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Validation of Esaso Classification of Diabetic Maculopathy

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Abstract

Purpose: To test reliability and reproducibility of ESASO morphologic OCT-based classification of diabetic maculopathy (DM).

Methods: This is a multi-center cross-sectional study including a coordination center (CC) and 18 participating centers (PCs). After instruction on the correct use of ESASO Classification, the validation process was carried out in two consecutive stages. In the first retrospective phase, we evaluated the concordance between PCs and CC in the staging of OCT images collected during PCs' daily activity (608 images). In a second prospective phase, we analyzed the inter-observer agreement of staging assigned by each PCs to OCT images selected by the CC (22 images).

Results: The overall concordance achieved in the retrospective phase was 89.8% (Kappa = 0.83 (95% CI: 0.78–0.87); p<0.0001). In 99.5% of cases, concordance did not differ by more than one stage. In the prospective phase, PCs reached an inter-operator agreement of 93.0% (Krippendorff's Alpha = 0.953, 95% CI: 0.929–0.977, p<0.0001). Any discrepancy among the 22 images was within one stage.

Conclusion: The results achieved in this study confirm that ESASO OCT-based Classification can be considered as an easy and reproducible method to stage DM during clinical practice. A diffused use of a common and validated method to describe the progression of retinal damage in DM may offer several clinical and scientific advantages.

Keywords

ESASO classification, diabetic macular edema (DME), diabetic maculopathy (DM), optical coherence tomography

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Introduction

More than 530 millions of adults are affected by diabetes, and it has been estimated that this number will rise to 643 millions by 2030 and to 783 millions by 2045.[1] Diabetic retinopathy (DR) is the most common neurodegenerative and microvascular complication affecting patients with diabetes,[2] and diabetic maculopathy (DM) can develop independently at any stage of retinopathy. DM is now responsible for 75% of diabetes-related vision loss,[3] but with the rising prevalence of diabetes and the longer lifetime, this visual burden is expected to rise worldwide.[4]

Spectral-domain optical coherence tomography (SD-OCT), associated in selected cases to fluorescein angiography (FA), is the technique of choice for assessment and follow-up of DM.[5] The high-definition images generated by SD-OCT allow the definition of quantitative and qualitative parameters of retinal damage known as biomarkers due to their correlation with visual function and therapeutic response.

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An International panel of experts elaborated a morphologic OCT-based classification, recently published under the name of ESASO Classification.[6] This classification relies on seven OCT biomarkers scored according to their severity, and defines four stages of DM: early, advanced, and severe diabetic macular edema (DME), and atrophic maculopathy. The ESASO classification is based on standard OCT pictures to facilitate the use also by non-experts, but its reliability and reproducibility in the clinical practice has not yet been formally tested. This nation-based multi-center study aims to assess the inter-rater agreement of DM staging using the ESASO classification among retina specialists across Italy. This validation process is meant to be a step forward for the use of this tool both for clinical and scientific purposes.

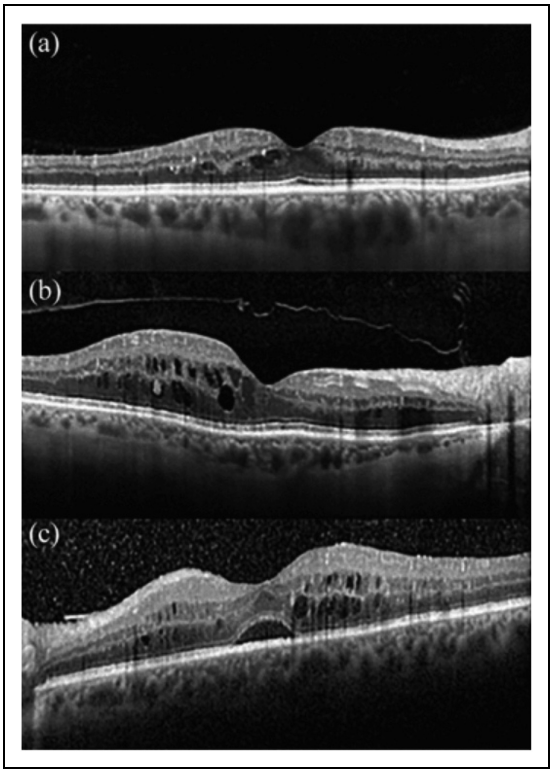

Figure 1. Reference OCT-images of Early DME.

Material and Methods

This was a multi-center cross-sectional study including a coordination center (CC) located at the ESASO Headquarter in Lugano (Switzerland), and 21 Italian participating centers (PCs). This study followed the criteria of the Helsinki Protocol and was approved by the Ethics Committee of each PC.

The validation process was carried out in three stages:

1. Education: The CC sent the ESASO Classification paper to each PC, including the 4 standard images defining the stages of DM (Fig. 1–4): Stage 1 (S1) = Early DME; Stage 2 (S2) = Advanced DME; Stage 3 (S3) = Severe DME, Stage 4 (S4) =Atrophic Maculopathy, along with an exhaustive description of the distinctive features of each stage.
2. Retrospective validation: PCs were asked to classify a minimum of 30 SD-OCT images of DM found in their archives or during daily activity into the four ESASO stages (S1-S4). The SD-OCT images were selected according to the following criteria: evidence of DME, defined as the presence of intraretinal or subretinal fluid in the central macula, or evidence of atrophic maculopathy; absence of evident masking artifacts from ocular media or intraretinal features (e.g. hard exudates); high image quality to grade the various biomarkers; absence of any macular condition unrelated to DM. The SD-OCT images were anonymized and sent to the CC together with the assigned stage. The CC blindly re-staged the images and kept the two separate datasets for statistical comparisons.
3. Prospective validation: the CC selected 22 SD-OCT images representative of various stages of DM and sent them to PCs. The images were the same for

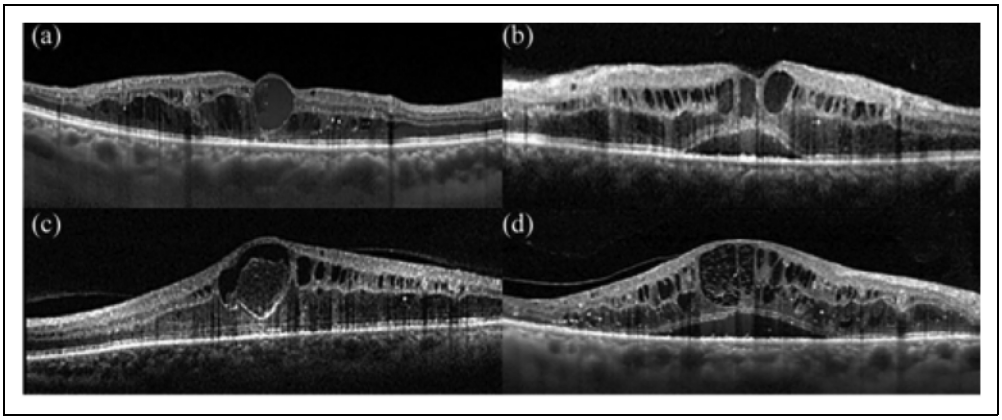

Figure 2. Reference OCT-images of Advanced DME.

all PCs and blindly classified by CC as: S1: 6 cases, S2: 6 cases, S3: 5 cases, S4: 5 cases. The PCs were asked to blindly re-classify the SD-OCT images according to the same criteria.

The staging assigned by the PCs during the retrospective phase was used to determine the classification concordance. The comparison between the staging assigned by each PC during the prospective phase was used to calculate the inter-operator agreement.

All SD-OCT images evaluated in the validation process were captured with the same type of instrument (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany).

Statistical Analysis

Assessments from PCs and CC were cross-tabulated and the overall concordance between the raters was calculated as the ratio between the sum of the absolute frequencies on the main diagonal and the total number of observations. The kappa statistics was calculated to consider concordance as randomly determined: values of kappa greater than 0.75 indicate an excellent concordance beyond chance.[7] The symmetry of the contingency table in terms of off-diagonal cells was evaluated by the McNemar-Bowker test.

The inter-operator agreement on the 22 images prospectively evaluated was calculated with the Krippendorff's alpha coefficient for ordinal data. Values greater than 0.90 were interpreted as excellent agreement.[8]

No missing data were present in the dataset. All analyses were performed using IBM-SPSS v.27.0 and R v. 4.1.0, package 'krippendorff's alpha', as statistical software.

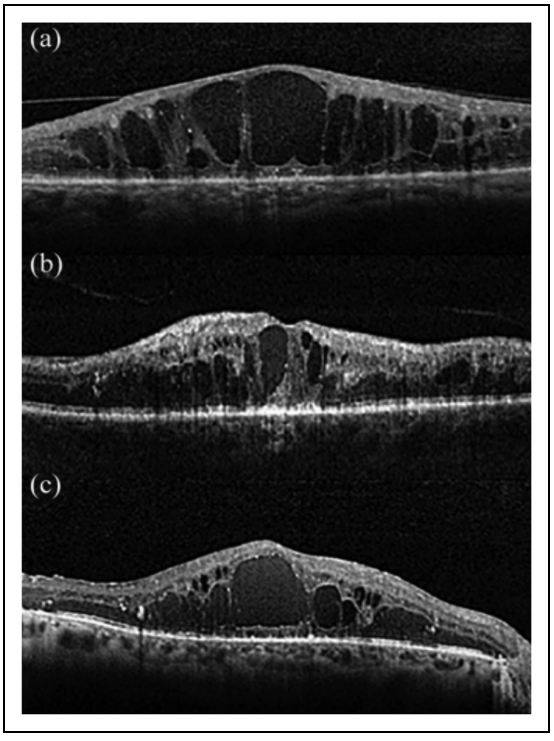

Figure 3. Reference OCT-images of Severe DME.

Results

Retrospective validation: Eighteen out of 21 invited retinal Centers agreed to participate to the study and provided the minimum number of cases requested for the retrospective analysis.

The CC received a total of 625 images. Seventeen images (2.7%) were discarded for the following reasons: 7 were of poor image quality, 5 were not fovea-centered, 3 had marking artifacts due to hard exudates, and 2 because of concurrent macular disease not related to DM. A total of 608 images were eventually included in the retrospective arm of the study.

The overall concordance between the staging assigned by the PCs and by the CC was 89.8% (546 out of 608 cases) (Kappa = 0.83 (95% CI: 0.78–0.87); $p<0.0001$) (Table 1). In 99.5% of cases (605 out of 608) concordance did not differ by more than one stage. The discrepancies in classification were 62 (10.8%). Of these, 27 (43.5%) were underestimations compared with CC staging, and 35 (56.5%) were overestimations. The difference between the frequency of underestimations and overestimations was not statistically significant at the McNemar-Bowker test ($p=0.42$).

Considering each stage separately, the PCs sent 148 images classified as S1. The concordance with CC in this group was 89.2%, with 16 images (10.8%) overestimated and classified as S2. A total of 337 images were classified by PCs as S2, and the concordance in this group was 92.0%, with 11 images (3.3%) underestimated and classified

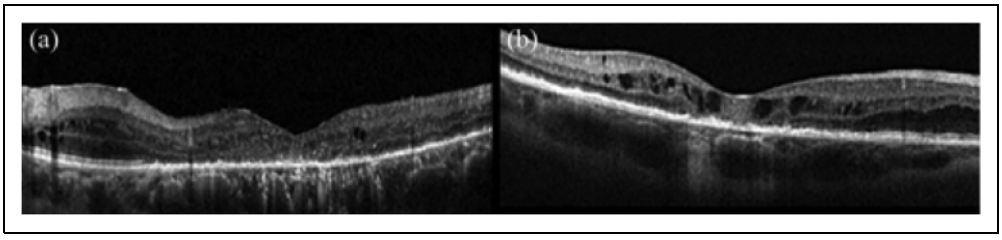

Figure 4. Reference OCT-images of Atrophic Maculopathy.

as S1, and 16 images (4.7%) overestimated and classified as S3. A total number of 111 images were sent and classified as S3, reaching a concordance of 88.3%; 1 image was underestimated to S1 (0.9%), and 9 images (8.1%) underestimated to S2, while 3 images (2.7%) were overestimated and classified as S4. Only 12 images from all 18 PCs were staged as S4 and this number was too small to reach a statistically significant concordance; therefore the analysis for S4 was limited to the prospective validation.

Prospective validation: 3 out of 18 PCs failed to meet the deadline established for images evaluation, and were excluded from this phase of the study. Fifteen PCs staged 22 images for a total number of 330 cases. PCs assigned the same staging in 308 images, reaching an inter-operator agreement of 93.0% (Krippendorff's Alpha = 0.953, 95% CI: 0.929–0.977, p<0.0001). The inter-operator agreement rate is reported in Figure 5. The discrepancy of the 22 images was always within one stage, with 13 case of underestimation (56.5%) and 10 cases of overestimation (43.5%). The difference between the frequency of underestimations and overestimations was not statistically significant at the McNemar-Bowker test (p=0.63).

For S1 cases the agreement was 94.4% (85 out of 90 cases), and 5 out of 90 cases (5.6%) were overestimated and classified as S2. For S2 cases, the agreement was 87.8%, and 7 out of 90 cases (7.8%) were underestimated and classified as S1, while 4 out of 90 cases (4.4%) were overestimated as S3. For S3 cases, the agreement was 90.7%, and 6 out of 75 cases (8.0%) were underestimated as S2, while 1 out of 75 cases (1.3%) was overestimated as S4. 75 out of 75 (100%) S4 cases were correctly classified.

Table 1. Results of the retrospective phase of validation: staging assigned by the participating centers (PCs, in column) and by coordinating centers (CC, in line).

		PCs Staging				
		1	2	3	4	Total
CC Staging	1	132	16	0	0	148
	2	11	310	16	0	337
	3	1	9	98	3	111
	4	1	1	4	6	12
Total		145	336	118	9	608

Discussion

In this study, we tested the reproducibility and clinical validity of ESASO Classification. The validation process was carried out in three consecutive steps. In a first phase, the CC instructed 18 Italian ophthalmic centers (PCs) on the correct staging of DM according to ESASO Classification. In a second step, the CC blindly evaluated the concordance with the staging assigned by PCs to 608 OCT images collected during daily activity . In a third step, we analyzed the inter-observer agreement between the staging blindly assigned by each PCs to 22 OCT images selected by CC. The staging concordance and the inter-observer agreement were excellent, 89.8% (Kappa = 0.83) and 93.0% (Krippendorff's Alpha = 0.95) respectively. In both phases only three images were classified with an error of more than one stage.

ESASO Classification is an innovative morphological grading of DM based on SD-OCT parameters (biomarkers) known to be representative of the level of retinal damage.[6] It divides DM in 4 different stages which are considered as

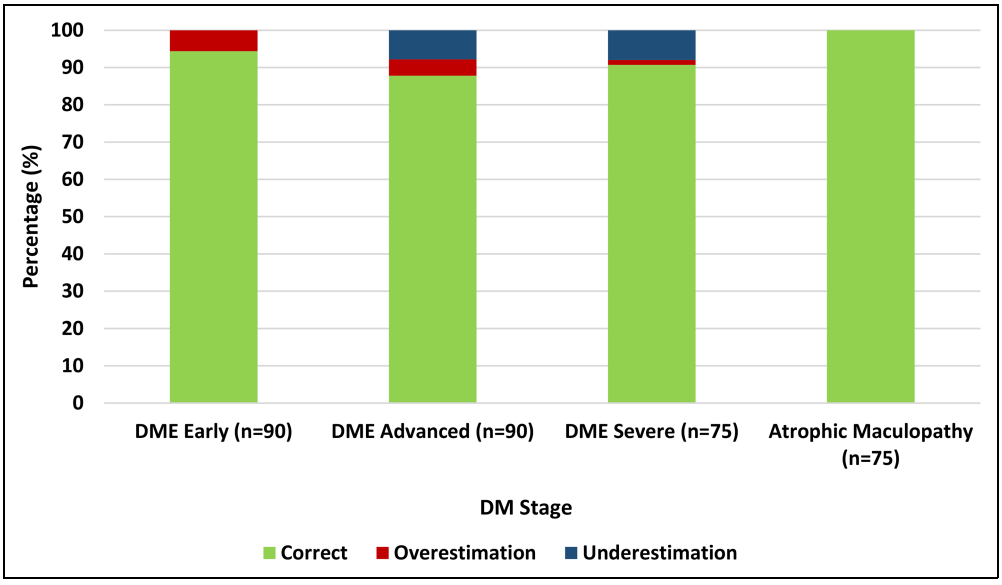

Figure 5. Inter-operator agreement rate between the staging assigned by the participating centers (PCs) in the prospective phase of validation.

progressive severity steps of the disease. To be easily reproducible in clinical practice even by non-retinal specialists this classification includes standard figures of the four stages of progression. A precise numerical score associated with each DM stage is also provided for scientific purposes. ESASO classification is focused in describing the progression of DM and differs from other published classifications in which the pathology is categorized according to location (central vs non-central),[9] extension (focal vs diffuse)[10] or nature (vasogenic vs non-vasogenic).[11,12]

The high resolution of OCT images available nowadays allows us to define the grade of retinal damage generated by the breakdown of blood retinal barrier secondary to diabetes. Progressive staging of DM is important in clinical practice and for scientific purposes, since it may lead to important therapeutic and prognostic implications.

The strong results achieved in this study confirm that ESASO Classification may be considered as an easy and reproducible method to describe the progression of DM in every day clinical practice. As a validated and repeatable staging system, it can also encourage an objective comparison between the effectiveness of the different treatment options, as well as of the management of DM in different ophthalmic centers.

Conclusions

This validation process shows that ESASO Classification may be a reproducible but also exhaustive method to grade the progression of DM in four stages (Early, Advanced, Severe DME, and Atrophic Maculopathy). Using a common and validated classification to describe the progression of retinal damage offers several clinical and scientific advantages, and we hope that this method may be diffusely used both for clinical and scientific purposes.

Abbreviations

CC	Coordination Center
DM	Diabetic Maculopathy
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
SD-OCT	Spectral-Domain Optical Coherence Tomography
PC	Participating Center

Disclosure

Maria Vittoria Cicinelli and ***Francesco Bandello*** confirm they are, respectively, an editorial assistant and the Editor in Chief of this journal and were not involved in the peer review process of this paper.

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Supplemental Material

Supplemental material for this article is available online.

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