.58, $P < 0.0001$) were positively associated with CST fluctuations. Type 2 diabetes (-7.37 , 95% CI -13.64 to -1.11 , $P = 0.0209$) and prompt anti-VEGF injections (-6.51 , 95% CI -9.07 to -3.96 , $P < 0.0001$) were negatively associated with CST fluctuations.

Conclusions: Worse visual acuity at baseline, baseline renal disease, hypertension, female gender, type 1 diabetes, and delayed anti-VEGF treatment may be associated with increased CST fluctuations in patients with DME. Addressing these parameters may limit CST fluctuations and help identify patients requiring more frequent monitoring or treatment. *Ophthalmology Science* 2023;3:100226 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Diabetic macular edema (DME) is a complication of diabetic retinopathy (DR) and a major cause of vision loss in patients with diabetes mellitus (DM), with approximately 75 000 new cases per year in the United States.¹ Risk factors for DME include a greater duration of DM, higher hemoglobin A1c, proteinuria, pregnancy, dyslipidemia, and hypertension.^{2,3}

Although visual acuity (VA) has largely been used as the primary treatment outcome for DME, another potential end point includes central subfield thickness (CST) measured by OCT.⁴ However, current literature has established a highly

variable and only moderate relationship between CST and VA, challenging the potential to use one as a reliable surrogate for another.^{5,6} Moreover, a single end point measurement of CST was shown to be confounded by other variables such as age, hemoglobin A1c, and leakage at the central subfield and macular level as seen through fluorescein angiography.⁵ Therefore, examination of CST through discrete time points may not be sufficient to demonstrate the influence of CST on visual outcomes. However, in patients with age-related macular degeneration, a discrete CST end point has consistently been shown

to be associated with improved VA.^{7,8} Additionally, fluctuations in CST in patients with exudative age-related macular degeneration have also been correlated with worse visual outcomes, increased rates of subretinal fibrosis, and increased geographic atrophy.⁹ More recently, using the same clinical trials included in this study (Diabetic Retinopathy Clinical Research [DRCR] Protocols T and V), our previous study established that fluctuations in retinal thickness have been associated with worse VA outcomes in patients with DME as well.¹⁰

While CST fluctuations may serve as a more reliable marker of treatment response and visual outcomes in patients with DME than individual CST readings as described in our previous study, it is still unclear as to what baseline characteristics may predict which patients may be prone to CST fluctuations over time.¹⁰ Consequently, it is difficult to prevent and control CST fluctuations without any established contributing factors. Therefore, the goal of this study was to expand on our previous study's findings by establishing baseline factors that are associated with CST fluctuations using DRCR Protocols T and V.

Methods

This study received approval from the Institution Review Board at Wills Eye Hospital and complies with the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. The study used 2 large, publicly available clinical trial databases (Protocol T, NCT 01627249 and Protocol V, NCT 01909791) through the DRCR Network. Although the source of the data is from the DRCR Network, the analyses, content, and conclusions presented herein are solely the responsibility of the authors and have not been reviewed or approved by DRCR Network. Briefly, DRCR Protocol T involved a randomized trial of central DME treatment with intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg) for 1 year.⁴ The primary end point was the mean change from baseline in VA between the 3 agents. Diabetic Retinopathy Clinical Research Protocol V was a randomized trial of central DME treatment with focal laser photocoagulation, intravitreal aflibercept (2.0 mg), or observation in eyes with baseline VA of 20/25 or better, with a follow-up at 2 years.¹¹ The primary end point was comparing the change in VA from baseline between different treatment algorithms as previously discussed.

The inclusion criteria for Protocol T included age ≥ 18 years, type 1 or 2 DM, central DME (OCT central subretinal fluid ≥ 250 μm), VA 20/32 to 20/320, and no history of anti-VEGF treatment for DME in the last 12 months. Exclusion criteria included patients with renal disease on dialysis or transplant, systolic or diastolic blood pressure > 180 and 110 , respectively, and myocardial infarction in the last 4 months. The inclusion criteria for Protocol V included age ≥ 18 years, type 1 or 2 DM, central DME (OCT central subretinal fluid ≥ 290 μm and 275 μm in women at screening and randomization visit, respectively, and ≥ 305 μm and 320 μm in men at screening and randomization visit, respectively), and VA 20/25 or better. Exclusion criteria included anti-VEGF treatment in the last year, aphakia, vitrectomy, and macular edema unrelated to diabetes.

A post-hoc analysis was conducted separately for each clinical trial, given the differing treatment options and patient populations. Variables that were collected from both trials included baseline ocular and systemic factors and time-domain OCT CST

calculations graded by the Duke OCT reading center. Both trials utilized time-domain and spectral-domain OCTs, but converted all CST measurements to time domain for the purpose of statistical analysis; still, the overall number of time-domain OCTs was low (3% in Protocol T).^{5,12} Baseline factors included in our analysis were age, gender, ethnicity, race, type of diabetes, insulin use, urine components (creatinine [mg/dL], albumin [mg/L]), albumin/creatinine ratio (mg/g), baseline ETDRS VA, baseline CST, baseline DR severity scale level, baseline systolic and diastolic blood pressure, treatment arm, and lens status. Of note, baseline factors on diastolic blood pressure were not available for Protocol T, while baseline urine creatinine, baseline urine albumin, and baseline urine albumin/creatinine ratio were not available for Protocol V. The standard deviation (SD) of all recorded CSTs (after the baseline CST reading) for each patient was calculated to identify the fluctuation of CST over the study period. The degree of SD correlated with the amount of CST fluctuations, wherein a lower SD indicated smaller CST fluctuations (and vice versa). To ensure reliable measurements of CST fluctuations, only patients with ≥ 3 CST calculations, including at the 52-week end point, were included in our analysis.

Univariate and multivariate linear regression analyses were separately conducted for the 2 clinical trials using the JMP software, version 15.0 (SAS Institute). Each baseline factor was analyzed using CST SD (corresponding to the degree of CST fluctuations) as the outcome for all patients. Point estimates from the analysis represented the correlation between each baseline factor and the degree of CST fluctuations. Confidence intervals (CIs) of 95% and a P value of < 0.05 were used to determine statistical significance.

Results

This study included a total of 1197 eyes; of which, 559 (47%) were obtained from Protocol T and 638 (53%) from Protocol V. The mean CST SD was 56.4 ± 35.1 microns and 36.6 ± 28.4 microns in Protocols T and V, respectively. The mean number of OCTs analyzed per patient in Protocol T was 22.1 ± 5.4 and in Protocol V was 14.0 ± 5.6 . In Protocol T, on univariate linear regression analysis, older age (for every 10 years, CST point estimate -3.58 , 95% CI -6.37 to -0.78 , $P = 0.0121$), insulin use (-3.53 , 95% CI -6.61 to -0.46 , $P = 0.0244$), and baseline VA (for every 10 ETDRS letters, -11.57 , 95% CI -13.94 to -9.20 , $P < 0.001$) had a negative correlation with CST fluctuations. Conversely, baseline CST (for every 10 microns, 2.15 , 95% CI 2.01 to 2.30 , $P < 0.0001$), baseline DR severity scale (for every 10 levels, 4.63 , 95% CI 1.62 to 7.63 , $P = 0.0026$), baseline urine albumin (for every 1000 mg/L, 5.73 , 95% CI 3.72 to 7.76 , $P < 0.0001$), and baseline urine/albumin creatinine ratio (for every 1000 mg/g, 5.64 , 95% CI 3.87 to 7.41 , $P < 0.0001$) had a positive association with CST fluctuations (Table 1).

Univariate linear regression analysis in Protocol V demonstrated that type 2 diabetes (-9.43 , 95% CI -17.09 to -1.77 , $P = 0.0156$) and baseline VA (for every 10 ETDRS letters, -9.47 , 95% CI -14.88 to -4.07 , $P < 0.0006$) were negatively associated with CST fluctuations. While the treatment arm of observation was associated with larger CST fluctuations (5.35 , 95% CI 2.29 to 8.41 , $P = 0.0006$), the type of anti-VEGF agent (-6.90 , 95%

Table 1. Univariate and Multivariate Linear Regression Analyses Assessing Baseline Characteristics of Eyes in the Diabetic Retinopathy Clinical Trial Protocol T for Associations of Fluctuations in Central Subfield Thickness

Variable	Univariate			Multivariate		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
Age (10 years)	-3.58	-6.37 to -0.78	0.0121	-0.88	-3.51 to 1.77	0.5172
Gender (Female)	1.36	-1.55 to 4.28	0.3602	1.87	-0.81 to 4.55	0.1715
Ethnicity (Hispanic)	3.81	-6.23 to 13.85	0.4562			
Race						
American Indian	32.00	-10.56 to 74.57	0.1403			
Asian	-7.11	-33.41 to 10.19	0.5957			
African American	6.44	-6.61 to 19.49	0.3326			
Native Hawaiian	-21.57	-64.13 to 20.99	0.3199			
White	1.31	-10.52 to 13.12	0.8282			
Diabetes type (Type 2)	4.32	-3.92 to 12.56	0.3037			
Insulin Use (Yes)	-3.53	-6.61 to -0.46	0.0244	-2.79	-5.61 to 0.03	0.0525
Baseline vision (10 ETDRS letters)	-11.57	-13.94 to -9.20	< 0.001	-9.52	-11.89 to -7.15	< 0.0001
Baseline CST (10 microns)	2.15	2.01 to 2.30	< 0.0001	0.87	0.58 to 1.16	< 0.0001
Baseline DRSS (10 levels)	4.63	1.62 to 7.63	0.0026	1.43	-1.34 to 4.21	0.3104
Baseline urine creatinine (mg/dl)	-0.008	-0.05 to 0.04	0.7398			
Baseline urine albumin (1000 mg/L)	5.73	3.72 to 7.76	< 0.0001	1.10	-2.23 to 4.44	0.5170
Baseline urine albumin/creatinine ratio (1000 mg/g)	5.64	3.87 to 7.41	< 0.0001	3.50	0.58 to 6.43	0.0190
Baseline systolic blood pressure (mmHg)	0.19	-0.05 to 0.44	0.1192			
Treatment arm						
Aflibercept	-0.60	-7.66 to 6.47	0.8683	-0.52	-6.90 to 5.85	0.8717
Ranibizumab	2.03	-5.14 to 9.21	0.5799	1.46	-4.96 to 7.88	0.6550
Bevacizumab	-1.14	-8.27 to 6.00	0.7544	-5.9	-12.42 to 0.60	0.0753
Lens status (Phakic)	-0.16	-3.40 to 3.08	0.9233			

DRSS = diabetic retinopathy severity score; CI = confidence interval; CST = central subfield thickness; mmHg = millimeters of mercury.

CI -9.99 to -3.81, $P < 0.0001$) negatively correlated with CST fluctuations. Baseline CST (for every 10 microns, 2.56, 95% CI 2.25 to 2.86, $P < 0.0001$), baseline systolic blood pressure (0.12, 95% CI 0.004 to 0.24, $P = 0.0424$), and baseline diastolic blood pressure (0.22, 95% CI 0.025 to 0.42, $P = 0.0272$) were positively associated with CST fluctuations (Table 2).

On multivariate regression in Protocol T—controlling for age, gender, insulin use, baseline ETDRS VA, baseline CST, baseline urine albumin, baseline urine albumin/creatinine ratio, and treatment arm for significant CST fluctuations—baseline CST (for every 10 microns, 0.87, 95% CI 0.58 to 1.16, $P < 0.0001$) and baseline urine albumin/creatinine ratio (3.50, 95% CI 0.58 to 6.43, $P = 0.0190$) were positively associated with CST fluctuations (Table 1). Baseline VA (for every 10 ETDRS letters, -9.52, 95% CI -11.89 to -7.15, $P = 0.0001$) was negatively associated with CST fluctuations (Table 1). In Protocol V—controlling for ETDRS VA, baseline CST, baseline systolic and diastolic blood pressure, and treatment arm for significant CST fluctuations—baseline systolic blood pressure (for every 1 mm of Mercury, 0.11, 95% CI 0.01 to 0.21, $P = 0.0261$) and initial observation (5.04, 95% CI 2.51 to 7.58, $P < 0.0001$) were positively associated with CST fluctuations (Table 2). Type 2 diabetes (-7.37, 95% CI -13.64 to -1.11, $P = 0.0209$) and prompt anti-VEGF treatment (-6.51, 95% CI -9.07 to -3.96, $P < 0.0001$) were negatively associated with CST fluctuations (Table 2).

Discussion

This study identified several baseline factors that were significantly associated with CST fluctuations based on a post-hoc analysis of 2 clinical trial databases. Our findings suggest that worse baseline vision, thicker baseline CST, baseline renal disease (indicated by albumin/creatinine ratio), type 1 diabetes, systolic hypertension, female gender, and observation with deferral of intravitreal anti-VEGF treatment may correlate with greater CST fluctuations over time. Although several factors including observation treatment arm in Protocol V were not found to result in significant VA changes during the Protocol's study period, recent studies that identified the relationship between CST fluctuations and VA suggest a connection between the 2 variables.¹⁰ Therefore, larger CST fluctuations still may correspond to worse VA over a longer follow-up period. As a result, the baseline factors identified in our study may correlate with CST fluctuations and vision changes, which can help guide physicians in determining which patients with DME may be more prone to CST fluctuations throughout their treatment course.^{10,11} Our previous study did not find an association between CST fluctuations and the type of treatment.¹⁰ Therefore, it is difficult to determine the clinical significance of these baseline metrics for influencing treatment and outcomes. Nonetheless, our findings could help retina physicians identify patients with certain clinical parameters during

Table 2. Univariate and Multivariate Linear Regression Analyses Assessing Baseline Characteristics of Eyes in the Diabetic Retinopathy Clinical Trial Protocol V for Associations of Fluctuations in Central Subfield Thickness

Variable	Univariate			Multivariate		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
Age (10 years)	-1.60	-3.81 to 0.61	0.1556	-1.45	-3.31 to 0.46	0.1271
Gender (female)	0.02	-2.25 to 2.29	0.9852	2.18	0.30 to 4.06	0.0227
Ethnicity (Hispanic)	-7.05	-16.37 to 2.27	0.1374			
Race						
American Indian	16.79	-17.47 to 51.04	0.3359			
Asian	-11.21	-28.23 to 5.81	0.1959			
African American	-6.10	-15.62 to 3.41	0.2078			
Native Hawaiian	13.68	-14.70 to 42.05	0.3440			
White	-5.92	-14.71 to 2.64	0.1746			
Diabetes type (type 2)	-9.43	-17.09 to -1.77	0.0156	-7.37	-13.64 to -1.11	0.0209
Insulin use (yes)	-0.22	-2.52 to 2.07	0.8475			
Baseline vision (10 ETDRS letters)	-9.47	-14.88 to -4.07	< 0.0006	-1.91	-6.54 to 2.71	0.4159
Baseline CST (10 microns)	2.56	2.25 to 2.86	< 0.0001	2.51	2.21 to 2.82	< 0.0001
Baseline DRSS (10 levels)	0.21	-1.26 to 1.68	0.7789	0.32	-0.88 to 1.52	0.6034
Baseline systolic blood pressure (mmHg)	0.12	0.004 to 0.24	0.0424	0.11	0.01 to 0.21	0.0261
Baseline diastolic blood pressure (mmHg)	0.22	0.025 to 0.42	0.0272	0.06	-0.10 to 0.23	0.4500
Treatment arm						
Observation	5.35	2.29 to 8.41	0.0006	5.04	2.51 to 7.58	< 0.0001
Laser	1.55	-1.52 to 4.61	0.3217	1.47	-1.07 to 4.01	0.2558
Anti-VEGF	-6.90	-9.99 to -3.81	< 0.0001	-6.51	-9.07 to -3.96	< 0.0001
Lens status (Phakic)	-4.11	-22.82 to 14.61	0.6665			

DRSS = diabetic retinopathy severity score; CI = confidence interval; CST = central subfield thickness; mmHg = millimeters of mercury.

their baseline visit that may predispose them to CST fluctuations, and with future studies further investigating the relationship between CST fluctuations and treatment, it may be possible to alter the treatment algorithms for these patients.

The visual outcome for patients with DME is influenced by baseline CST, age, baseline VA, hemoglobin A1c, proliferative DR, and anti-VEGF treatment.¹³ Moreover, an increasing number of studies have demonstrated the association between CST fluctuations and VA in the setting of different ocular pathologies. In patients with age-related macular degeneration, several studies have demonstrated that larger CST fluctuations are associated with worse VA despite anti-VEGF treatment.^{9,14,15} Extending these findings to patients with DME, our previous study demonstrated that larger CST fluctuations corresponded to worse VA.¹⁰ These findings were further corroborated by another study demonstrating that greater CST fluctuations correlated with worse VA after 1 year in eyes with DME treated with anti-VEGF injections, as well as a study showing that a decrease in CST fluctuations corresponded with concomitant improvement in VA after fluocinolone acetonide implant.^{16,17} Larger CST fluctuations have also been found to be associated with worse VA in patients with central retinal vein occlusion despite anti-VEGF treatment.¹²

While there is some literature outlining the relationship between CST fluctuations and VA, research on baseline factors that may contribute to CST fluctuations is limited. Existing data remain elusive on the relationship among

CST, CST fluctuations, and baseline renal disease. Urine albumin and hemoglobin A1c—factors associated with renal function—were found to be positively associated with chorioretinal thickness.¹⁸ Conversely, another study found that albuminuria was inversely correlated with choroid and retinal thickness, while patients with lower estimated glomerular filtration rate and chronic kidney disease have reduced choroidal and retinal thickness than patients with higher glomerular filtration rate and no chronic kidney disease.¹⁹ Interestingly, hemodialysis in diabetic patients with end-stage renal disease and DME resulted in decreased macular thickness.²⁰ This not only suggests that renal disease is associated with greater macular thickness, but also that systemic treatments improving renal function may improve the macular edema in patients with DM. Another study found that hemodialysis in diabetic patients decreased choroidal thickness but did not significantly change retinal thickness.²¹ Similarly, in nondiabetic patients, hemodialysis did not impact retinal thickness but corresponded with choroid thinning and decreased intraocular pressure.^{21,22}

While urine albumin excretion rate over 24 hours (representing microalbuminuria) is the gold standard for diabetic nephropathy, urine albumin and urine albumin/creatinine ratios have also been shown to be reliable markers.^{23,24} Although urine albumin was not a statistically significant factor predicting CST fluctuation in our study, urine albumin/creatinine ratio positively correlated with CST fluctuations. Since urine albumin and urine creatinine alone are influenced by many factors, such as gender and

body mass, CST fluctuations may have had a significant relationship with urine albumin/creatinine ratio by normalizing albumin using creatinine, which may control for extraneous variables.^{25,26} We hypothesize that patients with diabetes who have poor renal function, as indicated by diabetic nephropathy, will have an elevated urine albumin/creatinine ratio and perhaps greater CST fluctuations, not necessarily caused by the diabetic nephropathy. The endothelial damage occurring in the retinal vessels may be concurrently occurring in the renal vessels, which would explain the correlation between renal disease and CST fluctuations. Kirthi et al²⁷ identified several areas of significant macular thinning in diabetic and prediabetic patients with higher albumin/creatinine ratios, again highlighting the concomitant disease states. This would also imply that diabetic nephropathy may not necessarily result in larger CST fluctuations, but rather that both stem from vascular damage induced by hyperglycemia in patients with DM and thus help identify patients with higher CST fluctuations. Overall, renal function appears to correlate with visual parameters, but future studies are needed to explore the relationship of renal function components and renal disease with CST fluctuations and VA.

With regards to hypertension, an elevated systolic blood pressure increases the likelihood of DR in patients with type 2 diabetes within a 4-year period and corresponds to an increased risk of diffuse macular edema.^{28,29} In patients with nonproliferative DR, diastolic blood pressure was significantly associated with an increased retinal thickness; this effect was accentuated by elevated hemoglobin A1c.³⁰ Our findings demonstrated that systolic blood pressure is significantly correlated with larger CST fluctuations but could not establish a statistically significant relationship between diastolic blood pressure and CST fluctuations. It is possible that systolic and diastolic blood pressures have distinct impacts on baseline CST compared to CST fluctuations. On the other hand, our study had access to data for systolic and diastolic blood pressures in only 1 Protocol; therefore, more population samples may need to be investigated to reliably establish a correlation between blood pressure and CST fluctuations.

While no existing literature could be found on the effects of gender on CST fluctuations, multiple studies established that male gender was significantly associated with greater retinal thickness.^{31–33} Interestingly, our study found that female gender correlated with larger CST fluctuations, regardless of baseline CST. It is known that female patients with DME have also been found to have worse baseline VA than their male counterparts despite controlling for anti-VEGF treatment.³⁴ Thus, although CST fluctuations may be associated with VA, it may be difficult to generalize the effect of gender on CST fluctuations to VA, possibly because of confounding factors such as anti-VEGF treatment and body mass index.¹⁰ Further research is required to

examine the role of gender on CST fluctuations and visual outcomes, particularly in the context of DME.

This study is inherently limited by its retrospective nature. Although our study was able to establish several factors that correlate with CST fluctuations, our findings were derived from baseline values. Our study relies on OCT data and certainly the use of both time- and spectral-domain OCTs confounds the CST measurements; however, as previously mentioned, a standardized time-domain CST calculation was used for both studies. Perhaps our results may have differed if fluctuations in each baseline metric were measured against CST fluctuations (i.e., fluctuations in urine albumin or blood pressure may hold a stronger correlation with CST fluctuations). Additionally, although this study used clinical trial data, the data were not primarily meant for this analysis and thus may affect the results seen in this study. Finally, some factors were not significant in both studies such as gender, diabetes type, hypertension, and insulin use. Perhaps the different patient populations between the 2 studies led to the different findings, given that patients in Protocol V had better baseline vision and a significantly lower baseline DR severity scale than those in Protocol T. That is likely why many metrics were not consistent between the 2 studies; these protocols compared very different subsets of diabetic patients with very different treatment modalities. Still, these findings may offer some insight into why some patients experience CST fluctuations and others do not. Finally, although this study found larger CST fluctuations in patients managed with initial observation in Protocol V, the initial reports from Protocol V found no difference in VA outcomes at 2 years. It remains to be determined the true impact of these CST fluctuations on VA. Our study's large population sample from 2 clinical trials with reliable follow-up and measurements strengthens the relationships that have been established between baseline factors and CST fluctuations.

In conclusion, our study found that worse baseline VA, thicker baseline CST, baseline renal disease determined by the urine albumin/creatinine ratio, type 1 diabetes, elevated systolic blood pressure, female gender, and delayed treatment positively correlated with CST fluctuations in patients with DME. Our previous study found that larger CST fluctuations may indicate worse VA outcomes. Although the relationship between CST fluctuations and VA was nonlinear due to external factors such as treatment response and severity of macular edema—thereby making it difficult to determine the exact relationship among baseline factors, CST fluctuations, and VA—baseline factors established in this study may still hold the potential to serve as biophysical markers for CST fluctuations and perhaps visual prognosis. Additionally, given that some of the identified factors such as baseline albumin/creatinine ratio and hypertension are modifiable, our study highlights the potential for early treatment and lifestyle modifications of systemic components outside of the eye to reduce CST fluctuations and possibly improve VA.

Footnotes and Disclosures

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Abbreviations and Acronyms:

CI = confidence interval; **CST** = central subfield thickness; **DM** = diabetes mellitus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRCR** = Diabetic Retinopathy Clinical Research; **SD** = standard deviation; **VA** = visual acuity.

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