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Retinal Thickness and Morphology Changes on OCT in Youth with Type 2 Diabetes

Findings from the TODAY Study

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Objective: To evaluate changes in retinal thickness and morphology using OCT in youth with type 2 diabetes (T2D) and to identify systemic biomarkers correlating with these changes.

Design: Retrospective subgroup analysis of a prospective study.

Participants: Participants who underwent OCT imaging in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial and its follow-up study TODAY2.

Methods: In 2010−2011 (TODAY) and 2017−2018 (TODAY2), 6 × 6-mm macular volume OCT scans were acquired, segmented, and analyzed to generate total retinal thickness, inner retinal thickness, and outer retinal thickness. The main retinal morphologies graded were intraretinal cystoid spaces, subretinal fluid, and posterior vitreous detachment (PVD).

Main Outcome Measures: Changes in total and individual retinal layer thickness and development of abnormal vitreomacular morphology between TODAY and TODAY2.

Results: Participants had a mean age of 17.9 ± 2.4 years and glycated hemoglobin (HbA1c) of 8.2 ± 2.8% in TODAY and a mean age of 25.0 ± 2.4 years and mean HbA1c of 9.5 ± 2.8% in TODAY2. Longitudinally between assessments, there were overall decreases in outer retinal thickness from 167.2 ± 11.5 microns to 158.4 ± 12.8 microns ($P < 0.001$) and in photoreceptor thickness from 30.3 ± 2.9 microns to 29.8 ± 4.1 microns ($P = 0.04$) in the central subfield, while in the inner subfield, we noted a decrease in outer retinal thickness from 150.5 ± 10.1 microns to 144.9 ± 10.5 microns ($P < 0.001$) and an increase in inner retinal thickness from 136.9 ± 11.5 microns to 137.4 ± 12.6 microns ($P = 0.01$). Multivariate analysis showed that in the center subfield, HbA1c increases were associated with increases in total retinal thickness (r: 0.67, $P = 0.001$), whereas fasting glucose was positively correlated with inner retinal thickness (r: 0.02, $P = 0.02$). In the inner subfield, both systolic (r: −0.22, $P < 0.001$) and diastolic (r: −0.22, $P = 0.003$) blood pressures were negatively correlated with total retinal thickness. There was an increase in PVD (18.9%) and cystoid spaces (4.2%).

Conclusions: Youth with T2D develop retinal thickness changes on OCT, including increases in total retinal and inner retinal thickness in the center subfield that correlate with HbA1c and fasting glucose, respectively. Taken together with the increased prevalence of abnormal vitreomacular morphology in this cohort at risk, these findings emphasize the importance of controlling risk factors to prevent the development of sight-threatening retinal complications. *Ophthalmology Science 2022;2:100191 © 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/).*

Supplemental material available at www.ophthalmologyscience.org.

Diabetic retinopathy (DR) is the leading cause of visual impairment in working-age adults.[1] Retinal neurodegeneration occurs prior to the onset of microvascular changes and is typically associated with retinal thinning, especially at the level of the inner retina in patients with longstanding type 2 diabetes (T2D).[2−4]

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study and its observational follow-up study (TODAY2) provided longitudinal assessments of diabetes management and DR progression between 2004 and 2020 in an ethnically diverse cohort of 699 participants with newly diagnosed T2D, aged 10−17 years at enrollment. A subset of 334 participants underwent multimodal imaging in the form of digital fundus photography of 7 standard stereoscopic fields and OCT in 2010−2011 and approximately 7 years later. The original TODAY study

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reported a DR prevalence of 13.7% (with all cases being mild nonproliferative DR [NPDR]).[5] At follow-up, the same cohort demonstrated a significant rise in microvascular complications (kidney, nerve, and retinal disease), with DR prevalence increasing to 51%.[6]

The relationship between DR and the nature and extent of OCT changes is not fully understood. Accordingly, the aims of this paper are to evaluate longitudinal changes in OCT-derived total and individual retinal layer thickness between TODAY and TODAY2 and to describe the nature and prevalence of abnormal morphological changes in the macula in this cohort of youth with T2D.

Methods

Clinical Trial Design

The TODAY study was conducted at 15 sites in the United States and was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. The protocol and informed consent forms were approved by the respective institutional review boards, and the study adhered to the tenets of the Declaration of Helsinki. Parents of each participant provided written informed consent, and the participants provided their assent to participate in the study. As previously described in detail,[7] the TODAY study enrolled 699 participants over the course of 4.5 years and evaluated the effects of one of 3 treatments (metformin, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention) on the time to loss of glycemic control in youth-onset T2D participants. In the final year of the TODAY study (2010–2011), 482 participants (926 eyes) were imaged with either time-domain OCT (TD-OCT) (277 participants) or spectral-domain OCT (SD-OCT) (205 participants). In 2011, 572 (82%) TODAY participants enrolled in the TODAY follow-up study (TODAY2), which was conducted in 2 phases. All participants provided written consent to participate. Between 2011 and 2014 (phase 1), participants received diabetes-related care from the TODAY study team and were treated with metformin, with the addition of insulin if needed to maintain glycemic control. From 2014 to 2020 (phase 2), 518 TODAY participants transitioned to a fully observational study with annual visits for the study and medical management provided entirely by their health care providers. As part of this second phase, a total of 407 participants (812 eyes) underwent SD-OCT in 2017–2018. This analysis examines the 344 participants (661 eyes) with gradable OCT imaging in both TODAY and TODAY2.

OCT Imaging and Grading

Participants in the TODAY study were imaged using either TD-OCT technology (Stratus, Carl Zeiss Meditec, Inc) and SD-OCT technology (Spectralis, Heidelberg Engineering, Inc and Cirrus, Carl Zeiss), whereas all imaging in TODAY2 was in the form of SD-OCT, with 6 × 6-mm macular volume scans being acquired from each eye.

All OCTs were graded centrally at the Wisconsin Reading Center (Madison, WI) by graders (J.W.P. and A.D.) masked to treatment, age, duration of diabetes, glycemic control, and other clinical characteristics. There were 3 assessments available from the data set. A total of 67 OCT scans for which the measurement of central subfield thickness was deemed unreliable were excluded from this study. Reliable OCT scans were available for almost 70% of the TODAY participants with 84.4% of these having reliable follow-up imaging 7 years later during TODAY2.

Central Subfield Thickness. Total retinal thickness, measured from the internal limiting membrane (ILM) to the retinal pigment epithelium (RPE) in the central subfield, was considered within the normal range if the thickness was < 300 microns for males and 285 microns for females. Eyes with thickness outside the normal range at either time point were excluded from analyses involving change in retinal thickness between TODAY and TODAY2 (n = 8), as well as eyes with subretinal fluid or intraretinal cystoid spaces (n = 38), leaving 615 eyes in 332 participants for analysis.

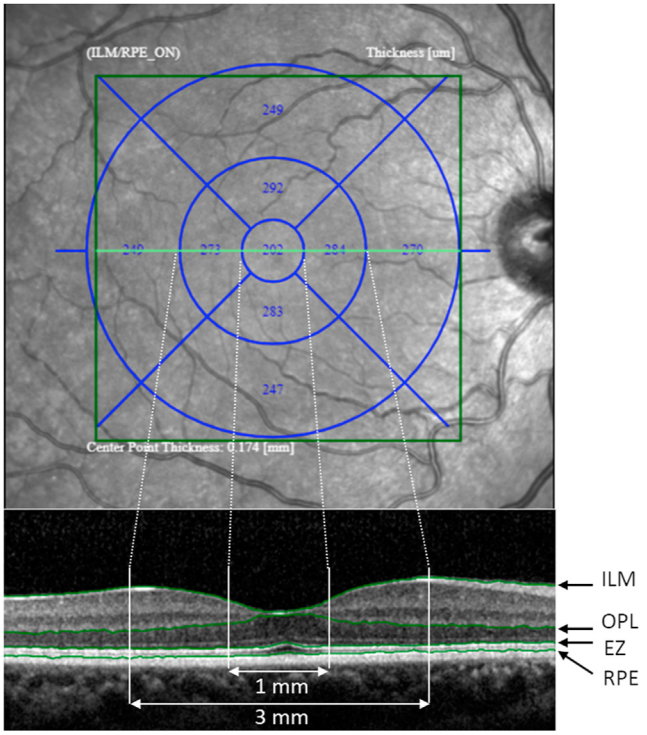

Figure 1. Retinal thickness measurement for the central subfield and inner subfield of the OCT grid based on segmentation of the retina. EZ = ellipsoid zone; ILM = internal limiting membrane; OPL = outer plexiform layer; RPE = retinal pigment epithelium.

Retinal Layer Thickness. The SD-OCT volume scans underwent a custom-built semiautomated segmentation software (independent of the manufacturer) analysis for ILM, outer plexiform layer (OPL), ellipsoid zone (EZ), and RPE layers. Any segmentation errors were reviewed and manually corrected to generate total retinal thickness (ILM to RPE), inner retinal thickness (ILM to OPL), outer retinal thickness (OPL to RPE), and photoreceptor thickness (EZ to RPE). The OCT thicknesses were calculated for the central 1-mm and the inner 3-mm circle diameter regions.

The thickness in the central 1 mm is referred to as the central subfield thickness and is the average of the distance between the ILM and the RPE of all B scans passing through the central 1000 microns. The inner subfield thickness in the 3-mm circle was calculated as the average thickness of the central and 4 inner quadrant subfields (superior, inferior, nasal, and temporal). Within each inner subfield, the thickness of all B scans passing through that specific subfield was averaged. The region of the B scan included in the measurements was restricted to the relevant subfield. For example, a single B scan passing through the center contributes its central 1000 microns to the central subfield measurements and the nasal and temporal 1000 microns to the inner nasal and inner temporal subfield measurements (Figure 1).

Morphology Assessment. Morphological abnormalities graded on OCT were subretinal fluid, intraretinal cystoid spaces, posterior

Table 1. Patient Characteristics in TODAY and TODAY2 (Participant Level)

Patient Characteristics	TODAY (2010–2011)	TODAY2 (2017–2018)
Patient characteristics		
Has retinal thickness data	342 (99.4)	–
Has morphology data	343 (99.7)	–
Sex		
Male	122 (35.5)	–
Female	222 (64.5)	–
Race/ethnicity		
Non-Hispanic White	66 (19.2)	–
Non-Hispanic Black	121 (35.2)	–
Hispanic	132 (38.4)	–
Other	25 (7.3)	–
Today treatment arm		
Metformin	121 (35.2)	–
Metformin + rosiglitazone	110 (32.0)	–
Metformin + intensive lifestyle	113 (32.8)	–
Age (years)	17.9 ± 2.4	25.0 ± 2.4
Duration of diabetes (years)	4.8 ± 1.4	11.9 ± 1.5
BMI (kg/m^2)	36.7 ± 8.3	36.0 ± 8.6
HbA1c (%)	8.2 ± 2.8	9.5 ± 2.8
Fasting glucose (mg/dl)	159.5 ± 77.4	188.1 ± 83.7
C-peptide (ng/ml)	3.0 ± 1.8	2.5 ± 1.8
Blood pressure		
Systolic (mm Hg)	116.4 ± 11.5	122.5 ± 14.6
Diastolic (mm Hg)	70.3 ± 9.2	75.8 ± 10.7
Lipids		
HDL (mg/dl)	41.0 ± 10.0	45.2 ± 12.4
LDL (mg/dl)	93.7 ± 28.0	102.1 ± 34.0
Triglycerides (mg/dl)	152.8 ± 169.7	155.6 ± 155.5
Microvascular complications		
Kidney disease	75 (21.9)	153 (45.8)
Nerve disease	22 (6.4)	90 (26.5)

BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TODAY = Treatment Options for Type 2 Diabetes in Adolescents and Youth.
Data are n (%) or mean ± standard deviation.

vitreous detachment (PVD), epiretinal membrane, retinal traction and distortion, and macular hole. The methodology for grading of PVD was previously described by Duker et al.[8] A subset of 343 participants (659 eyes) had data available at both points in time for analyses of changes in morphology between OCT assessments.

Risk Factor Assessment

Age, sex, and race-ethnicity were self-reported in the study, the latter using United States census–based questions. Height, weight, blood pressure, and laboratory data were measured using a study-wide protocol.[9] The body mass index was calculated as kg/m^2. Fasting glycated hemoglobin (HbA1c), glucose, c-peptide, and lipids were measured centrally at the Northwest Lipids Research Lab (University of Washington, Seattle, WA) using a dedicated high-performance liquid chromatography method (TOSOH Biosciences Inc).[9]

Microvascular Complications

The assessment and prevalence rates of microvascular complications in the TODAY2 cohort have been described elsewhere.[6] Briefly, diabetic kidney disease was defined as a ratio of albumin to creatinine $>$ 30 mg/g on 2 out of 3 consecutive determinations based on annual urine collection. For the assessment of diabetic nerve disease, the Michigan Neuropathy Screening Instrument and monofilament examinations were performed annually. The Michigan Neuropathy Screening Instrument exam was considered abnormal if the score (across both feet) was $>$ 2 on $\geq$ 2 consecutive exams. The monofilament exam was considered abnormal if there were $<$ 8 of 10 correct responses on $\geq$ 2 consecutive exams.

Statistical Analyses

Participant characteristics at the study visit closest to the eye exam at TODAY and TODAY2 were examined and summarized in descriptive analyses. For analyses of change in retinal thickness between TODAY and TODAY2 scans, participant characteristics at the closest visit to the TODAY OCT scan were used. Due to the small sample size, analyses of morphology are considered descriptive, and *P* values are not presented.

Because measurements between TD-OCT and SD-OCT technologies cannot be used interchangeably, a previously published formula[10] allowed for conversion from TD-OCT to SD-OCT. Utilizing the conversion permitted an evaluation of change in center subfield retinal thickness in the 331 eyes of 186 participants who had TD-OCT scans in TODAY and had gradable OCT images at both assessments. A subset analysis was conducted including only measurements from participants who underwent SD-OCT at both time points (Table S2).

Data are displayed as mean (± standard deviation) for continuous variables or n (percent, %) for categorical variables. Crude mean differences in retinal thickness measurements between TODAY and TODAY2 were estimated. Linear regression with multiple TD-OCT or SD-OCT measures, or a mixture thereof, accounted for within-subject correlation using a random intercept for the participant. Retinal thickness change was assessed with linear mixed-effects models using the outcome of the TODAY2 measurement as a function of the TODAY measurement. Analysis of associations between retinal thickness change (TODAY2-TODAY measurement) and participant characteristics was performed using linear mixed-effects models adjusting for within-participant variation. All models were adjusted for age, race/ethnicity, sex, and TODAY treatment assignment. Estimates for age, sex, race/ethnicity, and treatment arm came from models adjusting for all other covariates. Results are presented as linear regression coefficients and corresponding *P* values. All analyses were performed using R, version 3.6.0, and SAS, version 9.4.

Results

Demographics

The 344 participants (661 eyes) with gradable OCT images at both time points had a mean age of 17.9 ± 2.4 years and a mean HbA1c of 8.2 ± 2.8% in the TODAY study. In TODAY2, these participants had a mean age of 25.0 ± 2.4 years and a mean HbA1c of 9.5 ± 2.8%. Approximately 65% of participants were female, and 81% were members of racial/ethnic minorities. Diabetic kidney disease was seen in 46% of participants, while 27% had diabetic nerve disease (Table 1). Participants included in this analysis with eye examinations at both TODAY and TODAY2 were slightly younger at TODAY baseline (13.8 ± 2.0 years vs.

Table 2. Mean Change in Retinal Thickness (Microns) from TODAY to TODAY2 by Layer (Eye Level)

Layers	Mean ± SD		Unadjusted			Adjusted	
	TODAY N = 612	*TODAY2 N = 612*	*Crude Mean Difference*	*Regression Coefficient**	P *Value**	*Adjusted Regression Coefficient**,†	P *Value**,†
Central subfield							
Total retinal thickness	220.5 ± 22.3	221.0 ± 22.6	0.46	0.54	0.18	−4.64	0.10
Inner retinal thickness	59.2 ± 15.5	62.6 ± 15.2	3.48	5.24	**<0.001**	−0.95	0.65
Outer retinal thickness	167.2 ± 11.5	158.4 ± 12.8	−8.83	−9.13	**<0.001**	−10.44	**<0.001**
Photoreceptor thickness	30.3 ± 2.9	29.8 ± 4.1	−0.47	−0.64	**0.003**	−1.18	**0.04**
Inner subfield							
Total retinal thickness	278.1 ± 18.1	282.3 ± 17.4	4.17	4.19	**<0.001**	−0.76	0.75
Inner retinal thickness	136.9 ± 11.5	137.4 ± 12.6	0.53	0.83	**0.05**	−4.49	**0.01**
Outer retinal thickness	150.5 ± 10.1	144.9 ± 10.5	−5.73	−5.93	**<0.001**	−6.14	**<0.001**
Photoreceptor thickness	27.8 ± 3.3	27.4 ± 4.5	−0.36	−0.54	**0.02**	−0.48	0.45

SD = standard deviation; TODAY = Treatment Options for Type 2 Diabetes in Adolescents and Youth.
Mean ± SD are presented from overall means.
*Regression coefficients and *P* values accounting for within-subject correlation.
†Adjusted for age, sex, race/ethnicity, and treatment group.

14.2 ± 2.0 years, $P = 0.006$) and had slightly lower fasting glucose levels (109.5 ± 24.1 mg/dl vs. 113.3 ± 27.6 mg/dl, $P = 0.03$) than participants enrolled in TODAY who were not included (Table S1).

Retinal Thickness Analysis

There was an overall mean change in retinal thickness from TODAY to TODAY2 in individual layers, which persisted after adjusting for age, sex, race/ethnicity, and treatment group. Specifically, in the central subfield, the outer retinal thickness decreased from 167.2 ± 11.5 microns to 158.4 ± 12.8 microns ($P < 0.001$) and photoreceptor thickness decreased from 30.3 ± 2.9 microns to 29.8 ± 4.1 microns ($P = 0.04$), while in the inner subfield, there was a similar outer retinal thickness decrease from 150.5 ± 10.1 microns to 144.9 ± 10.5 microns ($P < 0.001$) as well as an increase of the inner retinal thickness from 136.9 ± 11.5 microns to 137.4 ± 12.6 microns ($P = 0.01$) (Table 2).

Multivariate linear regression analysis of thickness changes by specific risk factors at the time of the TODAY eye examination showed that for the central subfield, HbA1c was positively associated with an increase in total retinal thickness ($r = 0.67$, $P < 001$), while fasting glucose was positively correlated with inner retinal thickness increase ($r = 0.02$, $P = 0.02$). In the inner subfield, we found negative correlations between both systolic ($r = -0.22$, $P < 0.001$) and diastolic ($r = -0.22$, $P = 0.003$) blood pressures and total retinal thickness (Table 3). Additional multivariate linear regression analyses of thickness changes among only those eyes with SD-OCT at both time points (n = 283) also showed a positive association between HbA1C ($r = 0.90$, $P < 001$) and total retinal thickness change in the central subfield. No significant correlations were seen between participant characteristics and total retinal thickness change in the inner subfield (Table S2).

Macular Morphology Analysis

There was an increase in abnormal macular morphology between TODAY and TODAY2 (Figure 2). In particular, during the 7-year longitudinal follow-up, there was worsening of 27 eyes (4.1%) with cystoid changes and 118 eyes (17.9%) with PVD. At the time of the second assessment, the most common abnormal morphological changes in this cohort of youth with T2D were PVD (18.9%) and cystoid spaces (4.2%) (Table 4).

Discussion

We investigated longitudinal OCT changes that occurred over 7 years in youth with T2D enrolled in the TODAY and TODAY2 studies and found selected increases in retinal thickness correlating with HbA1c and fasting glucose levels, as well as an increased prevalence of abnormal vitreomacular features. OCT scans were available for almost 70% of the TODAY participants, with 84.4% of these having follow-up imaging 7 years later during TODAY2.

After adjusting for age, sex, race/ethnicity, and treatment group, we found a statistically significant decrease in the thickness of the outer retina (OPL to RPE) in both the central subfield and the inner subfield between the 2 assessments. Similar to the outer retinal thinning, we also found an overall decrease in the photoreceptor layer (EZ to RPE) in the central subfield over time. In addition to the increase in T2D duration, our study cohort also exhibited persistent body mass index elevations (higher than the 95th percentile at both assessments), reflecting a clinical profile with multiple comorbidities that affect the integrity and health of the retina. Outer retinal thinning has been described in other studies of people with T2D with hyperglycemia, dyslipidemia, and impaired sleep.[11]

Prior studies have also shown a decrease in the thickness of various retinal layers in T2D, representing

Table 3. Change in Total Retinal Thickness (Microns) by Patient Characteristics for the Central Subfield and Inner Subfield (Eye Level)

Patient Characteristics	TODAY2-TODAY Total Retinal Thickness (Regression Coefficient)*	*P* Value*	TODAY2-TODAY Inner Retinal Thickness*	*P* Value*	TODAY2-TODAY Outer Retinal Thickness*	*P* Value*	TODAY2-TODAY Photoreceptor Thickness*	*P* Value*
Patient characteristics								
Central subfield								
Gender								
Female	ref	.	ref		ref		Ref	
Male	−0.168	0.888	0.251	0.865	0.039	0.981	−1.102	0.134
Race/ethnicity								
Non-Hispanic White	ref		ref		ref		Ref	
Non-Hispanic Black	−0.069	0.965	−0.317	0.866	−2.332	0.261	−0.563	0.544
Hispanic	0.210	0.894	−0.713	0.729	−1.531	0.501	1.574	0.124
Other	−3.186	0.191	−0.166	0.947	−3.252	0.236	1.403	0.253
TODAY treatment arm								
Metformin	ref		ref		ref		Ref	
Metformin + rosiglitazone	−0.828	0.542	−0.881	0.603	1.766	0.345	−0.719	0.391
Metformin + intensive lifestyle	0.386	0.772	−1.718	0.316	3.128	0.099	−0.255	0.763
BMI (kg/m^2)	−0.086	0.204	−0.003	0.970	−0.089	0.331	0.049	0.239
HbA1c (%)	0.671	**0.001**	0.486	0.057	0.415	0.139	−0.078	0.540
Fasting glucose (mg/dl)	0.009	0.240	0.022	**0.015**	0.0009	0.925	−0.006	0.151
Blood pressure								
Systolic (mm Hg)	−0.092	0.074	−0.022	0.747	−0.0005	0.995	0.022	0.498
Diastolic (mm Hg)	−0.086	0.167	0.0007	0.992	−0.046	0.587	−0.007	0.849
Lipids								
HDL (mg/dl)	−0.043	0.444	−0.043	0.547	0.040	0.604	−0.026	0.459
LDL (mg/dl)	0.029	0.115	0.023	0.405	0.006	0.844	0.016	0.229
Triglycerides (mg/dl)	0.006	0.092	0.005	0.416	0.004	0.595	0.001	0.695
Microvascular complications								
Neuropathy	1.861	0.421	0.762	0.807	1.594	0.642	−0.164	0.915
Nephropathy	0.839	0.548	−0.747	0.673	3.118	0.108	0.644	0.462
Duration of diabetes (years)	0.080	0.864	0.758	0.199	−0.696	0.285	0.049	0.867
Inner subfield								
Gender								
Female	ref		ref		ref		Ref	
Male	0.700	0.624	0.227	0.878	1.015	0.487	−0.955	0.212
Race/ethnicity								
Non-Hispanic White	ref		ref		ref		Ref	
Non-Hispanic Black	0.663	0.729	−1.998	0.289	−0.255	0.890	−0.870	0.369
Hispanic	3.147	0.096	−0.099	0.962	0.553	0.785	2.031	0.057
Other	−3.937	0.180	−1.800	0.471	0.406	0.868	1.044	0.414
TODAY treatment arm								
Metformin	ref		ref		ref		Ref	
Metformin + rosiglitazone	−1.547	0.343	−1.389	0.413	1.343	0.421	−0.552	0.528
Metformin + intensive lifestyle	0.993	0.535	−1.694	0.325	2.667	0.115	−0.421	0.633
BMI (kg/m^2)	−0.041	0.615	0.029	0.737	−0.100	0.226	0.077	0.078
HbA1c (%)	0.256	0.312	0.085	0.742	0.302	0.223	−0.131	0.325
Fasting glucose (mg/dl)	−0.010	0.279	0.005	0.602	0.0003	0.971	−0.006	0.199
Blood pressure								
Systolic (mm Hg)	−0.218	**<0.001**	−0.009	0.890	−0.092	0.160	0.019	0.570
Diastolic (mm Hg)	−0.219	**0.003**	−0.024	0.760	−0.117	0.122	0.009	0.821
Lipids								
HDL (mg/dl)	−0.093	0.176	−0.068	0.334	0.045	0.514	−0.050	0.161
LDL (mg/dl)	0.009	0.703	0.004	0.893	0.004	0.892	0.013	0.345
Triglycerides (mg/dl)	0.006	0.148	−0.001	0.870	0.004	0.482	0.001	0.694
Microvascular complications								
Neuropathy	1.497	0.590	0.688	0.826	2.831	0.355	−0.062	0.969
Nephropathy	1.303	0.436	−0.254	0.886	2.654	0.126	0.509	0.577
Duration of diabetes (years)	0.545	0.329	0.729	0.219	−0.592	0.309	−0.046	0.879

BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TODAY = Treatment Options for Type 2 Diabetes in Adolescents and Youth.
*Regression coefficients and *P* values accounting for within-subject correlation.

neurodegeneration that is believed to be a precursor to DR vascular changes. Biallosterski et al[12] demonstrated decreases in pericentral macular thickness in patients with mild NPDR, while others have shown a reduction in the inner retinal thickness in the macula in individuals with diabetes with mild DR which suggests that this might be due to ganglion cell loss and thinning of the retinal nerve fiber layer.[3,13] Middle retinal thinning (at the level of the

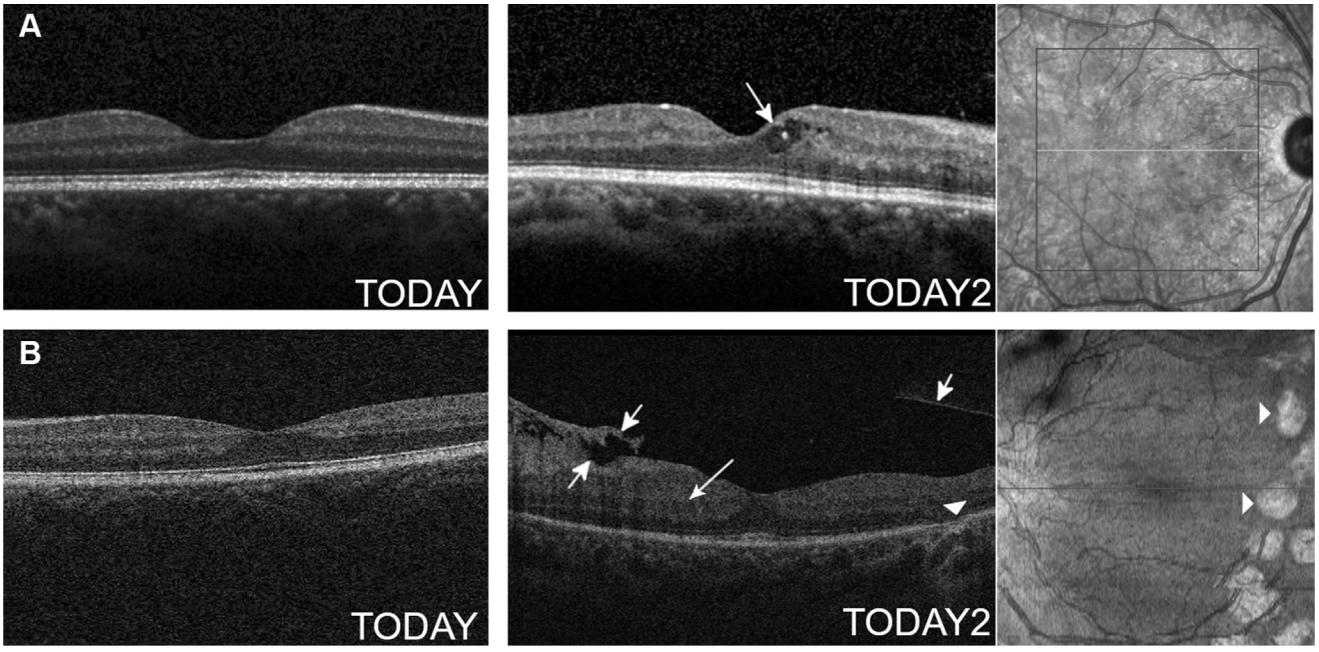

Figure 2. Representative OCTs showing thickness and morphological changes from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study baseline to TODAY2 follow-up. Case **A** (top) showed presence of cysts (arrow) in the TODAY2 visit, while the baseline in TODAY showed normal OCT. The diabetic retinopathy severity score (DRSS) level from the fundus photograph corresponding to the TODAY2 visit of case A was mild proliferative diabetic retinopathy (PDR) (61B). Case **B** (bottom) showed retinal thickening, posterior vitreous detachment (PVD) and epiretinal membrane (ERM) with retinal traction and distortion (RTD) (arrows), as well as photocoagulation scars (arrowheads) temporally while the baseline OCT was normal. The DRSS level from the fundus photograph corresponding to the TODAY2 visit of Case B was high-risk PDR (71C).

inner nuclear layer [INL]) has also been described and may be the first layer to show thinning in individuals with hypertension[14] and diabetes.[15] It is important to note that prior studies that have ascertained inner retinal thinning have primarily evaluated adult participants, whereas our study is analyzing a younger age group with T2D and preserved neural retinas. In this population, we did not find changes associated with inner retinal layer thinning that would suggest retinal neurodegeneration at this point in their T2D course.

On the contrary, we found an increase in inner retinal (ILM to OPL) thickness in the inner subfield over time, which was also seen in linear regression analysis of thickness changes by specific risk factors. Specifically, HbA1c increases were associated with increased total retinal (ILM to RPE) thickness in the center subfield, while higher levels of fasting glucose were associated with increased inner retinal thickness. These findings suggest that the level of glycemic control is an important predictor of change in retinal thickness over time. To prevent confounding effects of edema on retina layer thickness, we excluded scans with thickness outside the normal range, as well as those with intraretinal cystoid spaces or subretinal fluid. This confined the analysis to true retinal layer changes showing hypertrophy or degeneration.

Hypertrophy of retinal layers has been documented in the setting of elevated blood sugars in T2D and may precede more chronic thinning changes. Studies have shown that inner

Table 4. Prevalence of Abnormal Morphology in TODAY and TODAY2 in Eyes with TODAY and TODAY2 Data (Eye Level)

Morphology	TODAY N = 659	TODAY2 N = 659	Change from TODAY to TODAY2		
			No Change	*Improved*	*Worsened*
Morphology					
Serous sensory retinal detachment (SSRD)	0 (0.0)	3 (0.5)	565 (99.5)	0 (0.0)	3 (0.5)
Cystoid spaces	15 (2.3)	28 (4.2)	618 (93.8)	14 (2.1)	27 (4.1)
Epiretinal membrane (ERM)	1 (0.2)	7 (1.1)	651 (98.8)	1 (0.2)	7 (1.1)
Retinal traction detachment (RTD)	1 (0.2)	7 (1.1)	651 (98.8)	1 (0.2)	7 (1.1)
Posterior vitreous detachment (PVD)	21 (3.2)	125 (18.9)	527 (80.0)	14 (2.1)	118 (17.9)

TODAY = Treatment Options for Type 2 Diabetes in Adolescents and Youth.
Data are n (%).

retinal thickening is seen in participants with diabetes (even in the absence of DR) compared to healthy controls, particularly at the level of the INL.[4] This is believed to be due the hypertrophy of Müller cells, whose nuclei form in the INL and increase in number in response to hyperglycemia.[16]

In individuals both with and without impaired fasting glucose, systemic hypertension has been shown to be inversely associated with macular thickness in > 1 macular subfield.[17] Elevations in blood sugar and blood pressure can synergistically impact retinal health by causing small vessel dysfunction.[18] Our study confirms a negative correlation between both systolic and diastolic blood pressure levels and total retinal thickness in the inner subfield, a finding that underlines the importance of controlling blood pressure to prevent alterations in retinal anatomy.

There was an increase in abnormal macular morphological features between TODAY and TODAY2. The most notable change occurred in the prevalence of PVD, which increased from 3.4% at baseline to 18.9% at the time of the second assessment (average age = 25 years). By contrast, PVD rates in the general population are < 10% in people under the age of 50 years and reach 27% in adults aged 60−69 years.[19] The dramatic increase in prevalence of PVD in this study group suggests that abnormal vitreoretinal interface changes occur prematurely in youth with T2D, altering the intraocular ecosystem and potentially predisposing to visual complications over time.

The second most prevalent morphologic finding was the presence of cystoid spaces (4.2%), followed by subretinal fluid (0.5%). After an average of 12 years of T2D, 4.2% of participants developed intraretinal cysts at the macula, which can be a source of visual impairment and add to the list of comorbidities in this at-risk population. Data regarding the prevalence of diabetic macular edema from US-based population studies are scarce; values range from 2.7% to 3.8% and are higher in non-Hispanic Black individuals than those in non-Hispanic Whites.[20,21] Results from our study cohort of primarily minority youth are overall consistent with the higher range of these figures.

The changes in retinal thickness correlating with HbA1c and fasting glucose levels as well as the increased prevalence of abnormal vitreomacular features between the 2 assessments mirror the trend of DR progression seen in the study cohort.[22] Specifically, using graded color fundus photography, Gubitosi-Klug et al reported a 3-step progression of DR in 8.5% of study participants in TODAY2 and a significant increase in ocular complications over the 7-year follow-up. While the original TODAY cohort (mean age = 18 years, diabetes duration = 5 years) had a DR prevalence of 13.7% with at most mild NPDR, after 7 years, 51% of participants were noted to have DR, graded as very mild or mild NPDR (39%), moderate to severe NPDR (8.8%), and proliferative DR (3.8%).[19] A similar trend was also seen with nonocular microvascular complications such as diabetic kidney and nerve disease.[6]

Strengths and Limitations

This study benefitted from the longitudinal design, the use of masked graders, and the comprehensive analysis of risk factors affecting retinal thickness and morphology. Given the unique demographics of the trial (two-thirds of participants were female, and approximately 80% were members of racial/ethnic minorities), slight measurement variations from standard normative OCT values could have occurred. Nonetheless, our thickness analyses accounted for this study-specific demographic distribution, and results reflected the adjustment for multiple variables, including sex and race/ethnicity. Some of the differences in thickness (such as those for inner retinal thickness) are small but statistically significant due to the low variability in measurements. However, since statistically significant differences may not always be clinically relevant, it is important that future studies explore the clinical implications of such small differences. Additionally, our segmentation and grading protocols did not specifically measure INL thickness, so we were unable to track changes in this individual middle retinal layer which has been reported to be the first one to show thinning in patients with hypertension and diabetes.[14,15]

Lastly, because the study protocol did not include measurements of visual acuity at any point in time, we could not obtain correlations of vision with OCT changes or levels of DR. Future studies will benefit from measuring visual acuity in addition to providing objective assessments of visual function to shed more light on the visual impact of the structural abnormalities seen on OCT.

Conclusion

Youth with T2D are at an increased risk of early retinal complications, many of which can be seen on OCT. The changes in retinal thickness correlating with HbA1c, fasting glucose and blood pressure levels, and the increased prevalence of abnormal vitreomacular features place this unique patient population of primarily minority youth at an increased risk of vision loss. Appropriate management of systemic risk factors is essential to prevent the progression of these anatomic changes over time and the development of visual impairment in adulthood.

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A complete list of individuals in the TODAY Study Group is presented in the Online Supplemental Materials.

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Footnotes and Disclosures

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No animal subjects were used in this study.

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Abbreviations and Acronyms:
DR = diabetic retinopathy; **EZ** = ellipsoid zone; **HbA1c** = glycated hemoglobin; **ILM** = internal limiting membrane; **INL** = inner nuclear layer; **NPDR** = nonproliferative DR; **OPL** = outer plexiform layer; **PVD** = posterior vitreous detachment; **RPE** = retinal pigment epithelium; **SD-OCT** = spectral-domain OCT; **TD-OCT** = time-domain OCT; **TODAY** = Treatment Options for Type 2 Diabetes in Adolescents and Youth; **T2D** = type 2 diabetes.

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