Differentiation of Diabetic Macular Edema From Pseudophakic Cystoid Macular Edema by Spectral-Domain Optical Coherence Tomography

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PURPOSE. To differentiate diabetic macular edema (DME) from pseudophakic cystoid macular edema (PCME) based solely on spectral-domain optical coherence tomography (SD-OCT).

METHODS. This cross-sectional study included 134 participants: 49 with PCME, 60 with DME, and 25 with diabetic retinopathy (DR) and ME after cataract surgery. First, two unmasked experts classified the 25 DR patients after cataract surgery as either DME, PCME, or mixed-pattern based on SD-OCT and color-fundus photography. Then all 134 patients were divided into two datasets and graded by two masked readers according to a standardized reading-protocol. Accuracy of the masked readers to differentiate the diseases based on SD-OCT parameters was tested. Parallel to the masked readers, a computer-based algorithm was established using support vector machine (SVM) classifiers to automatically differentiate disease entities.

RESULTS. The masked readers assigned 92.5% SD-OCT images to the correct clinical diagnose. The classifier-accuracy trained and tested on dataset 1 was 95.8%. The classifier-accuracy trained on dataset 1 and tested on dataset 2 differentiated PCME from DME with 90.2%. The classifier-accuracy trained and tested on dataset 2 to differentiate all three diseases was 85.5%. In particular, higher retinal thickness/volume ratio, absence of an epiretinal-membrane, and solely inner nuclear layer (INL)-cysts indicated PCME, whereas higher outer nuclear layer (ONL)/INL ratio, the absence of subretinal fluid, presence of hard exudates, microaneurysms, and ganglion cell layer and/or retinal nerve fiber layer cysts strongly favored DME in this model.

CONCLUSIONS. Based on the evaluation of SD-OCT, PCME can be differentiated from DME by masked reader evaluation, and by automated analysis, even in DR patients with ME after cataract surgery. The automated classifier may help to independently differentiate these two disease entities and is made publicly available.

Keywords: multimodal imaging, diabetic macular edema, pseudophakic cystoid macular edema

Macular edema (ME) can be found in many different retinal diseases.1,2 Pathological events leading to this accumulation of fluid differ according to underlying diseases: in pseudophakic cystoid macular edema (PCME), ME is thought to be caused by proinflammatory cytokine release.3–5 In diabetic macular edema (DME), ME is induced by hyperglycemia-induced oxidative stress and deposition of advanced glycation end products (AGES), impaired blood flow, hypoxia, pericyte loss, endothelial cell loss, upregulation of vesicular transport, downregulation of glial cell-derived neurotrophic factor and inflammation.6,7 According to these different underlying pathological events, the morphologic appearance of ME might differ according to the underlying disease. In support of this hypothesis, the histopathologic appearance of ME varies according to the underlying pathology.8 Further, a recent SD-OCT study by our group showed that ME has characteristic patterns and morphologic features dependent on the underlying disease process and can be differentiated based on these typical features.9

Most of the time, the underlying ME pathology can be easily discovered by clinical history or by clinical presentation. Sometimes however, differentiation may be difficult, as in patients with diabetic retinopathy (DR) or with a history of DME right after cataract surgery. In these cases PCME as well as DME can cause fluid to accumulate. Here, the medical history and the presence of hard exudates (HE) or microaneurysms do not always lead to the correct diagnosis. In some cases fluorescein angiography may provide insight in the underlying cause, as the presence of a disc edema and a “hot disc” is
suspicious for PCME. Unfortunately, even this finding can be inconclusive: patients with ME attributed to diabetes may also have disc hyperfluorescence and not all patients with PCME display this feature.10,11
The incidence of clinically significant PCME after uncomplicated cataract surgery ranges between 0.1% to 2.3%, and peaks at approximately 5 weeks in a healthy population, but is significantly higher (16.3%) in patients with previous DME and in patients with diabetic retinopathy (DR), whose blood-retinal barrier has been compromised even before surgery.5,12–14
Previous studies which analyzed the incidence of ME after cataract surgery in diabetic patients did not differentiate between the incidence of DME and PCME.15–17 To properly treat these eyes, however, it is crucial to classify ME appropriately, as the treatment may vary, depending on the underlying condition.4,18,19

The aim of this study was to evaluate whether PCME can be differentiated from DME using SD-OCT. For this purpose, SD-OCT images were graded based on our previously established SD-OCT grading protocol to differentiate underlying etiologies in ME.9 Based on the collected SD-OCT data, two masked readers classified the SD-OCTs into the different disease entities. Furthermore, the collected data were used to train and subsequently test the performance of support vector machines, which are widely used machine learning classifiers, with the purpose to differentiate disease entities automatically. Machine learning classifiers as such are algorithms, which can be trained to classify the collected data for the input images based on a training data set where the classification (= diagnosis) is already known (a so-called supervised learning task)20 with the purpose of subsequently automatically classifying as yet unseen data (i.e., new patients). Support vector machine SVM classifiers in particular have already been used to determine the presence of DR, DME, AMD, and glaucoma using color fundus images, fluorescence angiography, and OCT.20,21

Methods

Patients and Setting

The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committees at Medical University of Vienna (Vienna, Austria), Duke University (Durham, NC, USA), and Northwestern University (Chicago, IL, USA). This study included Spectralis SD-OCTs of participant eyes with DME, PCME, and nonproliferative diabetic retinopathy (NPDR) with ME after cataract surgery. For inclusion, ME was defined as presence of a central 1-mm subfield thickness (CRT) greater than 250 μm in Spectralis SD-OCT and either presence of intraretinal cystoid spaces or areas of reduced intraretinal reflectivity.

Inclusion Criteria and Definition of DME Eyes. The eyes in the DME group were required to have ME due to diabetes. Eyes of patients with DME were excluded if they had ocular surgery within the preceding 4 months or if there was any possibility that the ME was not due to DME, but was related to ocular surgery or other retinal diseases such as vitreomacular traction.

Inclusion Criteria and Definition of PCME Eyes. The PCME group included eyes with ME after cataract surgery. Patients with previous ME due to uveitis, retinal vein occlusion, or diabetes were excluded.

Inclusion Criteria and Definition of NPDR Eyes With ME After Cataract Surgery. The third group included eyes which developed ME beginning 30 days, and up to 90 days post cataract surgery, with a history of NPDR with or without DME prior to cataract surgery. Included eyes were required to have a central 1-mm subfield thickness (CRT) less than or equal to 320 μm and absence of ME prior to cataract surgery in the Spectralis SD-OCT. Absence of any ME treatment within the preceding 6 months was also an inclusion criteria for this group.

OCT Scan Acquisition and Grading Protocol

All SD-OCT images were acquired using the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) system (acquisition software version 5.1.3.0.). Previous studies showed that scan distances ranging from 188 to 47 μm do not affect retinal thickness evaluation and that scan densities of 188 μm compared with scan densities of 94 μm do not change the detection rate of typical morphologic features.22–25 Accordingly, in the current study, images were included with horizontal raster scans of different scan densities ranging from 120 to 60 μm separation between scans. Each scan had a minimum of 10 frames averaged per B-scan (ART-mode) (Podkowski D, et al. IOVS 2014:ARVO E-Abstract 4804). Optical coherence tomography images were evaluated for signal-to-noise ratio (SNR in dB), and quality as reflected by readers’ ability to differentiate retinal layers and other morphologic features. Only high quality, well resolved raster scans were included for analysis. Spectralis uses SNR estimate in decibels for instrument quality score.26 For inclusion, raster scans had to have a minimum 20 dB SNR, which is considered best quality.26 Spectral domain-OCT raster scans of lower SNR and of insufficient quality and resolution were excluded.

All images were analyzed according to a standardized, previously established grading protocol, which had been proven to differentiate ME of different underlying pathologies using masked graders and SVM.7 Grading parameters included ME pattern, morphologic features, and quantitative parameters, and are listed in Table 1. Grading parameter definitions are provided in Table 2.

Before the analyses of the thickness parameters, if necessary, the center point was adjusted according to foveal depression, foveal intraretinal-layer convergence, central photoreceptor detachment and optic nerve head location, and segmentation line errors were corrected. The thicknesses of respective layers were measured on the central line scan with the distance measuring tool of the Spectralis software from the center of the fovea in nasal direction. Measurements were obtained at the center of the fovea (foveolarly), foveally (400 μm from the center of the fovea in nasal direction), parafoveally (1000 μm from the center of the fovea in the nasal direction), and extrafoveally (2000 μm from the center of the fovea in the nasal direction).9

Training and Testing Datasets. To establish the classifier and to test the evaluated parameters for their accuracy and generalizability included patients were divided into two different datasets: the first dataset included Spectralis SD-OCT scans of consecutive participants with DME and pseudophakic cystoid ME seen at the Medical University of Vienna. The second dataset included SD-OCTs of participants in interventional DME trials that were evaluated at the Duke Reading Center (Duke Eye center, Durham, NC, USA), those in an interventional trial with NPDR and ME post cataract surgery that were evaluated at the Vienna Reading Center (Medical University of Vienna) and consecutive eyes of participants with PCME seen at the Northwestern University, Department of Ophthalmology. Two independent observers from the Vienna Study Center (MMR, TM) assessed and graded the images of the first dataset based on the grading protocol to produce accurate data upon which we could establish our automated SVM classifier. Grading discrepancies were resolved by reader consensus. For numeric data, the mean of the two measurements was taken for further analyses.
Images from the participants of the second dataset were assessed to verify the accuracy of the SVM-classifier established in the first dataset and to assess its generalizability. Further, the second dataset was evaluated to determine the accuracy of the human masked graders to differentiate the disease entities based on the evaluated SD-OCT parameters. For the second dataset, the SD-OCT images of the participants with NPDR and ME post cataract surgery were individually graded by two unmasked experts (LJM and GJJ) with long-term clinical experience in DR and DME. Beside SD-OCTs, additionally, corresponding color fundus images were reviewed to help differentiate between PCME and DME. Based on this evaluation, each participant’s OCT images were categorized as DME, PCME, or “mixed,” if in the opinion of the experts, features of DME as well as PCME were identified in the SD-OCT scans and the color fundus images. Discrepancies were resolved by consensus grading. After the expert grading, SD-OCTs of all three groups, definite DME (images from the Duke Reading Center), definite PCME (images from Northwestern University) and NPDR with ME post cataract surgery (images from Vienna Reading Center, which were now divided according to the experts’ opinion into DME, PCME, and “mixed”) were mixed to create the second dataset. In this second dataset, two masked readers (MRM, TM) then evaluated the OCT parameters, and the final grade was determined by consensus. The grading-results of the second dataset were then fed into the SVM-classifier. Further, the masked graders classified the SD-OCTs into DME, PCME, and mixed based on the evaluated SD-OCT parameters and the accuracy of their presumed diagnosis was evaluated.

### Statistical Analyses

Statistical analyses were performed with R (in the public domain, www.r-project.org) and SPSS (IBM, SPSS statistics, Version 21; SPSS, Inc., Chicago, IL, USA) software. Figures were created using R. For the first dataset, the Pearson correlation coefficient was determined to assess the correlation between the retinal layer thickness measurements of both readers. A correlation coefficient greater than or equal to 0.95 was required. The mean of the measurements was then taken for further analyses.

Initially, the first dataset was examined using a 10-fold cross-validated support vector machine classifier. Ten-fold cross-validation is a standard procedure in the field of machine learning where the dataset is split 10 times into training and testing subjects: for each of the 10 sets, 9-folds of the dataset are used to train the SVM-classifier and the 10th is used to test its accuracy. With this procedure each of the 10-folds are used once as the testing set and the classification accuracy is then averaged over all 10 examinations. The purpose of this is to on the one hand maximize the amount of training data available and on the other hand still get an unbiased estimate for the expected classification accuracy on new data (i.e., future patients). This classifier was then tested on the second dataset to calculate an unbiased estimate for classification accuracy on independent datasets. An R-package of this automated classifier was then generated to enable clinicians to test their individual SD-OCT images for decision support (see Supplemental Material, data file "trained.svm.RData").

In addition, a 10-fold cross-validated support vector machine classifier was trained and tested on dataset 2 to get an impression about achievable classification accuracy for all three diagnoses included in this dataset.

Further, classification accuracy of the masked readers to identify the correct diagnose based on the findings on SD-OCT was determined for dataset 2. For inferential analyses P values less than 0.05 were considered statistically significant. Values are given as mean ± SD.

### RESULTS

This study enrolled images from 150 eyes of 150 participants. Out of these 150 participants, images from 16 were excluded from analyses. Thus, in sum, this cross-sectional study included...
images from eyes of 134 participants: 49 with PCME, 60 with DME, and 25 NPDR with ME after cataract surgery. The first dataset included images from eyes of 72 participants: 20 with PCME, 17 with DME, and 25 NPDR with ME post cataract surgery. The second dataset included images from eyes of 62 participants: 20 with PCME, 17 with DME, and 25 NPDR with ME after cataract surgery. Out of the 22 eyes with PCME in the second dataset, 12 had a foveal appearance with features of both PCME and DME, 11 had a mixed appearance with features of both PCME and DME, and 11 to the mixed group. Thus, in sum in the second dataset 22 eyes had PCME, 29 had DME, and 11 to the mixed group. One of the 22 PCME eyes was falsely graded as DME. The accuracy to differentiate between DME and mixed was 95%.

Automated and Cross Validated Classification Accuracy

Cross-Validated Classification Accuracy of Dataset 1. The automated 10-fold cross-validation on the findings of data set 1 showed an accuracy of 95.8%. In other words, by assessing SD-OCT parameters automatically, the accuracy of the automated model to correctly diagnose the underlying pathology in similar samples is approximately 96%.

Classification Accuracy With Classifier Trained on Dataset 1 and Tested on Dataset 2. The accuracy of the classifier trained on dataset 1 and tested on dataset 2 was as follows: based on the classifier assessed from the evaluated parameters in dataset 1, the computer determined correctly 29 of 29 DME eyes in the second dataset. Out of the 22 eyes with PCME, 17 were correctly assigned to the PCME group, whereas five were falsely graded as DME. The accuracy to differentiate DME and PCME was 90.2%. As the first dataset did not include any mixed patients, the computer classifier assigned the mixed.
FIGURE 1. Representative examples of DME, pseudophakic cystoid macular edema, and a “mixed” pattern. (A) Diabetic macular edema: the representative central line scan has a central ME pattern, due to focal leakage, mainly ONL/Henle’s layer cysts, hard exudates, microfoci, and disruption of the photoreceptor layers. (B) Pseudophakic cystoid macular edema: the representative line-scan has a central ME-pattern, SRF, and intact hyperreflective bands. (C) Mixed: This representative line scan shows features characteristic of both PCME and DME: subretinal fluid and small parafoveal INL cysts not related to microaneurysms and intact hyperreflective outer retinal bands are typical of PCME. Microfoci, hard exudates and focal retinal thickening due to leaking microaneurysms (not seen here) are characteristic of DME.
patients of the second dataset either to the PCME or to the DME group: interestingly only one eye from the mixed group was classified as PCME, and the remaining 10 eyes were assigned to the DME group. The calculated probability of the observations belonging to the DME or the PCME group can be found in Figure 2. The weight of each singular SD-OCT parameter on the automated overall decision made by the classifier is shown in Figure 3. The statistical R-package of the automated classifier can be found in the Supplementary Material in order to enable the clinician to test individual SD-OCT images for decision support (see Supplementary Material "trained.svm.RData"). The instruction to load the R-package and the description of parameters included in the classifier can be also found in the Supplementary Material (see Supplementary Material, Instructions R-package and parameter description).

**Cross-Validated Classification Accuracy on Dataset 2.**

The automated 10-fold cross-validated accuracy to differentiate between DME, PCME, and mixed patients of the second dataset was 85.5%. The classification accuracy to differentiate only between DME and mixed groups was 77.5%.

**DISCUSSION**

In the current study, we evaluated SD-OCT as a suitable tool to differentiate ME attributed to diabetes and PCME. We found that these two diseases can be differentiated on the basis of SD-OCT parameters by human graders as well as by automated classifiers.

In a previous study, our group established SD-OCT parameters to differentiate ME of different origins. In that study the pattern describing the distribution of ME on the SD-OCT scan, the presence of microfoci and the retinal nerve fiber layer (RNFL) thickness was particularly useful to determine underlying pathology. In the present study, we have now demonstrated that with SD-OCT, DME can be distinguished from PCME by an automated model as well as by trained masked readers. In particular, a higher CRT/retinal volume ratio, a thicker foveal ONL/Henle’s layer (HL), the absence of ERM and solely INL cysts highly favored PCME in the automated model, whereas a higher ONL/INL thickness ratio parafoveally, the presence of microaneurysms, hard exudates, and microfoci, the presence of additional ganglion cell layer (GCL) and/or RNFL cysts, and the absence of subretinal fluid (SRF) weighted strongly toward DME.

Pseudophakic cystoid-macular-edema usually presents with a central ME pattern and intraretinal cystoid fluid accumulation in the central millimeters and the inner Early Treatment Diabetic Retinopathy Study (ETDRS)-subfields. In contrast, DME typically has a higher retinal volume, diffuse or focal retinal thickening and preserved foveal depression. The findings that the CRT/volume ratio and foveal ONL/HL is higher in PCME than in DME patients support these observations.

The prevalence of ERM in eyes with DME is 22% to 25%,9,27 In contrast, a 7.7% prevalence of ERM in eyes with PCME has been reported, similar to the prevalence of idiopathic ERM in elderly people, which ranges between 7% and 11.8% (9,38). These data are consistent with the current finding that the absence of an ERM favors PCME over DME.

That the presence of solely INL cysts seems a relevant factor to distinguish PCME from DME may be explained by the fact that PCME is caused by proinflammatory cytokine release leading to a breakdown of the blood-retina barrier. As the superficial and the deep capillary plexuses are located in the GCL and INL, respectively, it seems therefore plausible that initially INL cysts appear.31,32 Diabetic macular edema in contrast, at least when focal, will initially show ONL/HL cysts caused by microaneurysms, located more deeply in the retina, which then leak into the respective deeper retinal layers.53 Besides leaking MA, outer retinal fluid accumulation may also result from outer blood-retina barrier breakdown and leakage, an impaired RPE pumping function and glia cell dysfunction. Fluid homeostasis may be disturbed due to changes of the hydrostatic pressure: a shift of molecules into the extravascular space enhanced by the prevalent hypertension in diabetes patients and a decreased oncotic pressure due to hypoalbuminemia, are likely to be significant contributing factors.34,55

Leaking MA and the other influencing factors discussed above may explain the higher ONL/INL ratio parafoveally, when compared with PCME.55 That the presence of HE, microaneurysms and microfoci was highly indicative for DME does not need to be discussed in detail as previous studies reported a prevalence of 98% to 100% of respective morphologic features in DME.9,36,57

In our series, the SRF frequency differed in eyes with DME, 26% (first dataset) and 10% (second dataset), when compared with those with PCME, 76% (first dataset) and 77% (second dataset). These differences are consistent with those previously reported; the prevalence of SRF in DME varies from 15% to 31%, depending on the series,9,38–40 and seems to be dependent on the disease duration.41 In PCME, percentages range from 47% to 100%.9,38–42 Thus, the absence of SRF is suggestive of DME. Breakdown of the outer blood-retina barrier and impaired function of the RPE have been considered to be associated with SRF. Externally limiting membrane (ELM) dysfunction promoting the diffusion of proteins into the subretinal space and inducing a positive oncotic pressure gradient may lead to SRF accumulation as well.43–46 Also traction of the Müller cell cone on the inner and outer segments of the foveal photoreceptors has been discussed to initiate SRF development.47 The different underlying pathomechanisms, of DME and PCME may be the major cause of the uneven prevalence of SRF. Diabetic macular edema patients usually have long-standing diabetes, that is, chronic hyperglycemia associated with advanced glycation endproducts (AGEs), activation of protein-kinase C, polypeptide and the hexosamine pathways, leading to gradual vascular changes such as the breakdown of cell-cell junctions, pericyte loss and thickening of basement membrane, and increased oxidative stress and inflammation.49–46 Such changes and overactivation may be approve and active for many years before the clinical symptoms and DME occur. Pseudophakic cystoid macular edema in contrast is induced by an acute and local inflammatory reaction leading to an acute release of a variety of proinflammatory cytokines, prostaglandins, proteases, and complement.49 Such an acute inflammation may rather lead to SRF due to an acute profound dysfunction of the RPE cells and an acute breakdown of the inner and/or outer blood-retina barrier contrasting the sustained chronic inflammation and degenerative processes as found in diabetes. This assumption seems to be in line with previous findings, demonstrating that the presence of SRF is associated with short disease duration and seems to be a positive prognostic factor for visual function outcome and treatment efficacy.42,43 Reason for this is obviously the tendency of acute inflammations to quickly resolve if the inflammatory trigger is removed, in contrast to the ongoing, chronic activation of the immune system (e.g., DME).

SRF accumulation may be also supported by the above mentioned Müller cell cone traction theory.45 In contrast to the PCME eyes, the majority of DME eyes had preserved foveal depression without any significant tractional forces of the Müller cell cone on the ELM and the foveal photoreceptors.
In previous reports of diabetic patients post cataract surgery, DME and PCME were found to coexist.\textsuperscript{50,51} This observation is in accordance with our findings: Many patients with NPDR could be clearly assigned to either DME ($n = 12$, [48\%]) or PCME ($n = 2$, [8\%]), but 44\% ($n = 11$) of these cases were mixed, and presented with characteristic features of DME as well as PCME. The masked readers (MRM, TM) were able to differentiate these conditions with 95\% accuracy. Only 2 eyes out of 11 that had a mixed pattern were falsely graded as DME. In contrast, although the automated classifier was highly accurate differentiating pure DME from PCME, the achieved accuracy to distinguish DME from the mixed pattern was only 77.5\%. One likely explanation for this finding is the rather low number of training cases for the mixed group. Future studies should include larger sample sizes to further examine this issue. Further explanation for the reduced accuracy to differentiate DME from the mixed pattern may be found in the evaluation of the classifier probabilities of the model trained on the first and tested on the second dataset. The calculated probability pointed toward DME in most of the “mixed” observations instead of being located between PCME and DME. This skewed probability may be due to the fact that in the automated evaluated model, HE, microaneurysms, and microaneurysms strongly favored DME and nearly all “mixed” observations showed respective features, whereas features such as SRF or solely INL cysts strongly favoring PCME were less common. Although HE, microaneurysms, and microaneurysms may be very helpful to distinguish pure PCME and pure DME from each other, they may be misleading in cases where both diseases coexist. Therefore, especially in these cases HE and microaneurysms should always be evaluated in combination with the remaining SD-OCT findings.

The main limitation of this study is lack of a “gold” standard method to differentiate DME from PCME. Therefore, differentiation could only be based on unmasked expert opinion to generate the dataset upon which subsequent comparisons were based. Furthermore, as described above, the “mixed-group” sample size was relatively small. Nonetheless, despite these limitations, PCME and DME could be differentiated on SD-OCT images by automated classification and by human readers, even in eyes with pre-existing DR that underwent cataract surgery. We believe that the high accuracy achieved by
the masked readers, and the automated classification resulted from evaluation of multiple SD-OCT parameters. The provided automated classifier will support the clinician's decision in making the correct diagnosis and in choosing appropriate treatment. In future studies, by including larger sample sizes upon which automated classification is based, we believe it will be possible for the automated classification to achieve even greater accuracy to differentiate DME from the mixed pattern. This improvement would then facilitate creation of even more accurate automated classifiers to enable software-based differentiation of pseudophakic and DME as a diagnostic and therapeutic tool for clinicians.

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