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ORIGINAL ARTICLE

Utility of Hard Exudates for the Screening of Macular Edema

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ABSTRACT

Purpose. The purpose of this study was to determine whether hard exudates (HEs) within one disc diameter of the foveola is an acceptable criterion for the referral of diabetic patients suspected of clinically significant macular edema (CSME) in a screening setting.

Methods. One hundred forty-three adults diagnosed as having diabetes mellitus were imaged using a nonmydriatic digital fundus camera at the Alameda County Medical Center in Oakland, CA. Nonstereo fundus images were graded independently for the presence of HE near the center of the macula by two graders according to the EyePACS grading protocol. The patients also received a dilated fundus examination on a separate visit. Clinically significant macular edema was determined during the dilated fundus examination using the criteria set forth by the Early Treatment Diabetic Retinopathy Study. Subsequently, the sensitivity and specificity of HEs within one disc diameter of the foveola in nonstereo digital images used as a surrogate for the detection of CSME diagnosed by live fundus examination were calculated.

Results. The mean (±SD) age of 103 patients included in the analysis was 56 ± 17 years. Clinically significant macular edema was diagnosed in 15.5% of eyes during the dilated examination. For the right eyes, the sensitivity of HEs within one disc diameter from the foveola as a surrogate for detecting CSME was 93.8% for each of the graders; the specificity values were 88.5 and 85.1%. For the left eyes, the sensitivity values were 93.8 and 75% for each of the two graders, respectively; the specificity was 87.4% for both graders.

Conclusions. This study supports the use of HE within a disc diameter of the center of the macula in nonstereo digital images for CSME detection in a screening setting.

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Key Words: clinically significant macular edema, hard exudates, diabetic retinopathy, teleophthalmology

The International Diabetes Federation recommends that patients with type 2 diabetes mellitus receive a dilated fundus examination by a qualified provider at the time of diagnosis of diabetes and annually thereafter if no retinopathy is present.[1] More frequent retinal examinations are indicated if any retinopathy is present. For patients with type 1 diabetes mellitus, a dilated fundus examination for retinopathy screening is recommended from age 11 years and after 2 years after the diagnosis and annually thereafter.[2] The current data indicate that, on average, only 60% of patients with diagnosed diabetes comply with these recommendations.[3] Even poorer compliance is reported among patients of lower socioeconomic status.[4] This underscores the need for a simple and effective screening tool for the detection of sight-threatening retinopathy because early detection and prompt treatment of retinal disease among diabetic patients can prevent vision loss.[5,6]

Teleophthalmology screening for diabetic retinopathy (DR) has been shown to be effective in detecting DR in a primary care setting.[7] Stereoscopic digital retinal photography with pupil dilation has been validated as an acceptable method for detecting and grading the severity of DR and diabetic macular edema (DME).[8,9] The international classification of DR developed by the International Council of Ophthalmology and adopted by the American Academy of Ophthalmology uses the presence and

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severity of retinal lesion types to stratify the risk of progression to sight-threatening complications from DR.[10,11] Several organizations throughout the world, including the Canadian Teleophthalmology Network in Alberta and Inoveon DR screening program in Oklahoma, have implemented DR detection programs using stereoscopic retinal photography and the international classification of DR.[12,13]

Nonmydriatic retinal cameras have been developed to reduce the discomfort and potential hazards of pupil dilation. However, stereoscopic photography without pharmacological pupil dilation is difficult to perform, and it results in images ungradable for retinal thickening in up to 20% of eyes.[14,15] On the other hand, determining retinal thickening in nonstereoscopic images is not possible. Therefore, a number of DR detection programs, such as the Scottish Diabetic Retinopathy Screening Program[16] and the Veterans Administration Diabetic Retinopathy Screening Program,[17] use the presence and location of hard exudates (HEs) close to the center of the macula as a surrogate to detect and stage DME. There has been only limited validation of HEs as a surrogate for DME. Bresnick et al.[18] performed a retrospective analysis of the photographic database of the Early Treatment Diabetic Retinopathy Study (ETDRS) using the criterion of HEs within one disc diameter of the foveola and identified CSME with a sensitivity of 94% and a specificity of 54%. Rudnisky et al.[19] reported the sensitivity of HE within two disc diameters of the foveola to be 93.9% in detecting ophthalmoscopically confirmed CSME; the specificity was reported to be 81.6%. Retinal images, in both of these studies, were obtained after pupillary dilation.

The purpose of the present study was to test, using a prospective clinical design, the validity of using HEs located within one disc diameter of the foveola in nonmydriatic, nonstereo, digital retinal images as a criterion for referring diabetic patients suspected of having CSME compared with the standard clinical technique of stereo biomicroscopy using a condensing lens or a contact fundus lens.

METHODS

This study was conducted at the Alameda County Medical Center in Oakland, CA, a DR screening site within the EyePACS telemedicine network.[20] This clinic serves uninsured local patients, and the limited clinic budget did not provide optical coherence tomography (OCT). Adult patients with known type 2 diabetes were recruited for the study. The recruitment process was purposely enriched by patients who were deemed likely to have DR based on a greater than 5-year history of diabetes, elevated HbA1c greater than 9.0, older than 40 years, and self-reported comorbidities such as angina or stroke. Written informed consent for the use and disclosure of protected health information was obtained from all subjects before being enrolled in the study. Institutional review board approval was granted by the Alameda County Medical Center, the University of California, Berkeley, and Indiana University.

The study protocol required two patient visits to the clinic, one for retinal photography alone and the other for a dilated retinal examination. This procedure mimics the actual screening process in the county system where a patient undergoes fundus imaging during the first visit to the clinic, images are reviewed, and the follow-up appointment with the clinician is scheduled based on the outcomes of the image review. The time between the two visits varies according to a number of factors. Such factors include physician and photographer availability issues coupled with reliability and scheduling issues of this indigent population. It was important to mimic that process to assess the utility of HEs as a referral criterion for CSME in a practical setting. If, because of logistical issues, the interval between the first and the second clinic visits exceeded 100 days, the patient was excluded from the study. The actual mean (±SD) interval was 33 ± 31 days. Retinal imaging was performed during the first clinic visit using the nonmydriatic fundus camera CR6-45NM (Canon Inc., Tokyo, Japan) without pupillary dilation. Nonstereoscopic 45-degree images of three retinal fields per eye were obtained in accordance with the EyePACS imaging protocol.[21] The primary field included the macula and the optic nerve, the centers of which were located equidistant from the center of the image (default position of the camera; Fig. 1A left). The second field was obtained with the optic nerve at the center of the image (Fig. 1A center). The third field was captured with the optic nerve to the far nasal side of the field, with the macula below and nasal to the center of the picture (Fig. 1A right). An EyePACS image in the primary position is shown with large HEs within one disc diameter of the foveola (Fig. 1B) and an image with smaller HEs (Fig. 1C).

The captured images were uploaded to the EyePACS Web site[20] and graded independently for macular edema by two graders (T.J.G. and T.V.L.) according to the EyePACS grading protocol.[22] A presumptive diagnosis of clinically significant macular edema (CSME) was made when HEs were noted at or within one disc diameter of the foveola. During the second clinic visit, patients received a dilated fundus examination of the macular region by T.V.L. using a noncontact 90D condensing lens and a biomicroscope. The examiner was masked to the retinal imaging findings. As previously stated, there was typically a delay between imaging and the examination and the patients were not necessarily seen sequentially, lessening the potential bias of results from grading the images to examination results. The presence, extent, and location of retinal thickening were noted, as well as the presence and location of HEs. In cases of uncertainty about the presence of macular edema, Goldmann macular contact lens was also used. The diagnosis of CSME on the dilated fundus examination was made according to the criteria set forth by the ETDRS[23]: (1) retinal thickening within 500 μm of the center of the macula; or (2) HEs within 500 μm of the center of the macula with adjacent retinal thickening; or (3) retinal thickening of one disc area in size or greater, any part of which is located at or within one disc diameter from the center of the macula.

The sensitivity and specificity values for CSME detection using HEs at or within one disc diameter of the foveola graded in the retinal images were calculated and compared with those for CSME identified during the dilated fundus examination as the standard. The statistical analysis was performed separately for the right and the left eyes.

RESULTS

One hundred forty-three adult diabetic patients were recruited for the study. Forty of these patients were excluded from the study

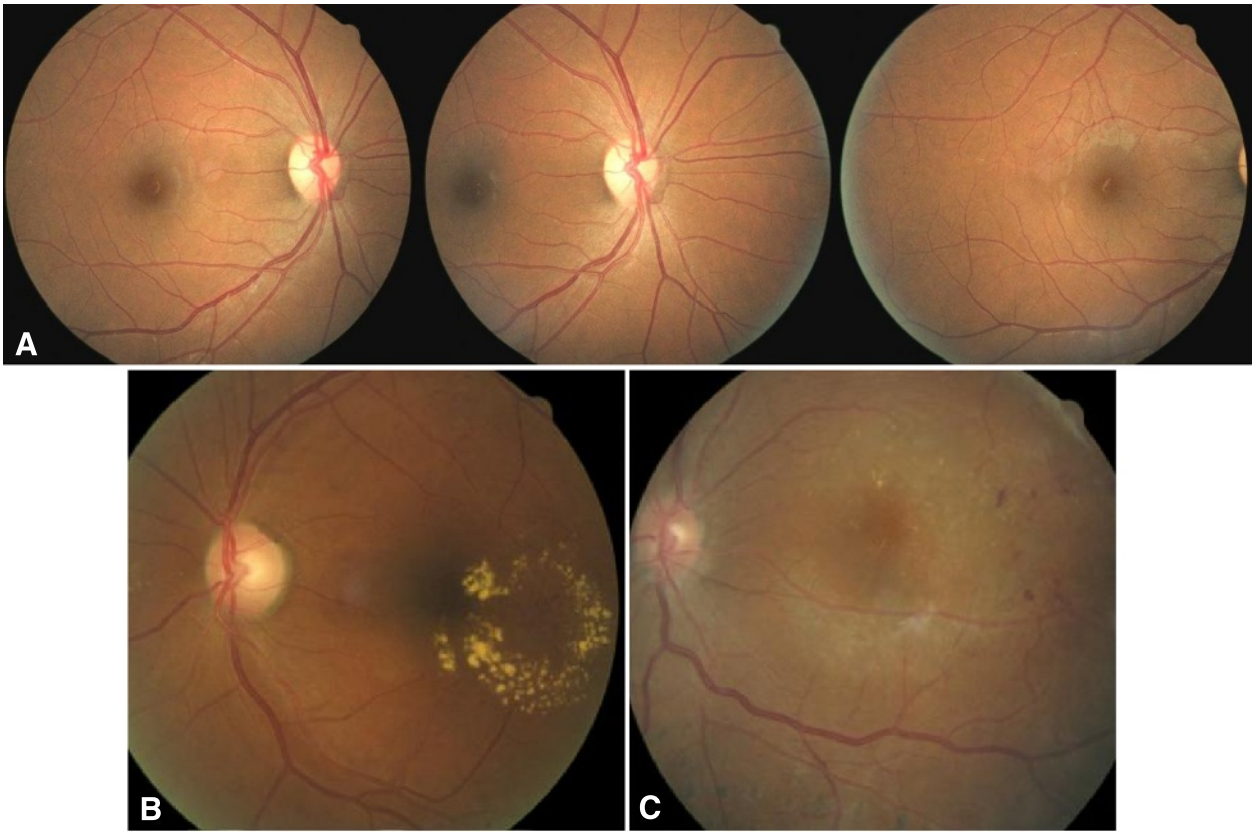

FIGURE 1.

Images obtained according to the EyePACS imaging protocol. (A) Normal retina of the right eye: left image, primary field (temporal retina and the optic nerve); center image, field centered on the optic nerve; right image, optic nerve to the far nasal side of the field. Panels B and C would each yield referrals for retinal edema because of hard exudates within one disc diameter of foveola. (B) Circinate ring of hard exudates involving macula OS; (C) small hard exudates within one disc diameter of foveola.

because the time between the first and the second clinic visits exceeded 100 days, reinforcing the scheduling difficulties in this patient population. The mean (±SD) time interval between the first and the second clinic visits of the remaining 103 patients was 33 ± 31 days. Forty-nine percent were females. The mean age of the included patients was 56 ± 17 years. Ethnic composition of the study population is presented in Fig. 2.

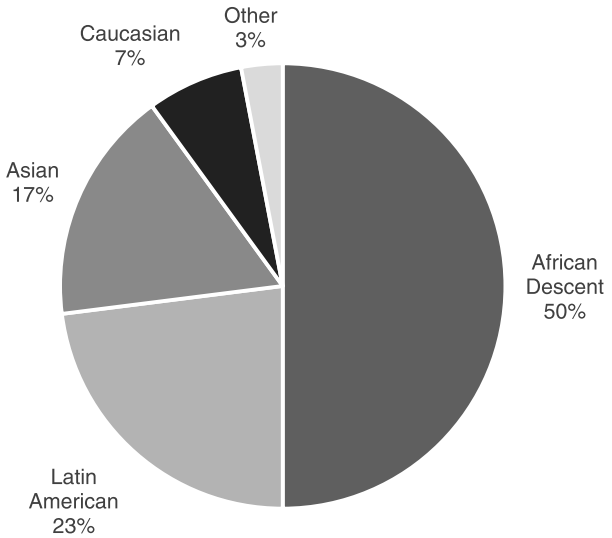

FIGURE 2.

Ethnicity of patient group.

For the right eyes, CSME was diagnosed in 16 (15.5%) eyes by biomicroscopy during the dilated examination. Based on retinal images, a presumptive diagnosis of CSME was made independently by the two graders in 28 (26.4%) and in 25 (24.2%) cases, respectively (Table 1). In the right eyes, the sensitivity of HEs located within one disc diameter from the center of the macula as a surrogate for detecting CSME was 93.8% for each of the graders; the specificity values were 88.5 and 85.1%; positive predictive values were 60 and 53.57%; and negative predictive values were 98.7 and 98.7% (Table 2).

For the left eyes, CSME was diagnosed in 16 (15.5%) cases by biomicroscopy during the dilated examination. Based on retinal

TABLE 1.

CSME: dilated biomicroscopic examination versus image grading

	CSME on fundus examination		CSME grader 1 on image grading		CSME grader 2 on image grading	
	OD	OS	OD	OS	OD	OS
No. eyes	16	16	28	26	25	23
Percent value	15.5	15.5	26.4	25.2	24.2	22.3

TABLE 2.
Predictive power of the surrogate method of CSME detection

	Grader 1		Grader 2	
	OD	OS	OD	OS
Sensitivity, %	93.75	93.75	93.75	75
Specificity, %	88.51	87.36	85.05	87.36
Positive predictive value, %	60	57.69	53.57	52.17
Negative predictive value, %	98.72	98.70	98.67	95

images, CSME was diagnosed by grader 1 in 26 (25.2%) cases, whereas grader 2 diagnosed CSME in 23 (22.3%) (Table 1). Based on the results of the left eye analysis, the sensitivity values of HEs located within one disc diameter from the center of the macula as a surrogate for detecting CSME were 93.8 and 75% for each of the two graders, respectively; the specificity was 87.4% for both graders; positive predictive values were 57.7 and 52.17%; and negative predictive values were 98.7 and 95%, respectively (Table 2).

CONCLUSIONS

When HEs were present at or within one disc diameter from the foveola in undilated nonstereoscopic fundus photos, CSME was detected (determined by a dilated biomicroscopic fundus examination) with good sensitivity, with an acceptable level of overdiagnosis for a screening situation. These results indicate that HEs are a valid surrogate marker for the detection of CSME when stereophotography and OCT are inadequate or simply unavailable for financial reasons.

Having a valid inexpensive alternative for the detection of CSME is important for several reasons. It ensures that DR screenings can successfully detect sight-threatening macular edema without dilation, stereoscopic photos of the macula, or OCT. In addition, DR screenings that rely on nonmydriatic stereoimaging can result in a high proportion of ungradable images for the detection of retinal thickening.[14,15] When one image of a macular stereopair is unusable, a surrogate marker for CSME is very useful. The results of this study also suggest that HEs near the center of the macula can be used by primary care providers to screen for CSME using direct ophthalmoscopy, with some consequent overreferral to retinal specialists. We do not suggest that direct ophthalmoscopy is a substitute for a dilated retinal examination.

Our sensitivities are comparable to results published by Bresnick et al.,[18] comparing HEs within one disc diameter of the center of the macula versus the then current "gold standard for CSME" graded in ETDRS stereoscopic photographs. Our specificities are somewhat higher than those reported by Bresnick et al.,[18] although both sensitivities and specificities are similar to data published by Rudnisky et al.[19] in 2006, reporting the ability of HEs within two disc diameters of the fovea to detect CSME that was confirmed by a dilated fundus examination using a retinal contact lens. However, our study is different from these other two studies because we obtained our retinal images undilated, more closely matching the common screening condition of nonmydriatic nonstereo retinal imaging.

With regard to the quality of the grading, the lower sensitivity demonstrated by grader 2 in detection of CSME in the left eyes prompted further investigation. Of the three CSME cases that grader 2 missed, one case showed unmistakable exudates well within one disc diameter of the foveola and therefore may have been a case of data entry error. The other two cases showed a single small exudate at the border of one disc diameter from the foveola. The difference in grading in those cases may be attributed to variability in judgment between graders for the threshold of HE detection by each grader. This highlights the importance of testing grading systems for intragrader and intergrader repeatability and of performing quality control of image grading in DR screening programs.

Low positive predictive values point to a relatively high rate of "overreferral," although it may be acceptable in a screening setting especially in a patient population with generally poor access to health care. This study shows the utility of the use of HE surrogate for detection of DME by screening programs using nonstereoscopic images. In our opinion, this is important for rapid screening of large diabetic populations with relatively low equipment expense, low false-negative rates, and reasonable false-positive rates. It is better to err on the positive side and send the patient to a retina specialist who does not find serious pathology than miss an actually active disease and lead to blindness on the part of the patient.

This study has limitations. First, the mean (±SD) time interval between imaging and dilated eye examinations was 33 ± 31 days, whereas ideally imaging and examination would have been done at the same visit. In the framework of population screening, it is common to have a screening visit and then a follow-up examination of those subjects showing clinically significant retinopathy so some interval is largely unavoidable. For the specific situation of DME, the ETDRS reported that macular edema tended to be chronic and that spontaneous visual recovery was unusual.[23] In addition, a recent study by Kwon et al.[24] followed two groups of patients with mild and moderate DME measured by OCT for a period of 6 months without treatment and found no significant changes in the 250- to 300-μm central macular thickness group. There was significant progressive decrease in retinal thickness in the 300- to 500-μm group, but the eyes still were at an average of 318 μm at 1 month and 284 μm at 6 months. Thus, although it is possible that there were some changes in degree of edema during this 1-month period between imaging and examination, it is unlikely that there were significant changes having a major impact on our results. In addition, our findings are similar to those reported by Rudnisky et al.[19] In their study, fundus photos were obtained on the same day as a dilated fundus examination and the presence of HEs within 2DD of the fovea was used as a surrogate for CSME detection. They report that HE within 2DD of the foveola has a sensitivity of 93.9% and a specificity of 81.6% for CSME detection. Thus, it may be inferred that any significant changes in retinal thickening occur slowly, and that the elapsed time in our study likely did not have a major impact on our results.

Second, the historically accepted gold standard for detecting CSME is the use of 30-degree, film-based, stereo macular photos performed and graded according to the ETDRS protocol.[25] However, our use of the dilated biomicroscopic examination

as the standard in the present study is supported by the high correlation reported between CSME detected by contact lens biomicroscopy compared with CSME detection by the ETDRS protocol.[26]

In addition, further validation studies to compare the HE surrogate for macular thickening with more objective means such as OCT are planned. Although OCT is widely accepted as an objective method for detecting diabetic maculopathy, it is currently too costly and technically challenging to integrate into existing retinopathy detection programs in primary care settings. Low-cost and reliable methods of detecting CSME, such as the use of an HE surrogate marker described here, are needed to meet the challenge of widespread screening for this vision-threatening condition.

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