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

David J. Browning, **Michael M. Altaweel**, **Neil M. Bressler**, **Susan B. Bressler**, and **Ingrid U. Scott for the Diabetic Retinopathy Clinical Research Network**

Abstract

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 and diffuse diabetic macular edema are frequently used without clear definitions. Published definitions often use different examination modalities and are often inconsistent. Evaluating published information on prevalence of focal and diffuse DME, response of focal and diffuse DME to treatments, and importance of focal and diffuse DME in assessing prognosis is hindered because the terms are inconsistently employed. 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 will be important tasks.

Conclusion—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 usage of the terms when describing management of DME. Further studies to address the issues are needed.

Introduction

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, and less severe retinopathy severity.[22] Some authors have implied that the classification is predictive regarding outcomes following various treatments, although the ETDRS, when defining the terms with respect to the source of fluorescein leakage, did not

Corresponding Author: David J. Browning, c/o Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647; Phone: (813) 975-8690, Fax: (800) 816-7601, DRCR.netX4@jaeb.org.

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support such a conclusion.[10, 12, 23–27] Others have contended that focal and diffuse DME differ in the need for fluorescein angiography as a guide in planning focal/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 are often 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/grid photocoagulation.[44]

The published definitions for focal and diffuse DME have been based on four examination methods including fundus biomicroscopy, color fundus photography, fluorescein angiography, and optical coherence tomography (OCT). These modalities 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

Tables 1–7 (online at www.ajo.com) summarize the frequency with which various definitions have been used for the different modalities. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined clinically significant diabetic macular edema as edema satisfying any one of the following three criteria: a.) any retinal thickening within 500 microns of the center of the macula, b.) hard exudates within 500 microns of the center of the macula with adjacent retinal thickening, or c.) retinal thickening 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 use of the terms focal or diffuse, and was also used by clinicians using stereo slit lamp biomicroscopy to determine whether laser re-treatment was indicated. The Global Diabetic Retinopathy Project Group based its definition of DME on clinical examination 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 distance of the thickening and exudates from the fovea.[45] The Global Diabetic Retinopathy Project Group based its definition of DME on clinical examination 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 distance of the thickening and exudates from the fovea.[45]

Some authors who use fluorescein angiography and OCT to evaluate patients nevertheless conceive of classifying DME as diffuse or focal based on clinical examination alone.[32, 36, 46] Paucity of lipid exudates has been associated with diffuse edema in ophthalmoscopic definitions, whereas 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 require absence of edema at the center of the macula for focal DME, but others do not.[49]

Color Fundus Photographs

Definitions involving color fundus photographs often involve area criteria. Larssen and colleagues state, “Diffuse macular edema was defined as having two or more disk areas of retinal thickening and involving the center of the macula”, and “Focal edema was defined as an area of retinal thickening less than two disk areas in diameter not affecting the center of the macula”.[50] The cut-point for area and the necessity of involvement of the macular center for defining diffuse edema have not been uniform. Kang and colleagues chose diffuse DME to

mean an area of retinal thickening greater than one disk area rather than two disk 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 number 5, “Fluorescein leakage without retinal thickening was not included as part of the definition of macular edema in the ETDRS.”[51] However, fluorescein angiograms 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% of leakage associated with microaneurysms were classified as focal, those with 33–66% of leakage associated with microaneurysms as intermediate, and those with <33% of leakage associated with microaneurysms as diffuse.[23] Others have adopted this definition.[52] Historically, the reproducibility of grading fluorescein angiograms 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/diffuse spectrum.

The use of the term focal in the ETDRS and elsewhere can be confusing. It is used in one sense in the fluorescein angiogram 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/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 fluorescein angiographic 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 disk 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 colleagues use a fluorescein angiogram 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 colleagues also use the presence of cystoid spaces on fluorescein angiography as a criterion for diffuse DME.[4]

Blankenship reported an alternative definition based on fluorescein angiography 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 appears to be a trend toward decreasing use of fluorescein angiography 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 fluorescein angiogram before treatment.[11] In a 2007 study from the Diabetic Retinopathy Clinical Research Network, 50% of eyes were managed without fluorescein angiography.[63] Any system of classifying DME that relies substantially on fluorescein angiography will suffer from inutility by the large minority and possibly majority of clinicians who eschew this ancillary study in their management of the condition. This trend in usage of fluorescein angiography might change were some evidence of usefulness in planning treatment or predicting outcome to be discovered, but despite extensive investigation, such 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 the 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 colleagues have 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 colleagues have 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 colleagues have 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 microns with the Stratus OCT scanner.[68, 69] No analogous definition of focal DME has been put forth. Definitions that are based on the morphology 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 OCT 2 scanner might be categorized as having cysts by a Stratus OCT scanner, and excluded from some definitions of diffuse DME.[68] Chieh and colleagues claim “some cystoid spaces demonstrated by optical coherence tomography 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 fluorescein angiographic criteria and a subgroup using clinical examination, fluorescein angiographic and OCT criteria. The differences in criteria between the studies are summarized in tables 1 and 2 (online at www.ajo.com), along with undefined terms. In broad outline, 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 fluorescein angiography, and how thick the central subfield must be on OCT.[3, 25, 62, 68, 70–76]

Potential Problems with Different Definitions

Lobo and colleagues simultaneously obtained color fundus photographs, images with the Retinal Leakage Analyzer, and thickness measurements with the Retinal Thickness Analyzer 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 modalities might 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 fluorescein angiographic scheme for fluorescein source leakage to categorize the eyes from the DRCR network 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 might reflect different samples, but could also 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 visual acuity 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 logMAR visual acuity improvement at three and six months than intravitreal triamcinolone monotherapy.[74]

The ETDRS looked at source of fluorescein leakage as a possible factor that might 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 colleagues reported that, "Our 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 paper, and did not perform a subgroup analysis by DME type.

A Fresh Look at the Definitions

Within the Diabetic RetinopathyClinical Research Network (DRCR.net), a working group has been attempting to clarify the terms focal 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 words focal 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, as 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 Network is underway to test definitions and 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 visual acuity 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 fluorescein angiographic 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 done 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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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	implied	absence* or paucity	NPD	extensive* areas	NPD
Bresnick, 1986	implied	usually* absent	NPD	NPD	NPD
ETDRS, 1995					
Akduman, 1999; Akduman 1997	NPD	NPD	NPD	≥2DAs	NPD
Lovestam-Adrian, 2000	within 1 DD of center	none within 1 DD of center	NPD	≥1 DD	NPD
Martidis, 2002	implied	scarcity*	NPD	extensive* areas	NPD
Funatsu, 2003					
Audren, 2004	yes	few*	NPD	NPD	no
Ciardella, 2004	yes	NPD	NPD	entire macula	NPD
Kang, 2004	NPD	NPD	NPD	> 1DA	NPD
Laursen, 2004	yes	NPD	NPD	>2 DAs	NPD
Massin, 2004	yes	few*	NPD	NPD	no
Bonini-Filho, 2005	yes	NPD	NPD	NPD	NPD
Catier, 2005	yes	few* or no exudates	NPD	NPD	NPD
Cardillo, 2005	yes	few*	NPD	NPD	NPD
Luttrull, 2005	yes	NPD	NPD	involves all 4 quadrants of macula	NPD
Tunc, 2005	NPD	NPD	NPD	NPD	NPD
Audren, 2006	yes	few*	NPD	NPD	NPD
Jensen, 2006	NPD	NPD	NPD	nearly the entire macula*	NPD
Kang, 2006	within 1 DD of center	NPD	NPD	> 1 DA	NPD
Kim, 2006					
Zein, 2006	yes	NPD	NPD	all 4 quadrants of macula involved	NPD
Brasil, 2007	yes	NPD	NPD	NPD	NPD
Carpineto, 2007	yes	NPD	NPD	entire macula*	NPD
Shimura, 2007; Shimura, 2004	NPD	NPD	NPD	≥2DAs	NPD
Kang, 2008	yes	NPD	NPD	NPD	no

DD=disk diameter, DA= disk area, NPD=not part of definition, either=yes or no, mas=microaneurysms, FAZ= foveal avascular zone, GS=graded separately,

*=undefined term. Blank cells indicate that the modality is not used in the definition in the reference of the row in question. This table is not represented to reflect an exhaustive review of the literature.

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*	NPD	NPD	NPD	NPD
Bresnick, 1983	entire capillary system	extensive* areas	implied to involve center	yes	yes
Bresnick, 1986	microaneurysms, capillaries, and arterioles	throughout posterior pole*	implied to involve center	NPD	NPD
ETDRS, 1995	<33% of leakage associated* with microaneurysms	NPD	NPD	NPD	NPD
Akduman, 1999; Akduman 1997	NPD	≥2 DAs	involves FAZ	NPD, GS	NPD
Lovestam-Adrian, 2000					
Martidis, 2002	posterior* capillary bed	extensive* areas	implied to involve center	yes	NPD
Funatsu, 2003	diffusely* dilated capillaries	throughout posterior pole*	involves center	NPD	NPD
Audren, 2004	diffuse*	most* of macula	implied to involve center	NPD	NPD
Ciardella, 2004	diffuse*	entire* macula	involves center	yes	NPD
Kang, 2004	ill defined*	widespread*	involves circumference of the fovea	either	NPD
Laursen, 2004					
Massin, 2004	diffuse*	most* of macula	implied to involve center	NPD	NPD
Bonini-Filho, 2005	diffuse*	most* of macular area	involves center	NPD	NPD
Catier, 2005					
Cardillo, 2005	diffuse*	most* of macula	involves center	NPD	NPD
Luttrull, 2005	NPD	NPD	NPD	no	no
Tunc, 2005	mas, dilated capillaries	entire* macula	NPD	NPD	no
Audren, 2006	diffuse*	NPD	involves center	NPD	NPD
Jensen, 2006					
Kang, 2006	diffuse*	NPD	involves center	NPD	NPD
Kim, 2006					
Zein, 2006	NPD	all 4 quadrants of macula involved	involves center	NPD	NPD
Brasil, 2007					
Carpineto, 2007	not mas	throughout posterior pole*	involves center	either	NPD
Shimura, 2007; Shimura, 2004	NPD	NPD	involves FAZ	NPD	NPD
Kang, 2008	diffuse*	NPD	involves center	NPD	NPD

DD=disk diameter, DA= disk area, NPD=not part of definition, either=yes or no, mas=microaneurysms, FAZ= foveal avascular zone, GS=graded separately,

*=undefined term. Blank cells indicate that the modality is not used in the definition in the reference of the row in question. This table is not represented to reflect an exhaustive review of the literature.

Table 3

Diffuse Edema

OCT		
Reference	**CSMT Cutpoint**	**Morphology**
Blankenship, 1979		
Bresnick, 1983		
Bresnick, 1986		
ETDRS, 1995		
Akduman, 1999;		
Akduman 1997		
Lovestam-Adrian, 2000		
Martidis, 2002		
Funatsu, 2003		
Audren, 2004	>300μ	no vitreomacular traction
Ciardella, 2004		
Kang, 2004		
Laursen, 2004		
Massin, 2004	>380μ	no vitreomacular traction
Bonini-Filho, 2005		
Catier, 2005		
Cardillo, 2005		
Luttrull, 2005		
Tunc, 2005		
Audren, 2006		
Jensen, 2006		
Kang, 2006	>250μ	reduced reflectivity outer retina or subfoveal fluid
Kim, 2006	>200μ	reduced reflectivity or expanded areas of lower reflectivity in outer retinal layers
Zein, 2006		
Brasil, 2007	>200μ	reduced reflectivity or expanded areas* of lower reflectivity in outer retinal layers
Carpineto, 2007		
Shimura, 2007;Shimura, 2004		
Kang, 2008	>300μ	reduced reflectivity outer retina or subfoveal fluid

DD=disk diameter, DA= disk area, NPD=not part of definition, either=yes or no, mas=microaneurysms, FAZ= foveal avascular zone, GS=graded separately,

*=undefined term. Blank cells indicate that the modality is not used in the definition in the reference of the row in question. This table is not represented to reflect an exhaustive review of the literature.

Table 4

Diffuse Edema

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

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	NPD	frequent*, but not necessary	often* in rings	NPD	NPD
El Asrar, 1991	NPD	frequent*, but not necessary	bordering area of edema	NPD	NPD
ETDRS, 1995					
Martidis, 2002	NPD	NPD	NPD	NPD	NPD
Kang, 2004	NPD	NPD	NPD	NPD	NPD
Ciardella, 2004	NPD	yes	circinate	NPD	NPD
Laursen, 2004	no	NPD	NPD	<2Das	NPD
Jeppesen, 2006	no	yes	NPD	area <1 DD in diameter, > 1DD from center	NPD
Luttrull, 2005	NPD	NPD	NPD	<4 quadrants of macula[a]	NPD
Tunc, 2005	NPD	frequent*, but not necessary	often* circinate	NPD	NPD
Jensen, 2006	NPD	yes	circular	limited*	NPD

DD=disk diameter, DA= disk area, NPD=not part of definition, either=yes or no, mas=microaneurysms, FAZ= foveal avascular zone, GS=graded separately,

*=undefined term. Blank cells indicate that the modality is not used in the definition in the reference of the row in question. This table is not represented to reflect an exhaustive review of the literature.

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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*	NPD	NPD	NPD	NPD
Bresnick, 1983	microaneurysms, dilated capillary segments	NPD	NPD	NPD	NPD
El Asrar, 1991					
ETDRS, 1995	≥67% of leakage associated* with microaneurysms	NPD	NPD	NPD	NPD
Martidis, 2002	microaneurysms, dilated capillary segments	NPD	NPD	NPD	NPD
Kang, 2004	microaneurysms and localized* dilated capillaries	NPD	NPD	NPD	NPD
Ciardella, 2004	microaneurysms	NPD	NPD	NPD	NPD
Laursen, 2004					
Jeppesen, 2006					
Luttrull, 2005	NPD	NPD	NPD	no	no
Tunc, 2005					
Jensen, 2006	NPD	limited*	NPD	NPD	NPD

DD=disk diameter, DA= disk area, NPD=not part of definition, either=yes or no, mas=microaneurysms, FAZ= foveal avascular zone, GS=graded separately,

*=undefined term. Blank cells indicate that the modality is not used in the definition in the reference of the row in question. This table is not represented to reflect an exhaustive review of the literature.

Table 7

Focal Diabetic Macular Edema

Comments	
Reference	**Comments**
Blankenship, 1979	
Bresnick, 1983	
El Asrar, 1991	
ETDRS, 1995	
Martidis, 2002	
Kang, 2004	
Ciardella, 2004	
Laursen, 2004	method to determine area clinically not stated
Jeppesen, 2006	method to determine area clinically not stated
Luttrull, 2005	cyst and nonperfusion detection methodologies not defined for fluorescein angiography
Tunc, 2005	
Jensen, 2006	

DD=disk diameter, DA= disk area, NPD=not part of definition, either=yes or no, mas=microaneurysms, FAZ= foveal avascular zone, GS=graded separately,

* =undefined term. Blank cells indicate that the modality is not used in the definition in the reference of the row in question. This table is not represented to reflect an exhaustive review of the literature.