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·Clinical Research·

Impact of COVID-19-related lifestyle changes on diabetic macular edema

Bryce P. Johnson, Yu-Guang He, Zachary M. Robertson, Angeline Wang, Rafael L. Ufret-Vincenty

Department of Ophthalmology, UT Southwestern Medical Center, Dallas, Texas 75390-9057, USA

Correspondence to: Rafael L. Ufret-Vincenty. Department of Ophthalmology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9057, USA. Rafael.Ufret-Vincenty@UTSouthwestern.edu

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Abstract

● **AIM:** To assess diabetic macular edema (DME) progression during the early phases of the COVID-19 pandemic, when severe societal restrictions raised the concern of possible deterioration of health in patients with systemic conditions, particularly those requiring frequent office visits.

● **METHODS:** This is a multicenter retrospective chart review of 370 patients (724 eyes) with an established diagnosis of DME seen on 3 separate visits between January 2019 and July 2021. Period 1 was January 2019 to February 2020 (considered pre-COVID-19), period 2 was March 2020 to December 2020 (considered the height of the pandemic; highest level of pandemic-related clinical and societal regulations) and period 3 was January 2021 to July 2021 (re-adjustment to the new "pandemic norms"). Main outcome measures included visual acuity, body mass index (BMI), blood pressure (BP), hemoglobin A1c (HbA1c), macular thickness, patient adherence to scheduled ophthalmology visits, and DME treatment(s) received at each visit. To facilitate measurement of macular thickness, each macula was divided into 9 Early Treatment Diabetic Retinopathy Study (ETDRS)-defined macular sectors as measured by OCT imaging.

● **RESULTS:** There was no change of BMI, systolic BP, and diastolic BP between any of the time periods. HbA1c showed a very small increase from period 1 (7.6%) to period 2 (7.8%, $P=0.015$) and decreased back to 7.6% at period 3 ($P=0.12$). Macular thickness decreased for 100% of macular regions. The central macular thickness decreased across all 3 periods from 329.5 to 316.6 μm ($P=0.0045$). After analysis of multiple variables including HbA1c, BMI, adherence to scheduled appointments, different clinic centers, and treatment interventions, there was no easily identifiable subgroup of patients that experienced the increase in DME.

● **CONCLUSION:** DME doesn't worsen during the COVID-19 pandemic, instead sustaining a very small but statistically significant improvement. While identifying a mechanism behind our findings is beyond the scope of this study, potential explanations may include a delay in retinal changes beyond our study period, an unexpected increase in treatment frequency despite pandemic restrictions, and an unanticipated pandemic-related improvement in some lifestyle factors that may have had a positive impact on DME.

● **KEYWORDS:** COVID-19; diabetic macular edema; diabetic retinopathy; optical coherence tomography

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INTRODUCTION

Diabetic macular edema (DME) is a leading cause of vision loss in the developed world[1]. The hallmark of DME is an alteration of the blood-retinal barrier, mediated by advanced glycogen end-products and vascular endothelial growth factor (VEGF)[2]. The compromised capillaries lead to fluid buildup causing the macula to swell and thicken, which leads to distorted vision. There is often a delay from the time when systemic factors (*e.g.* poor diet with high sugar content) are affected to when DME mediators elicit biological changes in the macula and clinical changes in vision. Optical coherence tomography (OCT) has become the gold-standard for the diagnosis and monitoring of DME[3-4].

Controlling risk factors like blood sugar, lipids and blood pressure is important in the management of diabetic retinopathy (DR) and in preserving vision[5-6]. Impactful factors in achieving this control include regular exercise, proper nutrition, and regular ophthalmology visits[7-9]. Studies have also demonstrated that treatment of DME using anti-VEGF agents, steroids, and laser photocoagulation have significant benefits[10-11]. Individuals with DME who received anti-VEGF treatment were significantly more likely to show improvement in their DR when compared to individuals with DME who did not receive treatment. Importantly, those with severe non-proliferative DR are at risk of rapid disease progression and vision loss without treatment[12].

The severe and widespread societal restrictions imposed during the COVID-19 pandemic may have had a population-wide impact on both lifestyle factors and on the ability to receive the necessary treatment to preserve vision[13]. However, it is unclear if these changes affected the progression of DME. The purpose of the current investigation is to assess changes in systemic and ocular health parameters and the progression of DME since the onset of the COVID-19 pandemic in patients with diabetes *via* a retrospective chart review. This knowledge may help us improve patient care, education, and prevention of potential vision loss.

SUBJECTS AND METHODS

Ethical Approval This is a retrospective chart review of patients seen by the ophthalmology service at the Parkland Health & Hospital Systems and Aston Ambulatory Care Center (UT Southwestern Medical Center) in Dallas, Texas. Both of these centers provide care to a very large diabetic population. The UT Southwestern Medical Center Institutional Review Board and Ethics Committee approvals were obtained for both institutions (study number 33642), and the study is in accordance with HIPAA regulations. A waiver of authorization was obtained and approved in order to include all subjects in this study. All methods were carried out in accordance with relevant guidelines and regulations.

Study Population The inclusion criteria were defined as: age of 18y or older, diagnosis of DR of any severity (diabetes mellitus type 1 or 2), but with an established diagnosis of DME in at least one eye, having completed at least one ophthalmology visit in each of three specified time intervals: period 1 was January 2019 to February 2020 (considered pre-COVID-19), period 2 was March 2020 to December 2020 (considered the height of the pandemic; highest level of pandemic-related clinical and societal regulations in Dallas, Texas) and period 3 was January 2021 to July 2021 (re-adjustment to the new "pandemic norms"). These 3 periods correlate with the University of Oxford's COVID-19 stringency index of the government response for the United States[14]. Using these criteria, 370 patients (724 eyes) were included in the study. Patients without the appropriate visits (*e.g.* completed one visit during period 1 but failed to follow up in the subsequent periods 2 or 3) or incomplete records (*e.g.* OCT for each of the qualifying visits) were excluded. Because this is an observational study in which we are interested in documenting how DME progressed over time in patients who already have established DME, and we are not attempting to study a specific intervention/treatment, a non-diabetic control group was not included.

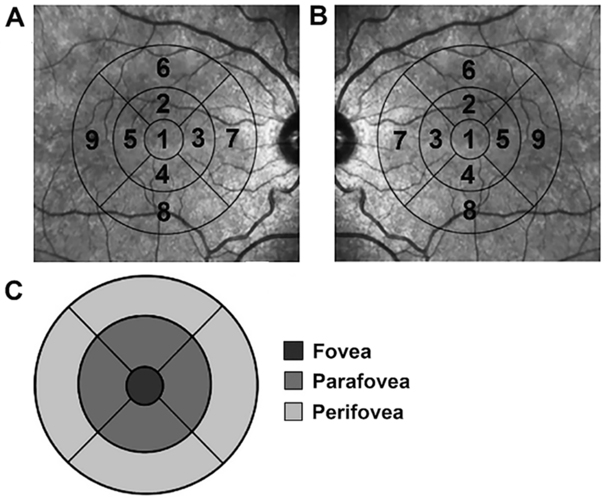

Figure 1 Macular depictions A: Macula divided into 9 ETDRS-defined sectors of right eye; B: Macula divided into 9 ETDRS-defined sectors of left eye; C: Macula divided into 3 regions of both eyes.

Outcome Measures Charts were assessed for age, gender, race and ethnicity, visual acuity (VA), body mass index (BMI), blood pressure (BP), hemoglobin A1c (HbA1c), and OCT parameters. Snellen chart measurements were documented at the time of the patient visit with corrective lenses (if available/needed) and/or pinhole in order to obtain the best corrected visual acuity (BCVA). BMI, BP, and HbA1c for each visit were pulled from the most recent values on file at the time of the visit. Most values were obtained within 2wk from the time of the ophthalmology visit, although a minority of HbA1c values deviated up to 2mo from the time of the visit.

A Spectralis OCT was used for taking images of patient retinas at each visit, which generated thickness measurements in μm for 9 Early Treatment Diabetic Retinopathy Study (ETDRS)-defined macular sectors (Figure 1A, 1B). Analyses were done *via* 3 macular regions: fovea, parafovea and perifovea (Figure 1C). The foveal region corresponded to sector 1, the parafoveal region consisted of sectors 2-5, and the perifoveal region was composed of sectors 6-9. For eyes that had OCT scans with poor resolution (macular sectors with no output measurements), this conversion was not done. In total, 570 eyes were included in all OCT analyses.

All of the outcome parameters were evaluated for each of the study periods. Changes from period 1 to period 2, period 2 to period 3, and period 1 to period 3 were assessed.

Compliance Classification To study the impact of non-compliance on our outcome measures, we divided the subjects according to adherence to scheduled ophthalmology appointments. Poor patient adherence was defined as missing >25% of scheduled appointments; satisfactory adherence was defined as ≤25%. Reasons for not attending include cancellation, leaving before being seen by a provider, or not showing up. In total, 170 patients (46%) maintained satisfactory adherence while 200 patients (54%) exhibited poor adherence.

Treatments Among the high adherence and low adherence groups, treatment trends were documented. At each period, the number of anti-VEGF injections per month and the number of panretinal photocoagulation (PRP) treatments per month were calculated. Given the retrospective nature of this study, there was no proactive randomization nor categorization of patient populations based on treatments received.

Statistical Analysis For statistical analysis and assessment of VA changes, we converted Snellen chart values to logarithmic minimum angle of resolution (logMAR) values[15]. For statistical analysis, eyes with no light perception, or with vision limited to light perception or hand motion were excluded. In total, 22 eyes were excluded from VA statistical analysis. Therefore, statistically analysis of VA included 702 eyes. For eyes that could only count fingers, we assumed that the fingers are approximately the size of the elements of a 200 letter. logMAR values were then converted back to Snellen chart measurements for clearer understanding of any changes in VA. The standard error of the mean (SEM) is reported as lines of VA, calculated as the SEM in logMAR units divided by 0.1 log units[16].

All systemic (BMI; BP; HbA1c) and ocular (VA) health parameters were analyzed using the Student's *t*-test to compare changes between two time points. OCT macular thickness, the effect of baseline systemic health factors on macular thickness, the effect of patient adherence on macular thickness, and treatment frequency within a given adherence group were analyzed *via* paired *t*-tests. Treatment trends and retinal thickness comparisons between different adherence groups were analyzed *via* unpaired *t*-tests. A *P* value <0.05 was considered statistically significant.

RESULTS

Demographics, Systemic and Ocular Health Parameters A total of 370 patients were included in the initial analysis. Demographic data of the study population is shown in Table 1. Systemic and ocular health parameters were measured at the three separate time periods (Table 2). BMI, systolic BP and diastolic BP did not show any significant changes between any of the time periods. HbA1c showed a very small increase from period 1 (7.6%) to period 2 (7.8%; *P*=0.015). It subsequently decreased back to 7.6% at period 3 (*P*=0.12). Therefore, there was no change from period 1 to period 3.

The average VA showed a mild, but statistically significant worsening from period 1 to period 2 (20/60.4 to 20/66.4, *P*=0.014), before sustaining a nonsignificant improvement during period 3 (20/62.4, *P*=0.14). Overall, average VA remained stable throughout the study with a non-significant decrease from period 1 to period 3 of 20/60.4 to 20/62.4 (*P*=0.39).

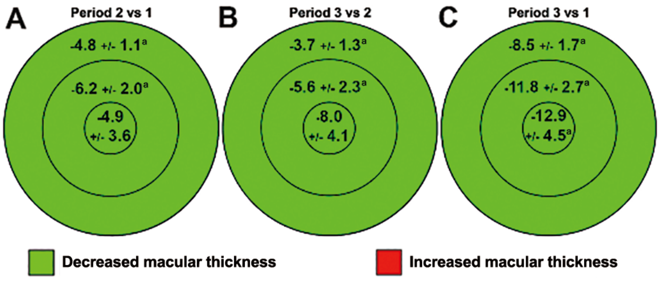

Figure 2 Differences in macular thickness throughout COVID-19

Macula divided into 3 regions (*n*=570). $^a P<0.05$.

Table 1 Demographics

Demographics	*n*=370
Male/female	195/175
Race/ethnicity	
Asian	22
Black	73
Hispanic	193
White	82
Age, y	
18–40	17
41–64	222
65+	131
BMI, kg/m^2	
<25	63
25-35	227
>35	80
DM	
Type 1	14
Type 2	356
HbA1c	
<6.5%	89
6.5%–8%	177
>8%	104

BMI: Body mass index; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c.

Macular Thickness Changes The analysis of OCT images for macular thickness considering 3 macular regions included 570 eyes. Out of 9 comparisons across the various periods, all 9 demonstrated a decrease in macular thickness, with 7/9 decreases being statistically significant (Figure 2, Table 3). The central macular thickness decreased across all 3 periods from 329.5 to 316.6 μm (Table 3). One of these decreases was statistically significant (period 3 *vs* 1, *P*=0.0045).

The patient populations at the two clinical centers included in this study were different. The race/ethnicity breakdown of the study patients from Parkland was 3.9% Asian, 14.8% Black, 72.4% Hispanic, and 8.9% White. Meanwhile, at

Table 2 Changes in systemic and ocular health parameters throughout COVID-19 mean±SEM

Parameter	Period 1	Period 2	Period 3	P_1	P_2	P_3
BMI (kg/m^2)	31.0±0.4	30.9±0.4	31.3±0.4	0.74	0.62	0.31
Systolic BP (mm Hg)	136.5±1.0	137.2±1.1	137.2±1.0	0.39	0.94	0.49
Diastolic BP (mm Hg)	75.7±0.6	75.5±0.6	75.6±0.6	0.97	0.97	0.95
HbA1c (%)	7.6±0.1	7.8±0.1	7.6±0.1	0.015	0.12	0.58
Visual acuity	20/60.4±0.2	20/66.4±0.2	20/62.4±0.2	0.014	0.14	0.39

Systemic health parameters include BMI, systolic BP, diastolic BP, and HbA1c (*n*=370). BMI: Body mass index; BP: Blood pressure; HbA1c: Hemoglobin A1c; SEM: Standard error of the mean. Ocular health parameters include VA (*n*=724). P_1: Difference between periods 2 and 1; P_2: Difference between periods 3 and 2; P_3: Difference between periods 3 and 1.

Table 3 Change in macular thickness throughout COVID-19 mean±SEM, μm

Sector	Period 1	Period 2	Period 3	P_1	P_2	P_3
Combined clinics						
Central	329.5±4.6	324.6±4.5	316.6±4.3	0.17	0.053	0.0045
Parafoveal	359.7±2.9	353.5±2.8	347.9±2.8	0.0024	0.015	0.0001
Perifoveal	321.4±2.2	316.6±2.0	312.9±2.0	0.0001	0.0054	0.0001
Parkland						
Central	357.2±6.7	347.9±6.5	341.1±6.6	0.08	0.27	0.0282
Parafoveal	379.7±4.4	370.4±4.1	365.4±4.3	0.0021	0.13	0.0014
Perifoveal	336.2±3.2	329.7±3.0	325.9±3.2	0.0003	0.06	0.0002
Aston						
Central	296.9±5.3	297.3±5.8	287.7±4.7	0.94	0.08	0.06
Parafoveal	336.2±3.2	333.7±3.5	327.4±2.8	0.35	0.0456	0.0021
Perifoveal	303.9±2.4	301.3±2.3	297.7±2.0	0.0523	0.0310	0.0005

SEM: Standard error of the mean. *n*=570 combined clinics, *n*=308 Parkland, *n*=262 Aston. P_1: Difference between periods 2 and 1; P_2: Difference between periods 3 and 2; P_3: Difference between periods 3 and 1.

Aston the distribution was 8.4% Asian, 25.7% Black, 27.5% Hispanic, and 38.3% White. Thus, we decided to include an additional analysis of the macular thickness data looking at the two clinical centers separately. It revealed a similar macular thickness behavior in both patient populations. In the Parkland population, all macular regions decreased in thickness, with 5/9 comparisons being statistically significant (Table 3). In the Aston population, 8 out of the 9 comparisons exhibited a decrease in macular thickness (4/8 statistically significant), and one comparison exhibited a minimal (0.4 μm) increase that was not statistically significant (Table 3).

Effect of Baseline Systemic Factors on DME Changes The macular data was reanalyzed after subjects were stratified into tertiles based on HbA1c or BMI in order to determine if patients with more at-risk systemic factors showed some evidence of worsening DME during the COVID-19 pandemic. Based on BMI, the study population was split into <27.5 kg/m^2 (*n*=182), 27.5–32.3 kg/m^2 (*n*=200), and >32.3 kg/m^2 (*n*=188). For HbA1c, patients were split into <6.7% (*n*=202), 6.7%–7.8% (*n*=178), and >7.8% (*n*=190).

After stratification for BMI, the retinal thickness decreased across all time periods in all macular regions for all three tertiles (Table 4). For each tertile, there are 9 possible comparisons. Out of those 9 comparisons, the number with a decrease in thickness that reached statistical significance gradually decreased from the upper BMI tertile (7/9 comparisons), to the middle BMI tertile (5/9 comparisons), to the lower BMI tertile (2/9 comparisons). The upper BMI tertile is the only group that exhibited significantly decreased thickness in the central region. The upper tertile by BMI exhibited thicker maculae at baseline (period 1).

Regarding the HbA1c analysis (Table 5), the middle tertile exhibited thicker baseline retinae for most macular regions. Most macular regions showed some level of decrease in thickness. In fact, only 1 out of 27 possible comparisons showed an increase in retinal thickness, and it was not significant (middle tertile, central region, period 3 *vs* period 2). On the other hand, statistically significant reductions in thickness were observed in 5/9 comparisons in the lower tertile group, 5/9 in the middle tertile and 2/9 in the high tertile.

Effect of Adherence to Clinical Follow up on DME and Diabetic Retinopathy Treatment Frequency Since poor patient adherence to follow up was one of the predicted mechanisms for an impact of COVID-19 on DME, the OCT data and treatment trends were analyzed based on patient adherence to ophthalmology appointments. Totally 170 patients

Table 4 Change in macular thickness stratified based on BMI mean±SEM, μm

BMI tertile (kg/m^2)	Period 1	Period 2	Period 3	P_1	P_2	P_3
<27.5 (*n*=182)						
Central	322.7±7.1	322.2±7.7	316.3±7.7	0.93	0.46	0.39
Parafoveal	354.6±4.7	351.6±5.0	347.0±4.8	0.46	0.31	0.10
Perifoveal	318.2±3.5	313.8±3.3	311.0±3.6	0.035	0.23	0.019
27.5-32.3 (*n*=200)						
Central	331.5±8.0	323.5±7.4	323.1±7.6	0.12	0.95	0.30
Parafoveal	361.5±4.8	354.2±4.7	351.2±5.0	0.018	0.38	0.032
Perifoveal	322.1±3.7	317.7±3.6	313.1±3.5	0.033	0.033	0.0026
>32.3 (*n*=188)						
Central	334.0±8.5	328.2±8.5	310.0±7.0	0.43	0.015	0.0024
Parafoveal	362.9±5.7	354.7±5.1	345.4±4.5	0.020	0.022	0.0005
Perifoveal	323.6±3.9	318.3±3.6	314.7±3.5	0.0032	0.13	0.0016

BMI: Body mass index; SEM: Standard error of the mean. P_1: Difference between periods 2 and 1; P_2: Difference between periods 3 and 2; P_3: Difference between periods 3 and 1.

Table 5 Change in macular thickness stratified based on HbA1c mean±SEM, μm

HbA1c tertile (%)	Period 1	Period 2	Period 3	P_1	P_2	P_3
<6.7 (*n*=202)						
Central	329.6±7.3	328.3±8.3	308.4±6.5	0.85	0.0091	0.0011
Parafoveal	357.2±4.5	354.2±5.0	344.0±4.3	0.40	0.021	0.0007
Perifoveal	316.2±3.3	313.7±3.2	309.4±3.4	0.13	0.10	0.0078
6.7-7.8 (*n*=178)						
Central	334.3±7.9	323.3±7.0	323.4±7.2	0.11	0.99	0.19
Parafoveal	362.0±5.3	353.5±4.9	349.2±4.8	0.036	0.29	0.020
Perifoveal	323.2±4.1	318.4±4.1	312.9±3.8	0.043	0.023	0.0032
>7.8 (*n*=190)						
Central	324.9±8.5	321.9±8.1	318.9±8.5	0.56	0.67	0.50
Parafoveal	360.3±5.5	352.8±4.9	351.0±5.3	0.14	0.58	0.061
Perifoveal	325.0±3.8	318.1±3.2	316.7±3.3	0.0003	0.44	0.0037

HbA1c: Hemoglobin A1c; SEM: Standard error of the mean. P_1: Difference between periods 2 and 1; P_2: Difference between periods 3 and 2; P_3: Difference between periods 3 and 1.

Table 6 Change in macular thickness stratified based on patient adherence mean±SEM, μm

Adherence group	Period 1	Period 2	Period 3	P_1	P_2	P_3
Satisfactory (*n*=295)						
Central	333.5±6.3	325.6±5.9	321.0±5.7	0.14	0.47	0.066
Parafoveal	362.7±4.1	353.9±3.7	349.7±3.6	0.0041	0.24	0.0022
Perifoveal	321.7±3.0	315.2±2.7	311.5±2.8	0.0001	0.070	0.0001
Poor (*n*=275)						
Central	325.2±6.6	323.6±7.0	311.9±6.4	0.73	0.027	0.025
Parafoveal	356.5±4.2	353.2±4.4	346.1±4.2	0.21	0.014	0.0026
Perifoveal	320.9±3.1	318.2±3.1	314.5±3.0	0.094	0.027	0.0019

SEM: Standard error of the mean. P_1: Difference between periods 2 and 1; P_2: Difference between periods 3 and 2; P_3: Difference between periods 3 and 1.

met criteria for satisfactory adherence (≤25% of appointments missed), and 200 patients met criteria for poor adherence (>25% of appointments missed).

Both satisfactory (Figure 3A-3C, Table 6) and poor (Figure 3D-3F, Table 6) adherence groups exhibited some level of decrease in macular thickness in all 9 region comparisons across all time periods. In fact, in the poor adherence group, the difference reached significance in 6/9 region comparisons, while in the satisfactory group only 4/9 of the decreases were significant.

The two treatment modalities we analyzed were intravitreal anti-VEGF injections and PRP laser sessions. In this analysis

Table 7 Changes in treatment frequency throughout COVID-19 mean±SEM, times/mo

Treatment	Period 1	Period 2	Period 3	P_1	P_2	P_3
Combined clinics						
Satisfactory (*n*=170)						
Injections	0.416±0.031	0.491±0.038	0.555±0.047	0.0171	0.0471	0.0004
PRP	0.038±0.005	0.031±0.005	0.029±0.006	0.30	0.78	0.17
Poor (*n*=200)						
Injections	0.259±0.022	0.305±0.024	0.328±0.031	0.0454	0.35	0.0205
PRP	0.037±0.005	0.035±0.005	0.044±0.007	0.73	0.18	0.36
Parkland						
Satisfactory (*n*=108)						
Injections	0.478±0.040	0.585±0.049	0.694±0.062	0.0146	0.0212	0.0001
PRP	0.044±0.007	0.045±0.006	0.034±0.007	0.91	0.19	0.26
Poor (*n*=95)						
Injections	0.335±0.036	0.362±0.033	0.453±0.050	0.47	0.0391	0.0195
PRP	0.048±0.007	0.055±0.008	0.067±0.010	0.51	0.30	0.15
Aston						
Satisfactory (*n*=62)						
Injections	0.306±0.047	0.326±0.053	0.312±0.058	0.63	0.66	0.92
PRP	0.026±0.007	0.006±0.006	0.022±0.009	0.0085	0.0491	0.34
Poor (*n*=105)						
Injections	0.189±0.026	0.252±0.034	0.216±0.037	0.0263	0.19	0.45
PRP	0.027±0.007	0.017±0.008	0.024±0.008	0.18	0.40	0.70

PRP: Panretinal photocoagulation; SEM: Standard error of the mean. *n*=570 combined clinics, *n*=308 Parkland, *n*=262 Aston. P_1: Difference between periods 2 and 1; P_2: Difference between periods 3 and 2; P_3: Difference between periods 3 and 1.

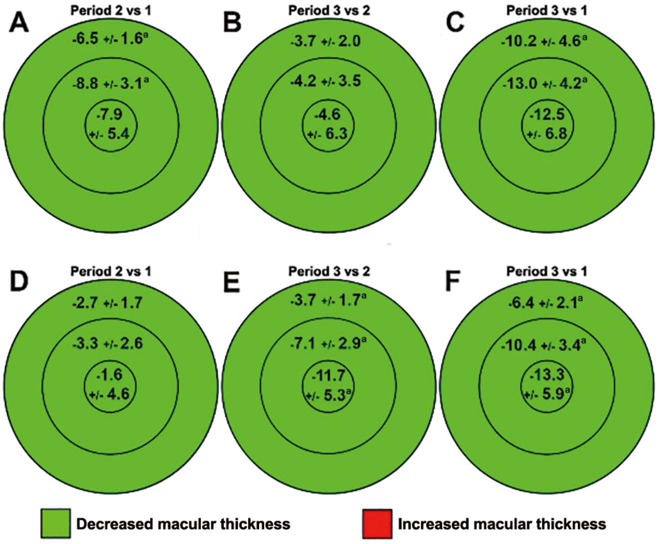

Figure 3 Differences in thickness of 3 macular regions throughout COVID-19 stratified based on patient adherence A-C: Satisfactory adherence (*n*=295); D-F: Poor adherence (*n*=275). [a]$P<0.05$.

(Table 7), the group of patients with satisfactory adherence was receiving 0.416 injections per month during period 1, and there was a statistically significant increase in treatment frequency in each subsequent period (0.416 to 0.555). They had a very small decrease in the average number of PRP treatments per month across all three periods, although none of the differences were statistically significant. Patients with poor adherence (Table 7) were receiving 0.259 injections per month at baseline, and they showed a statistically significant increase in the prevalence of injections when comparing period 2 to period 1 (0.259 to 0.305 injections/mo, P=0.0454) and period 3 to period 1 (0.259 to 0.328 injections/mo, P=0.0205). No statistically significant difference in the prevalence of PRP treatments per month was seen. Comparing the good *vs* low compliance groups revealed that the satisfactory adherence group had a higher number of injections per month compared to the poor adherence group (P=0.0001 for each of the three time point comparisons).

We then reanalyzed the treatment frequencies after separating the patients into Parkland and Aston clinic subpopulations. In the Parkland population, the tendency toward an increase in the frequency of injections throughout the study period was maintained for both the good and low compliance subgroups (Table 7). However, this was not the case at Aston where the injection rates remained stable for most comparisons.

DISCUSSION

Systemic Health Factors COVID-19 caused drastic changes in lifestyle since the early part of 2020. Although some estimates warned of potential adverse outcomes in patient health, actual changes since the pandemic are more inconclusive. Both stable and worsening HbA1c have been reported since the early phases of lockdown measures[17-20]. The current study attempted to assess what effects those lifestyle changes had on the systemic and ocular health parameters of patients with DME. Our chosen study time intervals correlate well with the University of Oxford's COVID-19 stringency index of the government response for the United States, which includes many components such as school closures, workplace closures, and travel bans[14].

BMI and BP stayed relatively unchanged throughout the three time periods. Even HbA1c was mostly stable, showing only a very small bump from the pre-COVID-19 period to the height of the pandemic lockdowns, before subsequently returning to baseline levels. The transient nature of this increase may be due to the multifactorial changes that occurred with the beginning of the lockdown measures, and its magnitude is unlikely to make it clinically significant. Potential COVID-related factors that could have an impact on HbA1c levels include a change in diet, change in exercise patterns, and stress. Since the BP and BMI did not change, and the HbA1c increase was transient, we were not able to document a COVID-19-associated drastic and systematic worsening in systemic health parameters of the kind we typically associate with DR progression, at least in our study population.

Ocular Health Factors VA demonstrated a pattern of transiently worsening from before COVID-19 to the height of the pandemic lockdowns before subsequently improving. This trend is similar to the pattern that HbA1c exhibited. One potential cause of these findings is that as a patient's HbA1c worsened, the VA worsened secondary to rising blood glucose levels. For instance, an elevation in glucose can lead to an accumulation of sorbitol in the lens, which subsequently distorts one's vision independent of any retinal pathology. The current results are consistent with other recent studies; while several studies note a decrease in VA in patients with DR (including with DME) after the COVID-19 lockdowns, at least one shows no significant difference[21-23].

Retinal Health Factors We analyzed macular thickness in three regions: central, parafoveal and perifoveal. Although the central macular thickness has the most impact on VA, we still included the parafoveal and perifoveal regions for two reasons: it may provide an assessment of the biological impact of systemic disease on the macular vasculature, and it is known that patient-perceived "quality of vision" is more complex than visual acuity, and parafoveal changes may affect it[24-25].

Our main hypothesis was that the severe societal restrictions imposed during the COVID-19 pandemic may have produced a combined negative impact on the health of diabetic patients and on their DME. The main factors we predicted would be at work were: COVID-19 restrictions forced many clinics to close or severely reduce the number of patients seen (this could potentially affect visits to primary care physicians, endocrinologists and ophthalmology clinics). So, this could in theory result in both poorer systemic health and also decreased ocular treatments; Many people reduced their physical activity as they were forced to stay indoors more. Thus, we predicted a worsening in DME during the COVID-19 pandemic, but instead we found a decrease in macular thickness. The decrease in macular thickness was documented universally across all time periods in all retinal regions, and, in many cases, it was statistically significant. One potential explanation would be that the appearance of retinal changes may be delayed. There can be a delay between when systemic health changes occur and when the subsequent retinal changes occur[26]. Our study finishes 16mo after the beginning of the pandemic. A future analysis looking 18mo after the peak of the pandemic and beyond may be able to address this issue.

Although statistically significant, the overall magnitude of change in macular thickness was very small. The clinical implications of this small decrease in macular thickness are not clear, and it would be difficult to measure their impact on the patients' quality of life. Nonetheless, the key finding of our study is that DME did not worsen during the early post-COVID-19 era.

We decided to explore a possible scenario in which a subpopulation of DME patients may have experienced worsening of their macular edema, while another subpopulation may have had a significant improvement that drove the overall results for the entire study population. First, we know that the Parkland and Aston outpatient clinics serve two different patient populations. The racial/ethnicity distribution is different. Also, Parkland serves many uninsured and underinsured patients, while most patients at Aston have private insurance. In our study population, the average HbA1c was also slightly higher in the Parkland subgroup (7.8%) compared to Aston's subgroup (7.3%, P=0.0036; data not shown). Therefore, we decided to do a separate analysis of each clinic population's macular edema behavior throughout the pandemic. It is interesting to note Parkland's higher baseline macular thickness and baseline treatment frequency compared to Aston's, which may indicate increased disease severity in this subpopulation. Still, neither subpopulation experienced a significant worsening of DME at any point during the pandemic, and many macular regions demonstrated a small decrease in macular thickness irrespective of baseline disease severity–similar to the overall results for the entire study population.

Then, we hypothesized that perhaps patients with the highest BMI would have the worst outcomes regarding DME. Yet, we found the opposite: patients in the high-BMI tertile exhibited the most macular regions with significantly decreased thickness as well as the largest magnitudes in decreases. A potential contributing factor for these findings is that these patients started with higher baseline retinal thickness and had more room for improvement. When applying this analysis to HbA1c we found the same overall conclusion: all three tertiles showed decreases in thickness, with some being statistically significant. There were no statistically significant increases.

We also wanted to determine if the parameter of adherence to follow up could identify a subpopulation of patients with worsening DME. Notably, despite the differences in adherence to ophthalmology appointments, both subgroups exhibited identical numbers of macular sectors with decreases in thickness. Furthermore, many of these comparisons were statistically significant for both subgroups.

Based on the combination of these analyses, we concluded that there was no easily identifiable subset of patients that actually experienced the predicted worsening in macular edema. Although, it is possible that patients completely lost to follow up may have experienced an increase in DME due to the lack of treatment, it is still interesting that the low *vs* high adherence groups did not show a marked split in terms of macular edema behavior. Future studies may look at the prevalence of loss to follow up, and particularly at the clinical characteristics of the subset of patients who were lost to follow up (*e.g.* the lost-to-follow-up subgroup biased towards patients with clinically unstable retinopathy or towards patients who knew they were unlikely to need treatment).

It should be noted that the natural history of DME disease over longer periods of time could predict small decreases in macular edema over time. Moreover, an important factor influencing the disease course in DME is the treatment frequency, particularly intravitreal anti-VEGF injections. Our patient population was not treatment naïve because one of the requirements for inclusion in this study was established, active DME. A potential reason for the observed decreases in macular thickness in our study could be that, despite the pandemic-related restrictions, treatment with anti-VEGF injections may not have been interrupted. To best assess this variable, we utilized period 1 as an established baseline for treatment regimens. The subsequent 2 time periods were then used to evaluate the effects of changes in treatment regimen. While, in general terms, patients with DME can expect a decrease in treatment frequency in the years following initiation of DME therapy[27-28], our entire study population experienced a slight increase in the frequency of anti-VEGF injections during our relatively short follow up. To explore this observation further, we again split the analysis between the two patient clinics. It was interesting to see that while the same trend of increased injection frequency was seen in the Parkland population, the Aston population maintained a relatively unchanged frequency of injection treatments. Despite this notable difference, the Aston clinic still did not show an increase in macular edema during the COVID-19 pandemic and instead still showed a slight decrease. Further, the poor adherence subpopulation experienced a more significant decrease in macular thickness despite lower average treatment frequencies throughout the study when compared to the high adherence group.

Finally, a possible explanation for the observed decrease in retinal thickness would be that our study population may have experienced a positive balance of lifestyle changes after the pandemic reached Dallas. For instance, with many school and work closures, individuals may have had more free time to dedicate to creating and adhering to a workout routine and healthy diet. Many restaurants and fast-food chains closed during the pandemic. Furthermore, even when available, many patients were trying to stay away from such public places. These issues may have prompted a search for alternative food choices which may have been healthier on average. One caveat is that we did not observe the overall improvements in BMI, BP or HbA1c that you would predict if this hypothetical change to a healthier diet was strongly dominant. Moreover, the middle- and low-BMI tertiles also experienced decreases rather than increases in retinal thickness.

Our thorough data analysis increases our confidence in our overall conclusions: 1) Contrary to our original hypothesis, DME did not increase during the early phases of COVID-19 (and may even have decreased); 2) None of the baseline BMI and HbA1c subgroups showed a worsening of DME; 3) We could not identify changes in systemic factors (BMI and HbA1c) that could explain the improvement in DME; 4) Levels of adherence to follow up could not explain the observed decrease in DME; 5) An increase in treatment frequency may be one explanation for the observed decrease in DME, although we were able to observe the same decrease in macular thickness in the Aston population despite not having an increase in treatment frequency. Still, the fact that in our study population treatment frequency did not seem to have been severely impacted by COVID-19 restrictions may be one of the contributing factors preventing our predicted worsening in DME.

It is possible that some COVID-19-related changes in lifestyle had a positive impact on health (*e.g.* the possibility of a decrease in fast food consumption), while others had a negative impact (*e.g.* the possibility of a decrease in exercise and decrease in medical care). Moreover, adjustments in the healthcare system including prioritization of patients needing treatment for in-person clinic visits, and the robust move towards virtual primary care visits may have helped significantly blunt potential systemic health effects of the pandemic. So, contrary to our prediction, the balance of these changes may have had more of a positive impact on DME. A future study using questionnaires (with the caveat of recall bias) and study of primary care physician notes may provide a more accurate picture of the specific lifestyle changes that occurred, and of their magnitude and direction. This information would allow for a more thorough understanding of the observed DME changes.

There are several limitations to the current study. First is its retrospective nature, which prevented the standardization of ophthalmology appointments, of lab testing, and of treatment protocols. In addition, we were not able to survey patients in real time on possible lifestyle changes as COVID-19 progressed. Finally, our study population was not treatment naïve.

As we continue to care for patients with DME in the current climate of COVID-19, vigilance must continue. Importance should be placed on proactively addressing any delayed-onset worsening of DME, continuing to monitor for additional improvements in clinical status, and further investigating what specific lifestyle changes occurred in this study population.

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REFERENCES

1 Moss SE, Klein R, Klein BE. The incidence of vision loss in a diabetic population. *Ophthalmology* 1988;95(10):1340-1348.

2 Das A, McGuire PG, Rangasamy S. Diabetic macular edema: pathophysiology and novel therapeutic targets. *Ophthalmology* 2015;122(7):1375-1394.

3 Sikorski BL, Malukiewicz G, Stafiej J, Lesiewska-Junk H, Raczynska D. The diagnostic function of OCT in diabetic maculopathy. *Mediators Inflamm* 2013;2013:434560.

4 Schimel AM, Fisher YL, Flynn HW Jr. Optical coherence tomography in the diagnosis and management of diabetic macular edema: time-domain versus spectral-domain. *Ophthalmic Surg Lasers Imaging* 2011;42 Suppl: S41-S55.

5 Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, Selvin E, Dolan C, Fine J, Colman S, Turpcu A. Prevalence of and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol* 2014;132(11):1334-1340.

6 Chou TH, Wu PC, Kuo JZ, Lai CH, Kuo CN. Relationship of diabetic macular oedema with glycosylated haemoglobin. *Eye (Lond)* 2009;23(6):1360-1363.

7 Wong TY, Sabanayagam C. Strategies to tackle the global burden of diabetic retinopathy: from epidemiology to artificial intelligence. *Ophthalmologica* 2020;243(1):9-20.

8 Yan X, Han X, Wu C, Shang X, Zhang L, He M. Effect of physical activity on reducing the risk of diabetic retinopathy progression: 10-year prospective findings from the 45 and up study. *PLoS One* 2021;16(1):e0239214.

9 Wong MYZ, Man REK, Fenwick EK, Gupta P, Li LJ, van Dam RM, Chong MF, Lamoureux EL. Dietary intake and diabetic retinopathy: a systematic review. *PLoS One* 2018;13(1):e0186582.

10 Schmidt-Erfurth U, Lang GE, Holz FG, *et al*. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology* 2014;121(5):1045-1053.

11 Romero-Aroca P, Reyes-Torres J, Baget-Bernaldiz M, Blasco-Suñe C. Laser treatment for diabetic macular edema in the 21st century. *Curr Diabetes Rev* 2014;10(2):100-112.

12 Bakri SJ, Malhotra M, Stoilov I. Course of diabetic retinopathy in untreated fellow eyes in RIDE and RISE: a post hoc analysis. *Ophthalmic Surg Lasers Imaging Retina* 2022;53(4):202-207.

13 Soleimani M, Mehrpour M, Mohammad-Rabei H. Ophthalmic practice during COVID-19 pandemic. *Int J Ophthalmol* 2021;14(5):639-642.

14 Hale T, Angrist N, Goldszmidt R, Kira B, Petherick A, Phillips T, Webster S, Cameron-Blake E, Hallas L, Majumdar S, Tatlow H. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nat Hum Behav* 2021;5(4):529-538.

15 Caltrider D, Gupta A, Tripathy K. Evaluation of Visual Acuity. In: *StatPearls*. Treasure Island (FL):StatPearls Publishing; February 21, 2022.

16 Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg* 1997;13(4):388-391.

17 Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: a systematic review. *Diabetol Metab Syndr* 2021;13(1):95.

18 Ojo O, Wang XH, Ojo OO, Orjih E, Pavithran N, Adegboye ARA, Feng QQ, McCrone P. The effects of COVID-19 lockdown on glycaemic control and lipid profile in patients with type 2 diabetes: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;19(3):1095.

19 D'Onofrio L, Pieralice S, Maddaloni E, Mignogna C, Sterpetti S, Coraggio L, Luordi C, Guarisco G, Leto G, Leonetti F, Manfrini S, Buzzetti R. Effects of the COVID-19 lockdown on glycaemic control in subjects with type 2 diabetes: the glycalock study. *Diabetes Obes Metab* 2021;23(7):1624-1630.

20 Jin J, Lee SW, Lee WK, Jeon JH, Kim JG, Lee IK, Choi YK, Park KG. Year-long trend in glycated hemoglobin levels in patients with type 2 diabetes during the COVID-19 pandemic. *Endocrinol Metab (Seoul)* 2021;36(5):1142-1146.

21 Chatziralli I, Dimitriou E, Kazantzis D, Machairoudia G, Theodossiadis G, Theodossiadis P. Effect of COVID-19-associated lockdown on patients with diabetic retinopathy. *Cureus* 2021;13(5):e14831.

22 Rush RB, Rush SW. Outcomes in patients resuming intravitreal anti-vascular endothelial growth factor therapy following treatment delay during the coronavirus-19 pandemic. *Retina* 2021;41(12):2456-2461.

23 Song W, Singh RP, Rachitskaya AV. The effect of delay in care among patients requiring intravitreal injections. *Ophthalmol Retina* 2021;5(10):975-980.

24 Ng H, Vermeer KA, van Meurs JC, La Heij EC. Visual acuity inadequately reflects vision-related quality of life in patients after macula-off retinal detachment surgery. *Invest Ophthalmol Vis Sci* 2020;61(10):34.

25 Kim KE, Kim JH, Kim YH, Ahn SJ. Clock-hour topography and extent of outer retinal damage in hydroxychloroquine retinopathy. *Sci Rep* 2022;12(1):11809.

26 Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol* 1998;116:874-886.

27 Peto T, Akerele T, Sagkriotis A, Zappacosta S, Clemens A, Chakravarthy U. Treatment patterns and persistence rates with anti-vascular endothelial growth factor treatment for diabetic macular oedema in the UK: a real-world study. *Diabet Med* 2022;39(4): e14746.

28 Blinder KJ, Dugel PU, Chen S, Jumper JM, Walt JG, Hollander DA, Scott LC. Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). *Clin Ophthalmol* 2017;11:393-401.