Macular Edema

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Member of Advisory Boards:
Alcon, Alimera, Allergan, Astellas, Bayer, GeneSignal, GSK, Novartis, Pfizer
Macular Edema

1. Definition – Classification

2. Frequency – Morbidity (DR, VO)

3. DR Clinical Evaluation – Macular Edema as complication

4. Biomarkers of Progression

5. Pathogenesis

6. Treatment of Macular Edema
1. Definition / Classification

Non specific sign of ocular disease

Wide variety of situations:
Diabetes, venous occlusions, trauma, uveitis, surgery, age-related macular degeneration, etc.

Retinal Edema = Increased thickening of the retina

Intracellular
Extracellular – due to a breakdown of the Blood-Retinal Barrier
Fovea - Macula

Cones in Fovea

300µ

1000µ
Clinically Significant Macular Edema (ETDRS)

Relevance for Visual Acuity - Location

1. thickening of the retina at or within 500 μm of the center of the macula;

2. hard exudates at or within 500 μm of the center of the macula (if associated with thickening of the adjacent retina);

3. zone(s) of retinal thickening of 1 DD or larger, any part of which is within 1 DD of the center of the macula.
Clinically Significant Macular Edema

- Hard exudates at or within 500 microns of center (if adjacent retina thickened)

**CLINICALLY SIGNIFICANT MACULAR EDEMA (ETDRS)**
Clinical Evaluation of DME

Replaced by **objective** measurements

Subjective
- Ophthalmoscopy
- Slit-lamp
- Stereo photography

Objective

- OCT

**Essential – Location of edema vs. fovea**
Amount of Edema

<table>
<thead>
<tr>
<th></th>
<th>Central Subfield Thickness (µm)</th>
<th>Cube Volume (mm³)</th>
<th>Cube Average Thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILM - RPE</td>
<td>325</td>
<td>14.7</td>
<td>409</td>
</tr>
</tbody>
</table>

Image of a retinal scan with annotations and a table showing measurements of thickness and volume.
Location vs. Fovea

Mapping CSME

With or Without Central Involvement (500 µm)

Fundus Photography

OCT – High Definition
- Spectral Domain
Proposed ME classification

The proposed classification for DME in an individual patient comprises:

1. **Location of edema**
   - Central-involved DME or
   - Peri-central inner-involved DME or
   - Peri-central outer-involved DME

2. **Amount of edema**
   - Mean thickness, volume and/or logOCT of location **PLUS** total volume of all 9 ETDRS subfields

3. **Vitreoretinal interface abnormalities**
   - Present/absent
     - Epiretinal membrane: present/absent/indeterminate
     - Posterior hyaloid detachment: present/absent/indeterminate

4. **Hard exudates**
   - Present/absent in central subfield
ME classification


**OCT assessment**

1. Is the central subfield involved? Yes No

1. Are the inner or outer subfields involved? Yes No

2. Volume of thickening and/or mean thickness (in the central subfield of outside the central subfield)

3. Presence of epiretinal membrane Yes No

**Clinical or retinal photographic image assessment**

4. Are there hard exudates present? Yes No

Location and extent†

* ≥2 SDs beyond the normative for the instrument
† ETDRS/Wisconsin Reading Centre descriptions
2. Frequency – Morbidity

- Diabetic retinopathy (DR) is a major cause of blindness and the primary cause of blindness in working-age individuals in developed countries\(^1\)

- DME is a common manifestation of DR\(^1,2\)

- DME is the main cause of visual impairment in patients with Type 2 diabetes\(^1,2\)

- Although DME does not cause total blindness, it frequently leads to a severe loss of central vision\(^1\)

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DME, diabetic macular edema
DR, diabetic retinopathy

Prevalence of diabetes expected to approximately double globally between 2000 and 2030\textsuperscript{1}

Number of diabetes cases estimated to reach 300 million worldwide by 2025\textsuperscript{2,3}

Burden of DME likely to increase due to predicted rise in diabetes prevalence\textsuperscript{3}

In the UK, prevalence of DME\textsuperscript{4}:
- Estimated to be 187,842 in 2010
- Expected to increase to 235,602 in 2020

Venous Occlusions - Frequency

- Macular Edema - 5-15% BRVO

(over 1 year period)

- 18% achieves resolution by 4.5 months
- 41% achieves resolution by 7.5 months
3. Clinical characterization

Diabetic retinopathy: a progressive disease

Nonproliferative DR (NPDR)
- Microaneurysms, intraretinal haemorrhages
- Barrier breakdown (leakage) – exudates
- Capillary closure
- Complication – DME

Proliferative DR (PDR)
- Neovascularisation
- Vitreous/preretinal haemorrhage

Symptoms
- None
- Vision loss
- Glare
- None
- Vision loss
- Floaters

Diabetic retinopathy (DR)

Nonproliferative DR

Leakage/microaneurysms → Inflammation
Focal thickening

Capillary closure → Ischemia

Complications

Macular edema

Proliferative DR

What is Diabetic Macular Edema?

- DME can develop at any stage of DR and is the most common cause of visual loss in nonproliferative DR\(^1\)
  - Retinal **thickening** due to accumulation of fluid
  - Accumulation of **hard exudates**\(^2\)
  - **Microaneurysms** in the central 1000\(\mu\)

- Severity of DME is based on distance of retinal thickening and/or exudates from the macular centre\(^2\)  - **Location to fovea**

Different evolution in different patients with similar metabolic control and duration of disease

- Not all patients develop persistent macular edema
- Not all patients develop neovascularization
# NPDR phenotypes: type 2 diabetes

<table>
<thead>
<tr>
<th>Phenotype A</th>
<th>Slow progression (&lt;2 red dots/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated ageing process (diabetes)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype B</th>
<th>Rapid progression (&gt;2 red dots/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased flow</td>
</tr>
<tr>
<td></td>
<td>Alterations of BRB – leakage</td>
</tr>
<tr>
<td></td>
<td>Increased retinal thickness – edema</td>
</tr>
<tr>
<td></td>
<td><strong>Haemodynamic changes predominate</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype C</th>
<th>Rapid progression (&gt;2 red dots/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decreased flow</td>
</tr>
<tr>
<td></td>
<td>FAZ outline changes</td>
</tr>
<tr>
<td></td>
<td><strong>Thrombotic changes predominate</strong></td>
</tr>
</tbody>
</table>

BRB, blood retinal barrier
FAZ, foveal avascular zone

4. Biomarkers of Progression

Microaneurysm Turnover

- Evaluation of Progression by counting microaneurysms (red dots) in sequential visits and identifying their exact location in the retina
  - Identifying new microaneurysms (formation rate)
    - Disease activity + Leakage
  - Identifying disappearing microaneurysm (disappearance rate) – Capillary Closure
Microaneurysm turnover
Methods

MA Turnover - “Retmarker DR”

Baseline  6-month  12-month  18-month  24-month

1 new 1 old 1 new 1 old 1 new 2 disap. 6 new 1 old 1 disap.
Microaneurysm turnover
Methods

MA Turnover - “Retmarker DR”

24-month

MA Formation rate of 4 MA/year

CFP
2-years follow-up

MA
Earmarking
For each visit
Microaneurysm turnover

- 17 patients with CSME (10-Year follow-up of 113 patients)

- Higher MA turnover
  \[ p < 0.001 \]

- MA turnover \( \geq 2 \text{ MA/Y} \)
  \[ \frac{12}{17} (70.6\%) \text{ vs } \frac{8}{96} (8.3\%) \]
  \[ P = 0.002 \text{ vs } p = 0.647 \]

Findings confirmed by Michael Ulbig et al., Munich, Germany.
Network of European certified clinical trial sites (75) from 16 European countries

Centralized infrastructure

6 Scientific Sections:
- AMD and Retinal Dystrophies
- Diabetic Retinopathy
- Glaucoma
- Cornea, Cataract & Refractive Surgery
- Ocular Surface & Inflammation
- Reading Centres
2. Protocol nº ECR-RET-2010-02

Title: Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures

ClinicalTrials.gov Identifier: NCT01145599

Principal Investigator: J. Cunha-Vaz

Nº Centres involved: 18 (450 patients)
  - One year follow-up (0, 3, 6, 12 months)
  - Centralized Reading Centre (CORC)
Progression to DME

- Microvascular disease activity - Fundus Photography
  - Microaneurysm Turnover - Retmarker

- Increase in Retina Thickness - OCT

- Association with vision loss (photoreceptors status) - OCT

- BCVA -
5. Macular Edema - Pathogenesis

- Breakdown of Blood-Retinal Barrier -

1. Diabetes - Multifactorial changes in the inner BRB

2. Venous Occlusion – Hemodynamic factors

3. Associated role of inflammation and outer BRB
Pathogenesis of diabetic retinopathy

**Multifactorial**

**Hyperglycaemia**

**Biochemical changes**
- Oxidative stress
- Polyol pathway
- AGEs
- PKC activation
- Endothelin:nitric oxide

**Functional changes**
- Blood flow alteration
- Permeability changes
- Intercellular junctions

**Structural changes**
- Endothelial loss
- Pericyte loss
- Capillary closure

**Growth factor alteration**

**Vascular occlusion/hypoxia**

**Growth factor alteration**

**Vascular permeability/vascular damage/neoangiogenesis**

AGE, advanced glycation end-product
PKC, protein kinase C

Diabetic Macular Edema – Key points

• DME is a major cause of visual impairment in patients with diabetes
• Burden of DME likely to increase as prevalence of diabetes expected to rise by ~50% globally from 2000 to 2030
• Several biochemical factors and pathways are implicated in the development of DR and DME (complex association to mechanisms)
• VEGF plays a major role in the pathogenesis of DR complications
• The pathogenic profile varies among patients, leading to differing disease characteristics, requiring personalised strategies to manage the disease effectively
6. Treatment of Macular Edema

**Systemic**
- Metabolic control
- Blood Pressure
- Lipid Lowering

**Local**
- Laser: Conventional vs substreshold
- Intravit. Antiangiogenics: Lucentis, etc
- Intravit. Steroids: Osurdex, Iluvien, etc
- Combination Tx
- Vitrectomy – ILM (?)
Laser Management of DR

Adapted from Sheetz MJ, King G. JAMA 2002;288:2579-2588.

Hyperglycemia → Vascular dysfunction → Hypoxia → VEGF induction → Laser photocoagulation

Retinal vascular leakage → Diabetic macular edema → Moderate vision loss

Retinal neovascularization → Vitreous hemorrhage → Tractional retinal detachment → Severe vision loss or blindness

Laser photocoagulation
Present view of DME treatment

DME

No centre involvement

Treat according to ETDRS guidelines

Centre involvement

No vision loss

Observe and treat according to ETDRS guidelines

Vision loss due to DME

Anti-VEGF monotherapy*

Note: ETDRS = Early Treatment Diabetic Retinopathy Study.
Different Responders to Anti-VEGF Treatment

Visual Acuity – recovery of photoreceptor function
Combination treatments for DME

- Anti-VEGF: Loading dose 3-4 injections
- Laser: After 1st injection (one week)
- Steroids for non-responders to anti-VEGF treatment
Characterization of Responders

Predominant Disease Mechanism

- Leakage
- Inflammation
- Ischemia

Edema
OCT

Disease Activity
MA Turnover + chronicity

Ischemia
Ganglion Cells
OCT
Treatment Macular Edema in Retinal Vein Occlusions

Macula perfused
- Intravitreal steroids
- Anti-VEGF

Macular ischemia
- Intravitreal steroids
- Anti-VEGF

Neovascularization
Scatter laser to area of ischemia
Consider
- Intravitreal Steroids
- Anti-VEGF

Macular Edema Treatment

Depends of response to treatment

Visual Acuity Improvement

Photoreceptors status

Retinal Tickness (Edema)

Leakage  intra-retinal fluid

subretinal fluid  (VA)
Macular Edema

1. Definition based on OCT (non-invasive, objective)
2. Increasing frequency
3. Different patients - Different rates of progression
4. Microaneurysm Turnover - Biomarker in diabetes
5. Pathogenesis – Complex/Alt of Blood-Retinal Barrier
6. Treatment of Macular Edema – Personalized / Response to Tx

→ Combination Therapy