OPTICAL COHERENCE TOMOGRAPHY CHARACTERISTICS OF MACULAR EDEMA AND HARD EXUDATES AND THEIR ASSOCIATION WITH LIPID SERUM LEVELS IN TYPE 2 DIABETES

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Purpose: To determine whether hyperreflective foci (HF) and macular thickness on spectral domain ocular coherence tomography are associated with lipid levels in patients with Type 2 diabetes.

Methods: Two hundred and thirty-eight participants from four sites had fundus photographs and spectral domain ocular coherence tomography images graded for hard exudates and HF, respectively. Regression models were used to determine the association between serum lipid levels and 1) presence of HF and hard exudates and 2) central subfield macular thickness, central subfield macular volume, and total macular volume.

Results: All patients with hard exudates on fundus photographs had corresponding HF on spectral domain ocular coherence tomography, but 57% of patients with HF on optical coherence tomography did not have hard exudates detected in their fundus photographs. Presence of HF was associated with higher total cholesterol (odds ratio = 1.13, 95% confidence interval = 1.01–1.27, $P = 0.03$) and higher low-density lipoprotein levels (odds ratio = 1.17, 95% confidence interval = 1.02–1.35, $P = 0.02$) in models adjusting for other risk factors. The total macular volume was also associated with higher total cholesterol ($P = 0.009$) and triglyceride ($P = 0.02$) levels after adjusting for other risk factors.

Conclusion: Higher total and low-density lipoprotein cholesterol were associated with presence of HF on spectral domain ocular coherence tomography. Total macular volume was associated with higher total cholesterol and triglyceride levels.

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Retinal hard exudates are seen often in eyes with diabetic retinopathy. The hard exudates are composed of lipid and proteinaceous material, such as fibrinogen and albumin that leak from the impaired blood–retinal barrier. They are deposited primarily in the outer plexiform layer of the retina.[1–3] With optical coherence tomography (OCT), hard exudates are observed as hyperreflective foci (HF).[1] In some cases, these HF may be seen without any corresponding hard exudate on fundoscopic examination. Comparison with histology suggests that these foci may represent subclinical features of lipoprotein extravasation after breakdown of the inner blood–retinal barrier in the initial stages of intraretinal hard exudate development.[4] Ota et al[5] demonstrated subretinal HF on spectral domain ocular coherence tomography (SD-OCT) in patients with diabetic macular edema (DME) may be associated with the future subfoveal deposition of hard exudates. Spectral domain ocular coherence tomography may provide an imaging technique to detect these early manifestations of diabetic retinopathy and macular edema and to elucidate the pathophysiology of extravasation and formation of retinal edema and hard exudates.

Data from the Early Treatment of Diabetic Retinopathy Study (ETDRS) and other studies have demonstrated that elevated serum lipid levels are associated with an increased risk of hard exudate in eyes with diabetic retinopathy. Furthermore, increasing amounts

of exudate seem to be associated independently with an increased risk of visual impairment.[6] This indicates a correlation between serum lipid levels and the development of hard exudates and intraretinal damage.[4] Previous studies have evaluated the association the hard exudates and lipid serum levels based on fundus photograph detection of exudates.[6–9]

The purpose of this study was to investigate whether higher serum lipid levels were associated with presence of HF on SD-OCT and macular thickness parameters. We also characterized these HF, which can represent either subclinical hard exudates or clinically apparent hard exudates, with regard to retinal layer location and correlation with presence of hard exudates on fundus photographs.

Materials and Methods

Participants

The African American Proliferative Diabetic Retinopathy (AAPDR) study is a multicenter, case–control study.[10] From 2011 to 2013, American African patients with Type 2 diabetes (T2D) were recruited from four sites: the University of Mississippi Medical Center (UMMC), Massachusetts Eye and Ear Infirmary (MEEI), Boston Medical Center (BMC), and Harvard Vanguard Medical Associates (HVMA) and their clinical characteristics have been previously described.[10] This research adhered to the tenets of the Declaration of Helsinki and was approved by institutional review boards of the UMMC, BMC, and MEEI.

Inclusion criteria for the study were 1) self-identified African American race and 2) diagnosis of T2D by American Diabetes Association criteria[11] and onset of diabetes at greater than or equal to 30 years old. All patients with fundus photographs and OCTs of sufficient quality for hard exudate and HF evaluation were included in the analysis. Patients with evidence of traction retinal detachment, epiretinal membrane, preretinal or subretinal hemorrhage, vitreomacular traction, and atrophic scarring in the macula were excluded.

Assessment of Hard Exudate and Hyperreflective Foci in Fundus Photographs and OCT

Dilated, digital seven-standard field fundus photography of both eyes, including a pair of stereoscopic photographs of each macula, was obtained using a Topcon TRC 50 DX camera (Topcon, Tokyo, Japan). The photographs were graded for presence of hard exudates and degree of diabetic retinopathy by two independent, masked ophthalmologist-investigators using the ETDRS adaptation of the modified Airlie House classification as previously described.[10] Any disagreements were arbitrated by a third ophthalmologist-investigator.

Optical coherence tomography imaging was performed with Spectralis SD-OCT (Heidelberg, Carlsbad, CA). Fovea-centered images were acquired (25 lines within a 20° horizontal scan and 25 lines within a 20° vertical scan). Every horizontal and vertical OCT line scan was assessed for the presence of HF due to hard exudate by a single ophthalmologist-investigator. For cases where the investigator was uncertain of the presence of HF, a decision was reached after review of the images with a second–ophthalmologist investigator. There were no minimum or maximum size criteria for the foci. Because HF can be due to presence of entities other than hard exudates, each OCT image with a hyperreflective focus was overlaid on the corresponding red-free image and a corresponding high-quality fundus photograph was placed next to the overlay to rule out other causes of hyperreflectivity (Figure 1).[4,12,13] More specifically, when a hyperreflective focus was identified on an OCT line scan, it was overlaid on the red-free image that is available for tracking on the Heidelberg Spectralis device using the device's software. At the same time, the investigator looked at a high-quality fundus photograph that was placed on the adjacent computer monitor. The region of interest was visually inspected on the red-free and color photograph for other pathologies. Vessels could be easily seen and excluded on the red-free images. For other pathologies, anatomical landmarks (primarily the retinal vessels) were used to identify the area of interest on the color photograph and inspect it for corresponding vessels, hemorrhages,

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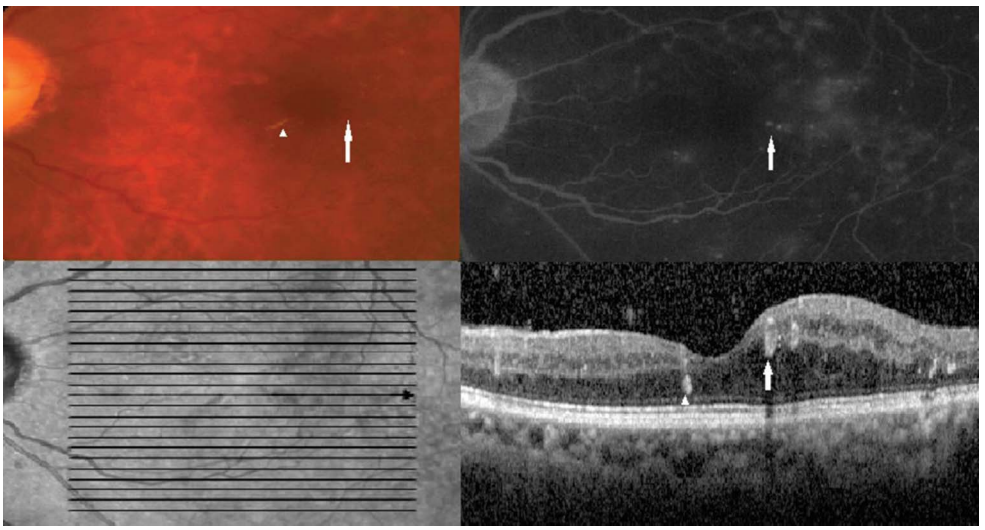

Fig. 1. Top left: color fundus photograph showing a microaneurysm (white arrow) and hard exudates (white arrowhead) (top left). Top right: late-phase fluorescein angiography shows leakage from the microaneurysm (white arrow). Bottom left: an infrared image shows the horizontal OCT section through which the image in the bottom panel was obtained (bold black arrow). Bottom right: OCT image through the indicated section in the infrared image shows a hyperreflective focus that corresponds to the hard exudates on fundus photography (white arrowhead) and a ring-shaped hyperreflective region (white arrow) that corresponds to the microaneurysm.

cotton–wool spots, microaneurysms, nerve fiber layer demyelination, or fibrovascular tissue. If any of these were found to account for the HF, these foci were excluded from the analyses. If there was shadowing behind a hyperreflective focus, we looked particularly carefully for corresponding hemorrhage or blood vessels on the red-free and color fundus photographs. If we did not find hemorrhage or vessels, we included that focus in the analysis. If the hyperreflective focus was a complete or incomplete ring or if the hyperreflective focus was adjacent to a cyst, it was excluded from further analyses as these are characteristics have been associated with microaneurysms.[13] For the HF that were included in the analyses, the retinal layer in which they were located was recorded. The assessment of HF was performed for research purposes only; the detection of HF was not communicated to the patients' treating retina specialists and thus did not influence their management.

To determine intraobserver reliability of HF grading, 50 randomly sampled images were regraded for total HF by the same reader 3 months after the initial grading. The kappa test for intraobserver agreement for HF detection was 0.975 indicating the method to be highly reproducible.

Assessment of Macular Thickness and Volumes

Spectral domain ocular coherence tomography images were evaluated for central subfield macular thickness (CSMT), central subfield macular volume (CSMV), and total macular volume (TMV). The presumed foveal center was determined as the area lacking inner retinal layers in the macular region. A horizontal foveal scan image was used to record these three measurements: CSMT and CSMV within the central 1 mm-diameter circle surrounding the fovea and TMV within the central 6 mm-diameter circle surrounding the fovea.

Covariate Data

The covariates examined in this study were age, sex, site of recruitment, duration of diabetes, hemoglobin A_{1c} (HbA_{1c}), systolic blood pressure, ETDRS diabetic retinopathy grade, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, use of lipid-lowering medication, and use of antihypertensive medication. Duration of diabetes was verified by review of the medical record. For each participant, a blood sample was sent for HbA_{1c} measurement at a centralized laboratory. One set of fasting lipid levels (total, LDL, and HDL cholesterol and triglycerides) closest to the study visit but within one year of the study visit was recorded from the medical record.

Statistical Analyses

For the statistical analyses, only one eye from each patient was used. If only one eye of a patient had HF, that eye was included in the analyses. If both eyes had HF, the eye with greater macular thickness was included. For the statistical analyses, duration of diabetes, HbA_{1c}, mean systolic blood pressure, ETDRS grade, serum fasting total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, CSMT, CSMV, and TMV were evaluated as continuous variables for maximal power. Presence of hard exudates and HF were evaluated as dichotomous variables. In addition to determining the associations between serum lipids and macular thickness and HF, we also

compared the presence of hard exudates on fundus photographs with the presence of HF on SD-OCT.

For all analyses, we used the subset of participants with complete information for the covariate of interest in that particular analysis to maximize the generalizability and power of the analysis.

For the univariate analyses examining presence of HF as an outcome, we performed the independent sample *t*-test for continuous variables and the chi-square test for dichotomous variables. For the univariate analyses examining CSMT, CSMV, and TMV as outcomes, we performed univariate analyses with Pearson correlation coefficient test for continuous variables. The full models for each outcome (presence of HF, CSMT, CSMV, and TMV) were built with logistic or linear regression. All regression models included age, sex, and recruitment site as well as any covariates that were significantly associated with the outcome in the univariate analyses. All analyses were performed using Stata/IC 12.1 (College Station, TX). A P value < 0.05 was considered statistically significant.

Results

Two hundred and thirty-eight patients with OCTs and fundus photographs were included in the analyses. Of total, 31.1% had hard exudates in at least 1 eye, whereas 70% had HF on OCT in at least 1 eye. All the patients with hard exudates on fundus photographs had HF on OCT, but 57% of patients with HF on OCT did not have hard exudates, or any other pathology, detected in the corresponding area on their fundus photographs. Table 1 summarizes the clinical characteristics of patients with and without HF. Participants with HF had a longer duration of diabetes, higher mean HbA_{1c}, higher mean systolic blood pressure, and higher mean ETDRS grade. The HF were identified in every retinal layer in at least some patients (Table 2). The outer plexiform layer was the most common layer to have HF. Thirty percent of patients with HF also had center-involving DME defined as a CSMT >305 μm in women and >320 μm in men.[14] The remainder of the patients had HF in the absence of macular edema.

Table 3 shows the results of the univariate and multivariate analyses examining the association between serum lipids levels and presence of HF. In the univariate analyses, presence of HF was associated with higher total cholesterol levels [(odds ratio (OR) = 1.08, 95% confidence interval (CI) = 1.01–1.15, P = 0.02]. In the multivariate model, after controlling for other retinopathy risk factors, higher total cholesterol was still significantly associated with HF (OR = 1.13, 95% CI = 1.01–1.27, P = 0.03). Higher LDL was also associated with presence of HF in the univariate analysis (OR = 1.10, 95% CI = 1.01–1.19, P = 0.02) and the association was significant after adjusting for other risk factors (OR = 1.17, 95% CI = 1.02–1.35, P = 0.02). Neither HDL cholesterol nor triglycerides were associated with presence of HF.

We performed the univariate and multivariate analyses examining the association between serum lipids levels and presence of hard exudates on fundus photography in the same 238 patients. In the univariate analyses, presence of hard exudates was associated with higher total cholesterol levels (OR = 1.07, 95% CI = 1.01–1.13, P = 0.009). In the multivariate model, after controlling for other retinopathy risk factors, higher total cholesterol was still significantly associated with presence of exudates (OR = 1.07, 95% CI = 1.003–1.14,

Table 1. Clinical Characteristics of Participants With and Without HF

Variables	HF Present		No HF Present		
	N	% or Mean ± SD	N	% or Mean ± SD	P*
Age, years	167	60.5 ± 11.6	71	62 ± 9.6	0.37
Sex (male %)	167	38.3	71	40.8	0.77
Duration of diabetes (year)	167	21 ± 10.2	71	17.6 ± 9.2	0.01
Hemoglobin A1C (%)	166	8.5 ± 2	71	7.9 ± 1.8	0.03
Systolic blood pressure (mmHg)	167	149.7 ± 22.9	71	140.6 ± 21.8	0.005
Lipid-lowering medication (% taking)	167	59.5	71	72.8	0.055
Antihypertensive medication (% taking)	167	90.1	71	91.4	1.0
Total cholesterol (mg/dL)	166	182.5 ± 52	71	165.4 ± 37	0.018
Low-density cholesterol (mg/dL)	162	105.2 ± 46.7	70	90.3 ± 29.7	0.014
High-density cholesterol (mg/dL)	165	51.3 ± 18.4	70	49.2 ± 17.3	0.41
Triglyceride (mg/dL)	162	134 ± 82	70	133.4 ± 68.5	0.95
ETDRS grade (% in each category)	164		71		1×10^{-6}
<15		3.1		60.5	
15–60		4.3		15.5	
>60		92.6		24	

*Categorical variables compared using the chi-square test, and continuous variables compared with the *t*-test.

Table 2. Retinal Layer Distribution of HF

Retinal Layer	Percent of Patients With HF in This Layer
NFL	29
GCL	37.1
IPL	52.5
INL	85
OPL	92.7
ONL	84.6
ELM	53.3
EL	26.3
Subretinal	7.3

NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; ELM, external limiting membrane; EL, ellipsoid layer.

$P = 0.04$). Higher LDL was also associated with presence of hard exudates in the univariate analysis (OR = 1.10, 95% CI = 1.03–1.18, $P = 0.003$) and the association was significant after adjusting for other risk factors (OR = 1.09, 95% CI = 1.01–1.19, $P = 0.02$). Neither HDL cholesterol nor triglycerides were associated with presence of retinal hard exudates.

In the analyses of lipid serum levels and CSMT, CSMV, and TMV, we found a significant correlation between TMV and higher total cholesterol and triglyceride levels. Table 4 shows the results of the univariate and multivariate analyses examining the association between serum lipids levels and TMV. In the univariate analyses, higher TMV was associated with higher total cholesterol levels (Pwcorr = 0.2, $P = 0.006$). In the multivariate model, after controlling for other retinopathy risk factors, higher total cholesterol was still significantly associated with higher TMV (Coef = 0.004, 95% CI = 0.001–0.007, $P = 0.009$). Higher LDL and triglyceride levels were also associated with higher TMV in the univariate analyses (Pwcorr = 0.16, $P = 0.03$ and Pwcorr = 0.17, $P = 0.02$, respectively). In the multivariate model, after controlling for other retinopathy risk factors, higher triglyceride levels were still significantly associated with higher TMV (Coef = 0.002, 95% CI = 0.0002–0.003, $P = 0.02$). The association was no longer significant for higher LDL when adjusting for other risk factors (Coef = 0.003, 95% CI = –0.0003 to 0.007, $P = 0.07$). High-density lipoprotein cholesterol was not associated with higher TMV.

Discussion

This investigation has found that higher total and LDL cholesterol levels were associated with presence of HF on SD-OCT after adjusting for other diabetic retinopathy risk factors and for the degree of diabetic retinopathy. We found similar associations between lipid serum levels and presence of hard exudates on fundus photographs in these same patients.

Previous studies have suggested that distinct HF associated with DME represent subclinical initial steps in the development of intraretinal hard exudates, including subclinical lipid deposits, lipid-laden macrophages, or proteinaceous material.[4,5,15] Our study provides additional evidence to support this hypothesis, both in the presence and absence of DME. However, for the instances, where there is no corresponding pathology on fundus photographs, we cannot prove that these foci are indeed subclinical hard exudates based on the cross-sectional data set in this study. Longitudinal studies that follow these subclinical HF to determine whether they evolve into clinically evident hard exudates are required.

This is the first study to determine the correlation between serum lipid levels and HF. All the studies performed in the past to assess the association between hard exudates and lipid levels have been performed based on the quantitative or qualitative grading of hard exudates visible on examination or fundus photographs.[6–9,16–22] Several studies, including the Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR), have found associations between higher total or/and LDL cholesterol levels and hard exudate presence in fundus photographs similar to what we find in this study.[6,7,9,16–21] However, there have been other studies that have not found an association between hard exudates and total[7,16,21] and LDL[20,21] cholesterol. We found that 57% of patients with T2D with HF on SD-OCT had no hard exudates on fundus

Table 3. Association Between Serum Lipid Levels and HF

	Univariate		Multivariate*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Total cholesterol (per 10 mg/dL)	1.08 (1.01–1.15)	0.02	1.13 (1.01–1.27)	0.03
Low-density cholesterol (per 10 mg/dL)	1.10 (1.01–1.19)	0.02	1.17 (1.02–1.35)	0.02
High-density cholesterol (per 10 mg/dL)	1.07 (0.90–1.26)	0.41	1.03 (0.80–1.32)	0.79
Triglyceride (per 10 mg/dL)	1.00 (0.96–1.03)	0.95	1.009 (0.95–1.06)	0.73

*Adjusted for age, sex, diabetes duration, hemoglobin A1C, diabetic retinopathy grade, systolic blood pressure, and site.

Table 4. Correlation of Serum Lipid Levels and TMV

	Univariate		Multivariate*	
	Pwcorr	*P*	Coef (95% CI)	*P*
Total cholesterol (per 1 mg/dL)	0.20	0.006	0.004 (0.001 to 0.007)	0.009
Low-density cholesterol (per 1 mg/dL)	0.16	0.03	0.003 (–0.0003 to 0.007)	0.07
High-density cholesterol (per 1 mg/dL)	0.04	0.58	0.001 (–0.0058 to 0.0086)	0.70
Triglyceride (per 1 mg/dL)	0.17	0.02	0.002 (0.0002 to 0.0034)	0.02

*Adjusted for age, sex, diabetes duration, hemoglobin A1C, diabetic retinopathy grade, systolic blood pressure, and site.
Pwcorr, Pearson correlation coefficient; Coef, linear regression coefficient.

photographs. This suggests that some patients in previous studies who did not have hard exudates on fundus photography could have had early exudates detectable as HF on SD-OCT. Spectral domain ocular coherence tomography HF, which can be less than 25 to 30 μm in diameter, seem to be a more sensitive measure of cholesterol deposition in the retina. Results between studies examining the influence of systemic metabolic risk factors on retinal exudate deposition may be more consistent when these foci are examined as the outcome instead of clinically apparent hard exudates.

The clinical impact of these HF remains to be determined. One previous study in 19 patients suggested that these HF may be predictive of future deposition of ophthalmoscopically visible hard exudates.[5] Two other studies, one in 51 patients and the other in 24 patients, found that these HF change in distribution and diminish in amount after intravitreal anti–vascular endothelial growth factor therapy.[23,24] Another study found no relationship between visual acuity and HF consistent with hard exudate in patients with different stages of diabetic retinopathy.[25] Larger longitudinal studies are needed to determine whether control of serum lipid levels and other clinical interventions can lead to a decrease in the number of HF and subsequent hard exudate deposition on fundus examination. Such longitudinal studies are also needed to determine whether these HF are a clinically relevant, early marker of diabetic retinopathy that can be used as an endpoint in research studies.

In addition to the association between serum lipid levels and presence of HF, we also found that higher total cholesterol was associated with higher TMV in T2D. Although there have been several studies that have examined the association between serum lipids and DME as graded on fundus photographs,[6,7,20,26,27] there have been very few studies using the more sensitive and clinically used parameter of SD-OCT macular thickness. Benarous et al[26] found no associations between serum lipids and CSMT or CSMV as measured using time domain OCT in 321 patients with various stages of diabetic retinopathy, although they found a significant association with funduscopically assessed clinically significant macular edema. Sasaki et al[28] showed higher LDL cholesterol levels were associated with increased CSMT and CSMV in 74 patients with diabetes without DME. Like Benarous et al, we did not find any association between lipid levels and CSMT or CSMV, the two most commonly used measures of macular thickness in clinical studies of DME. Central subfield macular thickness and CSMV are most clinically significant for visual acuity outcomes because they capture thickening in the central 1 mm of the macula. However, microvascular damage in diabetic retinopathy and DME can often begin outside the central 1 mm of the macula. We chose to examine TMV as well because it estimates the macular volume for the central 6 mm and thus is a more global assessment of macular thickening. Using this broader measure of macular edema, we were able to detect an association with total cholesterol and triglyceride levels consistent with what other studies have found with macular edema as graded on fundus photographs.

Most previous OCT studies and systematic reviews have reported that the HF that correlate to hard exudates are primarily found in the outer retina in diabetic retinopathy,[1,2,29] but we found them in all the retinal layers even after carefully excluding HF due to other pathologies by overlying OCT and fundus photographs. Bloz et al[4] also reported that the distinct HF associated with DME could be found scattered throughout all retinal layers. Our study is also the first to systematically report the percent of patients with HF in each retinal layer. We found the outer plexiform layer is the most commonly involved layer and the likelihood of finding HF in a given layer decreased as distance from the outer plexiform layer increased. This is consistent with histopathologic studies of hard exudates.[3,15,30]

The strengths of this study include the large sample of patients with diabetes with various degrees of retinopathy and the careful assessment of OCT images with fundus photograph correlation to exclude other pathologies that can appear as HF. The population studied was relatively homogenous; all patients were

of the same race and all had T2D. However, there are limitations to our study. First, the cross-sectional nature of the study does not allow us to assess the temporal sequence of these associations. Second, despite overlaying fundus photographs on the OCT images to exclude non–microexudate pathologies, it is still possible that we misclassified some HF as being microhard exudates when they in fact represented other retinal pathologies such tiny hemorrhages that were not visible on fundus photographs.[12]

In summary, presence of macular HF in patients with T2D is associated with higher total and LDL cholesterol. Because newer OCT technologies are developed to measure the extent of HF secondary DME in an automated fashion,[31] the clinical utility of this OCT characteristic for predicting progression of retinopathy will become clearer and may help us to counsel and treat patients at an earlier stage in their disease process more effectively.

Key words: hard exudate, hyperreflective foci, optical coherence tomography, diabetic retinopathy, type 2 diabetes.

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