

Diabetic Macular Edema: What Is Focal and What Is Diffuse?

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- **PURPOSE:** To review the available information on classification of diabetic macular edema (DME) as focal or diffuse.
- **DESIGN:** Interpretive essay.
- **METHODS:** Literature review and interpretation.
- **RESULTS:** The terms *focal diabetic macular edema* and *diffuse diabetic macular edema* frequently are used without clear definitions. Published definitions often use different examination methods and often are inconsistent. Evaluating published information on the prevalence of focal and diffuse DME, the responses of focal and diffuse DME to treatments, and the importance of focal and diffuse DME in assessing prognosis is hindered because the terms are used inconsistently. A newer vocabulary may be more constructive, one that describes discrete components of the concepts such as extent and location of macular thickening, involvement of the center of the macula, quantity and pattern of lipid exudates, source of fluorescein leakage, and regional variation in macular thickening and that distinguishes these terms from the use of the term *focal* when describing one type of photocoagulation technique. Developing methods for assessing component variables that can be used in clinical practice and establishing reproducibility of the methods are important tasks.
- **CONCLUSIONS:** Little evidence exists that characteristics of DME described by the terms *focal* and *diffuse* help to explain variation in visual acuity or response to treatment. It is unresolved whether a concept of focal and diffuse DME will prove clinically useful despite frequent use of the terms when describing management of DME. Further studies to address the issues are needed. (Am J Ophthalmol 2008;146:649–655. © 2008 by Elsevier Inc. All rights reserved.)

THE TERMS *FOCAL* AND *DIFFUSE* ARE USED FREQUENTLY to differentiate two types of diabetic macular edema (DME), although these two terms have not been defined consistently in the literature.^{1–16} Focal

DME defined in a variety of ways has been reported to be more common than diffuse DME, but many cases of DME subjected to these definitions have mixed features, making a clear distinction difficult.^{17–21} Focal DME has been associated with less macular thickening, better visual acuity (VA), and less severe retinopathy severity.²² Some authors have implied that the classification is predictive regarding outcomes after various treatments, although the Early Treatment Diabetic Retinopathy Study (ETDRS), when defining the terms with respect to the source of fluorescein leakage, did not support such a conclusion.^{10,12,23–27} Others have contended that focal and diffuse DME differ in the need for fluorescein angiography (FA) as a guide in planning focal or grid laser treatment.¹³ A more frequent association of diffuse DME than focal DME with subretinal fibrosis and atrophic creep after macular laser photocoagulation for DME has been reported.²⁸ Critical evaluation of the evidence to support these assertions is important, but is hindered because definitions often are lacking or are unclear.^{5–10,13,14,21,25,29–43} Additional confusion may ensue because the term *focal* is used to describe a technique of applying laser directly to microaneurysms when treating DME with focal or grid photocoagulation.⁴⁴

The published definitions for focal and diffuse DME have been based on four examination methods, including fundus biomicroscopy, color fundus photography, FA, and optical coherence tomography (OCT). These methods have been used singly and in combination in definitions. The list of published definitions for focal and diffuse DME is large, and the potential confusion arising from so many possible meanings for the two terms is apparent.

CLINICAL EXAMINATION

SUPPLEMENTAL TABLES 1 THROUGH 7 (AVAILABLE AT [AJO.com](http://ajoc.com)) summarize the frequency with which various definitions have been used for the different methods. The ETDRS defined clinically significant DME as edema satisfying any one of the following three criteria: 1) any retinal thickening within 500 μm of the center of the macula, 2) hard exudates within 500 μm of the center of the macula with adjacent retinal thickening, or 3) retinal thickening

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at least 1 disc area in size, any part of which is within 1 disc diameter of the center of the macula. The definition was based on analysis of stereo color fundus photographs by trained graders without the use of the terms *focal* or *diffuse* and also was used by clinicians using stereo slit-lamp biomicroscopy to determine whether laser retreatment was indicated. The Global Diabetic Retinopathy Project Group based its definition of DME on clinical examination results alone, without reference to the terms *focal* or *diffuse*. This group defined DME as present or absent based on thickening or lipid exudates in the macula. When present, DME was subclassified into mild, moderate, or severe, depending on the distance of the thickening and exudates from the fovea.⁴⁵

Some authors who use FA and OCT to evaluate patients nevertheless conceive of classifying DME as diffuse or focal based on clinical examination results alone.^{32,36,46} A paucity of lipid exudates has been associated with diffuse edema in ophthalmoscopic definitions, whereas the presence of lipid and lipid rings have been associated with focal edema.^{4,13,18,35,46-49} Area has been used by several authors as a discriminating point between focal and diffuse edema, but estimation of area by slit-lamp examination is subject to error.^{48,49} Jeppesen and Bek required absence of edema at the center of the macula for focal DME, but others did not.⁴⁹

COLOR FUNDUS PHOTOGRAPHS

DEFINITIONS INVOLVING COLOR FUNDUS PHOTOGRAPHS often involve area criteria. Larssen and associates state that “[d]iffuse macular edema was defined as having two or more disc areas of retinal thickening and involving the center of the macula” and that “[f]ocal edema was defined as an area of retinal thickening less than 2 disc areas in diameter not affecting the center of the macula.”⁵⁰ The cutpoint for area and the necessity of involvement of the macular center for defining diffuse edema have not been uniform. Kang and associates chose diffuse DME to mean an area of retinal thickening greater than 1 disc area rather than 2 disc areas and did not require center involvement.²²

Some authors imply that increased lipid exudates correlate with a more focal type of DME.⁴⁶ Others have defined focal edema in terms of having circinate rings of exudation.^{4,18,48} Yet others have stressed that diffuse edema has a paucity of lipid exudates.^{28,47} Lovestam-Adrian and Agardh categorize DME into diffuse DME and three other subcategories based on patterns of hard exudates without using the term *focal DME*.²⁸ In general, the fundus photographic criteria mirror the characteristics of published ophthalmoscopic definitions of focal and diffuse DME.

FLUORESCEIN ANGIOGRAPHY

IN THE ETDRS, DME WAS DEFINED CLINICALLY FROM STEREOSCOPIC biomicroscopy without reference to focal or diffuse descriptions of that clinical examination. As stated in ETDRS Report No. 5, “Fluorescein leakage without retinal thickening was not included as part of the definition of macular edema in the ETDRS.”⁵¹ However, FAs were analyzed by a reading center and the source of fluorescein leakage was graded categorically by proportion of leakage originating from microaneurysms for classification of edema as focal or diffuse. Eyes with 67% or more of leakage associated with microaneurysms were classified as focal, those with 33% to 66% of leakage associated with microaneurysms were classified as intermediate, and those with less than 33% of leakage associated with microaneurysms were classified as diffuse.²³ Others have adopted this definition.⁵² Historically, the reproducibility of grading FAs for leakage source has been only fair.⁵² Given that variable leakage patterns can occur in the same eye and the subjective nature of this assessment, it is doubtful that this question alone adequately categorizes eyes along the focal or diffuse spectrum.

The use of the term *focal* in the ETDRS and elsewhere can be confusing. It is used in one sense in the FA grading scheme, and in another sense in the description of laser treatments.^{27,53} In the grading scheme, fluorescein leakage sites distinct from microaneurysms do not influence grading with respect to focality. However, the focal part of focal and grid laser treatment includes treatment directed to microaneurysms and other, nonmicroaneurysmal leakage sites such as dilated capillaries.⁵⁴

Many research groups besides the ETDRS have subdivided DME into focal and diffuse categories based on FA characteristics.^{8,12,22,39,40,43,55,56} Some groups do not specify the differences between focal and diffuse categories.^{8,22} A subjective area criterion is used by some authors.²⁹ Others add a more objective criterion, requiring retinal thickening of two or more disc areas involving the foveal avascular zone or all four quadrants of the macula.^{12,15,57-60} Leakage from microaneurysms is included in some definitions, but not in others.^{55,61,62} Other authors exclude an area criterion in their definition of diffuse DME.⁹ Chieh and associates use a FA based definition of diffuse and focal DME in which cystoid macular edema is used as a criterion to place an eye into the diffuse category and out of the focal category.⁴³ Ciardella and associates also use the presence of cystoid spaces on FA as a criterion for diffuse DME.⁴

Blankenship reported an alternative definition based on FA by counting the number of leakage sites in a 30-degree photograph centered on the fovea 60 seconds after the fluorescein injection. Eyes with six or fewer leakage sites were classified as focal, whereas eyes with seven or more leakage sites were classified as diffuse.²⁶

As a practical matter, there seems to be a trend toward decreasing use of FA in management of DME. For example, in a 1998 audit of DME management, only 19.5% of British

ophthalmologists treating DME with focal laser photocoagulation obtained a FA before treatment.¹¹ In a 2007 study from the Diabetic Retinopathy Clinical Research Network (DRCR.net), 50% of eyes were managed without FA.⁶³ Any system of classifying DME that relies substantially on FA will suffer from inutility by the large minority and possibly the majority of clinicians who eschew this ancillary study in their management of the condition. This trend in use of FA may change if some evidence of usefulness in planning treatment or predicting outcome is discovered, but despite extensive investigation, this has not occurred.^{13,23,64}

OPTICAL COHERENCE TOMOGRAPHY

THE USE OF OCT TO DEFINE EDEMA AS FOCAL OR DIFFUSE HAS been developed from two differing perspectives—that of the regional map and that of cross-sectional scans. In the false color map, a sense of focality can be obtained when isolated islands of hot colors are surrounded by larger areas of cool colors, but this is difficult to quantitate. Browning and Fraser suggested that diffuse DME be understood to imply an increasing number of elevated subfields on the map display.⁶⁵ Sadda and associates developed software allowing areas of thickening to be calculated from OCT maps, and one could conceive of using this software to incorporate area criteria in an OCT-based definition of focal or diffuse edema.⁶⁶

Kim and associates based a definition of diffuse edema on morphologic analysis of cross-sectional scans.⁶⁷ Diffuse edema is defined as thickened areas of lower reflectivity in the outer retina but specifically without cystoid spaces.⁶⁷ Brasil and associates modified this idea by additionally stipulating that the retina show reduced internal reflectivity even in the inner retina and that the retinal thickness exceed 200 μm with the Stratus OCT scanner (Zeiss Meditec, Dublin, California, USA).^{68,69} No analogous definition of focal DME has been put forth. Definitions that are based on the morphologic features of cross-sectional scans risk dependence on scanner technology. The Stratus OCT has finer resolution than the earlier versions with better ability to discriminate small cysts. Thus, eyes categorized as diffuse DME by the OCT 2 scanner may be categorized as having cysts by a Stratus OCT scanner and may be excluded from some definitions of diffuse DME.⁶⁸ Chieh and associates claim that “some cystoid spaces demonstrated by OCT will be present in most if not all patients with diffuse macular edema.”⁴³

HYBRID DEFINITIONS

HYBRID DEFINITIONS HAVE BEEN USED FREQUENTLY TO define diffuse DME, but not focal DME. The definitions can be categorized into a subgroup using clinical examination and FA criteria and a subgroup using clinical examination, FA, and OCT criteria. The differences in criteria

between the studies are summarized in Supplemental Tables 1 and 2 available at AJO.com, along with undefined terms. Broadly speaking, the definitions differ in how much of the macula must be thickened or involved with fluorescein leakage, how many lipid exudates there are, whether cysts are present on FA, and how thick the central subfield must be on OCT.^{3,25,62,68,70–76}

POTENTIAL PROBLEMS WITH DIFFERENT DEFINITIONS

LOBO AND ASSOCIATES SIMULTANEOUSLY OBTAINED color fundus photographs, images with the Retinal Leakage Analyzer (Talia Technology, Lod, Israel) and thickness measurements with the Retinal Thickness Analyzer (Talia Technology) in diabetic eyes without and with retinopathy.^{77,78} They found that the areas of retinal leakage frequently did not coincide with the areas of increased retinal thickness. They also found, counterintuitively, that microaneurysms showed relatively little leakage and over time tended to show progressively less leakage. This raises the possibility that definitions of focal leakage by different methods may not be congruent.

When clinicians are asked to classify DME as focal or diffuse, the results may differ from nonclinical classifications. In a British prospective survey of laser treatment for DME in 546 patients, 8.6% of cases were classified as diffuse, 87.4% of cases were focal, 2.6% of cases were ischemic, and 1.4% of cases were indeterminate based on nonstandardized clinical assessment.¹¹ In contrast, using the Wisconsin Reading Center’s FA scheme for fluorescein source leakage to categorize the eyes from the DRCR.net Study of two methods of laser photocoagulation, 60% of eyes had focal edema, 7% were intermediate, 24% were diffuse, 4% were indeterminate, and 5% had no fluorescein leakage (data not shown). The 27% discrepancy between fractions categorized as focal by the two methods may reflect different samples, but also may suggest that the clinical and photographic methods capture different information about these eyes and suggests that caution is required in implicitly comparing statements about focal DME defined in different ways.

CLAIMS ABOUT DIFFUSE AND FOCAL DIABETIC MACULAR EDEMA

MANY AUTHORS HAVE CLAIMED THAT DIFFUSE DME IS refractory to macular photocoagulation and that diffuse DME is a prognostic factor for poorer VA at follow-up, but the evidence for these claims comes from case series and not prospective clinical trials in which strict definitions were applied.^{2,16,24,57,79,80} Others have suggested that diffuse DME responds better to intravitreal triamcinolone injection and focal DME to focal laser photocoagulation.^{43,62,81} The evidence to support the claims does not arise from studies

designed to test the issue, but rather from qualitative comparisons across studies of different designs.^{43,81} In one study of diffuse DME, combined therapy with intravitreal triamcinolone injection followed by focal laser photocoagulation produced more logarithm of the minimum angle of resolution VA improvement at three and six months than intravitreal triamcinolone monotherapy.⁷⁴

The ETDRS looked at the source of fluorescein leakage as a possible factor that may modify the beneficial effect of photocoagulation for DME on the development of moderate visual loss and found no difference when comparing eyes with leakage classified as predominantly focal and those classified as “intermediate to diffuse” (there were too few eyes with predominantly diffuse leakage for analysis).²³ In contrast, in an earlier small randomized trial comparing photocoagulation with no treatment for DME that used a different definition of focal and diffuse DME from that of the ETDRS, Blankenship reported no statistically significant differences between treated and untreated eyes and offered the subjective impression that “the strongest evidence of a treatment benefit occurred in those eyes with pre-treatment focal fluorescein leakage.”²⁶ More recently, Arevalo and associates reported that “[their] results indicate that intravitreal bevacizumab injections may have a beneficial effect on macular thickness and [VA], independent of the type of macular edema that is present (focal vs diffuse),”¹⁰ yet the authors did not define focal and diffuse DME in the article and did not perform a subgroup analysis by DME type.

A FRESH LOOK AT THE DEFINITIONS

WITHIN THE [DRCR.NET](http://www.drcr.net), A WORKING GROUP HAS BEEN ATTEMPTING to clarify the terms *focal DME* and *diffuse DME*. Its purpose is to determine if definitions can be developed that are clinically applicable and reproducible. Because of a variety of associations attached to the terms *focal DME* and *diffuse*

DME, it may be more constructive to recast the discussion with newer terms describing discrete parts of the concepts such as extent and location of thickening, involvement or not of the center of the macula, quantity and pattern of lipid exudates, source of fluorescein leakage, and a term designed to quantitate the regional variation in macular thickening. An obstacle in assessing the usefulness of any reformulation of the concept will be establishing reproducibility of methods of assessing the component variables. Cutpoints for classification of these component variables that are clinically meaningful will need to be determined. More reproducible methods of grading source and patterns of leakage, area of thickening, and quantitation of hard lipid exudates will need to be devised, because current methods show disappointing variability and are difficult to apply by clinicians in practice (unpublished data). Our inclination would be to suggest specific improved definitions for these concepts here, but we do not have the evidence to substantiate that our suspected improved definitions have predictive power. Work within the [DRCR.net](http://www.drcr.net) is underway to test definitions and to report on their performance

It is possible that a concept of focal and diffuse edema, possibly expressed with a new vocabulary, will prove to be important in explaining baseline variance in VA or in predicting treatment outcomes, as many authors have claimed. It is also possible that it will not add to the usefulness of variables of proven importance such as baseline central subfield mean thickness, age, hemoglobin A1C, and central and inner paracentral fluorescein leakage severity.⁸² In clinical trials involving reading center gradings of color photographic and FA images, further work will be required before definitions of focal and diffuse DME that correlate well with clinical impressions can be presented with confidence. Until more rigorous studies have been carried out to investigate the issues discussed, we suggest that authors writing about DME use the terms *focal* and *diffuse* with caution, providing clear definitions that can be replicated by others.

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THE DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK

- A current list of the Diabetic Retinopathy Clinical Research Network and investigator financial disclosures is available at www.drcr.net.

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SUPPLEMENTAL TABLE 1. Diffuse Edema: Clinical Examination or Fundus Photography

Reference	Center of the Macula Thickened?	Lipid Exudates	Pattern of Lipid	Area	Vitreomacular Traction
Blankenship, 1979					
Bresnick, 1983 ⁸³	Implied	Absence ^a or paucity	NPD	Extensive ^a areas	NPD
Bresnick, 1986	Implied	Usually ^a absent	NPD	NPD	NPD
ETDRS, 1995					
Akduman and Olk, 1999; Akduman and Olk 1997	NPD	NPD	NPD	≥ 2 DAs	NPD
Lovestam-Adrian and Agardh, 2000	Within 1 DD of center	None within 1 DD of center	NPD	≥ 1 DD	NPD
Martidis and associates, 2002	Implied	Scarcity ^a	NPD	Extensive ^a areas	NPD
Funatsu and associates, 2003 ⁸⁶					
Audren and associates, 2004	Yes	Few ^a	NPD	NPD	No
Ciardella and associates, 2004	Yes	NPD	NPD	Entire macula	NPD
Kang and associates, 2004	NPD	NPD	NPD	≥ 1 DA	NPD
Laursen and associates, 2004	Yes	NPD	NPD	≥ 2 DAs	NPD
Massin and associates, 2004	Yes	Few ^a	NPD	NPD	No
Bonini-Filho and associates, 2005	Yes	NPD	NPD	NPD	NPD
Cartier and associates, 2005	Yes	Few ^a or no exudates	NPD	NPD	NPD
Cardillo and associates, 2005	Yes	Few ^a	NPD	NPD	NPD
Luttrull and associates, 2005 ⁸⁴	Yes	NPD	NPD	Involves all 4 quadrants of macula	NPD
Tunc and associates, 2005	NPD	NPD	NPD	NPD	NPD
Audren and associates, 2006	Yes	Few ^a	NPD	NPD	NPD
Jensen and Knudsen, 2006	NPD	NPD	NPD	Nearly the entire macula ^a	NPD
Kang and associates, 2006	Within 1 DD of center	NPD	NPD	≥ 1 DA	NPD
Kim and associates, 2006					
Zein and associates, 2006	Yes	NPD	NPD	All 4 quadrants of macula involved	NPD
Brasil and associates, 2007	Yes	NPD	NPD	NPD	NPD
Carpineto and associates, 2007	Yes	NPD	NPD	Entire macula ^a	NPD
Shimura and associates, 2007, ⁸⁵	NPD	NPD	NPD	≥ 2 DAs	NPD
Shimura and associates, 2004					
Kang, 2008	Yes	NPD	NPD	NPD	No

DA = disk area; DD = disk diameter; either = yes or no; ETDRS = Early Treatment Diabetic Retinopathy Study; FAZ = foveal avascular zone; GS = graded separately; NPD = not part of definition.

Blank cells indicate that the method is not used in the definition in the reference of the row in question. This table does not reflect an exhaustive review of the literature.

^aUndefined term.

SUPPLEMENTAL TABLE 2. Diffuse Edema: Fluorescein Angiography

Reference	Source of Leakage	Area of Leakage	Relationship to Center of Macula	Cysts	Associated with Nonperfusion?
Blankenship, 1979	≥ 7 leakage sites ^a	NPD	NPD	NPD	NPD
Bresnick, 1983 ⁸³	Entire capillary system	Extensive ^a areas	Implied to involve center	Yes	Yes
Bresnick, 1986	Microaneurysms, capillaries, and arterioles	Throughout posterior pole ^a	Implied to involve center	NPD	NPD
ETDRS, 1995	< 33% of leakage associated ^a with microaneurysms	NPD	NPD	NPD	NPD
Akduman and Olk, 1999; Akduman and Olk 1997	NPD	≥ 2 DAs	Involves FAZ	NPD, GS	NPD
Lovestam-Adrian and Agardh, 2000					
Martidis and associates, 2002	Posterior ^a capillary bed	Extensive ^a areas	Implied to involve center	Yes	NPD
Funatsu and associates, 2003 ⁸⁶	Diffusely ^a dilated capillaries	Throughout posterior pole ^a	Involves center	NPD	NPD
Audren and associates, 2004	Diffuse ^a	Most ^a of macula	Implied to involve center	NPD	NPD
Ciardella and associates, 2004	Diffuse ^a	Entire ^a macula	Involves center	Yes	NPD
Kang and associates, 2004	Ill-defined ^a	Widespread ^a	Involves circumference of the fovea	Either	NPD
Laursen and Knudsen, 2004					
Massin and associates, 2004	Diffuse ^a	Most ^a of macula	Implied to involve center	NPD	NPD
Bonini-Filho and associates, 2005	Diffuse ^a	Most ^a of macular area	Involves center	NPD	NPD
Catier and associates, 2005					
Cardillo and associates, 2005	Diffuse ^a	Most ^a of macula	Involves center	NPD	NPD
Luttrull and associates, 2005 ⁸⁴	NPD	NPD	NPD	No	No
Tunc and associates, 2005	MAS, dilated capillaries	Entire ^a macula	NPD	NPD	No
Audren and associates, 2006	Diffuse ^a	NPD	Involves center	NPD	NPD
Jensen and associates, 2006					
Kang and associates, 2006	Diffuse ^a	NPD	Involves center	NPD	NPD
Kim and associates, 2006					
Zein and associates, 2006	NPD	All 4 quadrants of macula involved	Involves center	NPD	NPD
Brasil and associates, 2007					
Carpineto and associates, 2007	Not MAS	Throughout posterior pole ^a	Involves center	Either	NPD
Shimura and associates, 2007, ⁸⁵ Shimura and associates, 2004	NPD	NPD	Involves FAZ	NPD	NPD
Kang, 2008	Diffuse ^a	NPD	Involves center	NPD	NPD

DA = disk area; DD = disk diameter; either = yes or no; ETDRS = Early Treatment Diabetic Retinopathy Study; FAZ = foveal avascular zone; GS = graded separately; NPD = not part of definition; MAS = microaneurysms.

Blank cells indicate that the method is not used in the definition in the reference of the row in question. This table does not reflect an exhaustive review of the literature.

^aUndefined term.

SUPPLEMENTAL TABLE 3. Diffuse Edema: Optical Coherence Tomography

Reference	CSMT Cutpoint	Morphologic Features
Blankenship, 1979		
Bresnick, 1983 ⁸³		
Bresnick, 1986		
ETDRS, 1995		
Akduman and Olk, 1999; Akduman and Olk, 1997		
Lovestam-Adrian and Agardh, 2000		
Martidis and associates, 2002		
Funatsu and associates, 2003 ⁸⁶		
Audren and associates, 2004	> 300 μ m	No vitreomacular traction
Ciardella and associates, 2004		
Kang and associates, 2004		
Laursen and associates, 2004		
Massin and associates, 2004	> 380 μ m	No vitreomacular traction
Bonini-Filho and associates, 2005		
Catier and associates, 2005		
Cardillo and associates, 2005		
Luttrull and associates, 2005 ⁸⁴		
Tunc and associates, 2005		
Audren and associates, 2006		
Jensen and Knudsen, 2006		
Kang and associates, 2006	> 250 μ m	Reduced reflectivity outer retina or subfoveal fluid
Kim and associates, 2006	> 200 μ m	Reduced reflectivity or expanded areas of lower reflectivity in outer retinal layers
Zein and associates, 2006		
Brasil and associates, 2007	> 200 μ m	Reduced reflectivity or expanded areas ^a of lower reflectivity in outer retinal layers
Carpineto and associates, 2007		
Shimura and associates, 2007; ⁸⁵ Shimura and associates, 2004		
Kang, 2008	> 300 μ m	Reduced reflectivity outer retina or subfoveal fluid

ETDRS = Early Treatment Diabetic Retinopathy Study.

Blank cells indicate that the method is not used in the definition in the reference of the row in question. This table does not reflect an exhaustive review of the literature.

^aUndefined term.

SUPPLEMENTAL TABLE 4. Diffuse Edema: Comments

Reference	Comments
Shimura and associates, 2007; ⁸⁵ Shimura and associates, 2004	How to determine area clinically not stated
Kang and associates, 2004	Cyst detection methodology in fluorescein angiograms and how to determine area clinically not stated
Kang and associates, 2006	How to determine area clinically not stated
Akduman and Olk, 1999; Akduman and Olk, 1997	How to determine area clinically not stated
Lovestam-Adrian and Agardh, 2000	How to determine area clinically not stated
Laursen and associates, 2004	How to determine area clinically not stated
Brasil and associates, 2007	Epiretinal membranes allowed
Kim and associates, 2006	Cysts specifically excluded from definition

SUPPLEMENTAL TABLE 5. Focal Diabetic Macular Edema: Clinical Examination or Fundus Photography

Reference	Center of the Macula Thickened?	Lipid Exudates	Pattern of Lipid	Area	Vitreomacular Traction
Blankenship, 1979					
Bresnick, 1983 ⁸³	NPD	Frequent ^a , but not necessary	Often ^a in rings	NPD	NPD
Abu El Asrar and Morse, 1991	NPD	Frequent ^a , but not necessary	Bordering area of edema	NPD	NPD
ETDRS, 1995					
Martidis and associates, 2002	NPD	NPD	NPD	NPD	NPD
Kang and associates, 2004	NPD	NPD	NPD	NPD	NPD
Ciardella and associates, 2004	NPD	Yes	Circinate	NPD	NPD
Laursen and associates, 2004	No	NPD	NPD	< 2 DAs	NPD
Jeppesen and Bek, 2006	No	Yes	NPD	area < 1 DD in diameter, > 1 DD from center	NPD
Luttrull and associates, 2005 ⁸⁴	NPD	NPD	NPD	< 4 quadrants of macula ^a	NPD
Tunc and associates, 2005	NPD	Frequent ^a , but not necessary	Often ^a circinate	NPD	NPD
Jensen and Knudsen, 2006	NPD	Yes	Circular	Limited ^a	NPD

DA = disk area; DD = disk diameter; ETDRS = Early Treatment Diabetic Retinopathy Study; NPD = not part of definition.

Blank cells indicate that the method is not used in the definition in the reference of the row in question. This table does not reflect an exhaustive review of the literature.

^aUndefined term.

SUPPLEMENTAL TABLE 6. Focal Diabetic Macular Edema: Fluorescein Angiography

Reference	Source of Leakage	Area of Leakage	Relationship to Center of Macula	Cysts	Associated with Nonperfusion?
Blankenship, 1979	< 7 leakage sites ^a	NPD	NPD	NPD	NPD
Bresnick, 1983 ⁸³	Microaneurysms, dilated capillary segments	NPD	NPD	NPD	NPD
Abu El Asrar and Morse, 1991					
ETDRS, 1995	≥ 67% of leakage associated ^a with microaneurysms	NPD	NPD	NPD	NPD
Martidis and associates, 2002	Microaneurysms, dilated capillary segments	NPD	NPD	NPD	NPD
Kang and associates, 2004	Microaneurysms and localized ^a dilated capillaries	NPD	NPD	NPD	NPD
Ciardella and associates, 2004	Microaneurysms	NPD	NPD	NPD	NPD
Laursen and associates, 2004					
Jeppesen and Bek, 2006					
Luttrull and associates, 2005 ⁸⁴	NPD	NPD	NPD	No	No
Tunc and associates, 2005					
Jensen and Knudsen, 2006	NPD	Limited ^a	NPD	NPD	NPD

ETDRS = Early Treatment Diabetic Retinopathy Study; NPD = not part of definition.

Blank cells indicate that the method is not used in the definition in the reference of the row in question. This table does not reflect an exhaustive review of the literature.

^aUndefined term.

SUPPLEMENTAL TABLE 7. Focal Diabetic Macular Edema: Comments

Reference	Comments
Blankenship, 1979	
Bresnick, 1983 ⁸³	
Abu El Asrar and Morse, 1991	
ETDRS, 1995	
Martidis and associates, 2002	
Kang and associates, 2004	
Ciardella and associates, 2004	
Laursen and associates, 2004	Method to determine area clinically not stated
Jeppesen and Bek, 2006	Method to determine area clinically not stated
Luttrull and associates, 2005 ⁸⁴	Cyst and nonperfusion detection methods not defined for fluorescein angiography
Tunc and associates, 2005	
Jensen and Knudsen, 2006	

ETDRS = Early Treatment Diabetic Retinopathy Study.

Blank cells indicate that the method is not used in the definition in the reference of the row in question. This table does not reflect an exhaustive review of the literature.