# Correlation between Visual Acuity and Diabetic Macular Ischemia by Optical Coherence Tomography Angiography

Thesis

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Master Degree in Ophthalmology
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# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AO-cSLO:** | Adaptive Optics Confocal Scanning Laser Ophthalmoscopy |
| **AR:** | Axis Ratio |
| **ANOVA:** | Analysis of Variance |
| **Anti-VEGF:** | Anti- Vascular Endothelial Growth Factor |
| **BCVA:** | Best Corrected Visual Acuity |
| **CI:** | Circularity Index |
| **CRA:** | Central Retinal Artery |
| **CST:** | Central Subfield Thickness |
| **DCP:** | Deep Capillary Plexus |
| **DINL:** | Deep Inner Nuclear Layer |
| **DM:** | Diabetes Mellitus |
| **DME:** | Diabetic Macular Edema |
| **DMI:** | Diabetic Macular Ischemia |
| **DR:** | Diabetic Retinopathy |
| **DRIL:** | Disorganization of the retinal inner layers |
| **ETDRS:** | Early Treatment Diabetic Retinopathy Study |
| **EZ:** | Ellipsoid Zone |
| **FAZ:** | Foveal Avascular Zone |
| **FFA:** | Fundus Fluorescein Angiography |
| **GCL:** | Ganglion Cell Layer |
| **$HbA_1c$:** | Hemoglobin $A_1c$ |
| **ICC:** | Intraclass Correlation |
| **ICP:** | Intermediate Capillary Plexus |
| **ILM:** | Internal Limiting Membrane |
| **INL:** | Inner Nuclear Layer |
| **IPL:** | Inner Plexiform Layer |
| **IRMA:** | Intra-retinal Microvascular Abnormalities |
| **IVI:** | Intravitreal Injection |
| **LogMAR:** | Logarithm of the Minimum Angle of Resolution |
| **MA(s):** | Microaneurysm(s) |
| **mm:** | Millimeter |
| **$mm^2$:** | Square Millimeter |
| **NPDR:** | Non-Proliferative Diabetic Retinopathy |
| **NVD(s):** | New Vessel(s) at the Disk |
| **NVE(s):** | New Vessel(s) Elsewhere |
| **OCT:** | Optical Coherence Tomography |
| **OCTA:** | Optical Coherence Tomography Angiography |
| **OPL:** | Outer Plexiform Layer |
| **PRP:** | Pan-retinal Photocoagulation |
| **RBC(s):** | Red Blood Cell(s) |
| **RNFL:** | Retinal Nerve Fiber Layer |
| **RPCP:** | Radial Peripapillary Capillary Plexus |
| **PDR:** | Proliferative Diabetic Retinopathy |
| **SCP:** | Superficial Capillary Plexus |
| **SD-OCT:** | Spectral Domain Optical Coherence Tomography |
| **SINL:** | Superficial Inner Nuclear Layer |
| **SSADA:** | Split-spectrum Amplitude-decorrelation Angiography |
| **SSI:** | Signal Strength Index |
| **SVP:** | Superficial Vascular Plexus |
| **VA:** | Visual Acuity |
| **VAD:** | Vessel Area Density |
| **VEGF:** | Vascular Endothelial Growth Factor |
| **VLD:** | Vessel Length Density |
| **WHO:** | World Health Organization |
| **µm:** | Micrometer |

# LIST OF FIGURES

# LIST OF TABLES

# INTRODUCTION

Diabetes mellitus (DM) is a microangiopathic disorder which causes multi-organ ischemic effects including diabetic retinopathy (Zatz and Brenner 1986). According to the WHO, the global number of diabetic patients rose from 108 million in 1980 to 422 million in 2014 (WHO 2016). Approximately one-third of diabetics suffer from diabetic retinopathy (DR), and one-third of DR patients have vision-threatening disease (Lee et al. 2015).

Diabetic macular ischemia (DMI) is a complication of DR which may occur exclusively or in association with diabetic macular edema (DME). It is a leading cause of visual impairment in diabetic patients (Mansour et al. 1993). One study demonstrated that about 41% of DR patients had some degree of DMI (Sim et al. 2013a).

DMI is irreversible and results in poorer response in patients treated for DME by intravitreal bevacizumab (Chung et al. 2008) and triamcinolone (Jonas et al. 2005). Furthermore, patients with DMI at baseline starting ranibizumab treatment were reported to progress to neovascularization more rapidly than those who had no DMI (Ip et al. 2015).

There is a need to accurately diagnose and quantify DMI in order to predict the visual prognosis for those patients and to guide future studies aiming to find more effective treatments for this condition.

Clinical protocols for diagnosing and grading DMI set by the Early Treatment Diabetic Retinopathy Study (ETDRS) have been applied to fundus fluorescein angiography (FFA) which is still the current gold standard. DMI was described as an enlargement of the foveal avascular zone (FAZ), an increase in its irregularity, and a decrease in capillary perfusion characterized by ‘capillary drop out’ [Figure 1] (ETDRS 1991a).

However, FFA is an invasive procedure and numerous potential complications of dye administration have been reported. Also, the two-dimensional view of the retina and the dynamics of dye transit limit its feasibility to examine the separate retinal vascular plexuses (de Carlo et al. 2015).

The introduction of optical coherence tomography (OCT) allowed three-dimensional cross-sectional views of the macula (Huang et al. 1991, Hee et al. 1995, Puliafito et al. 1995). However, despite its revolutionary advancements in the management of cases of diabetic macular edema (DME), it did not aid in the visualization or quantification of DMI.

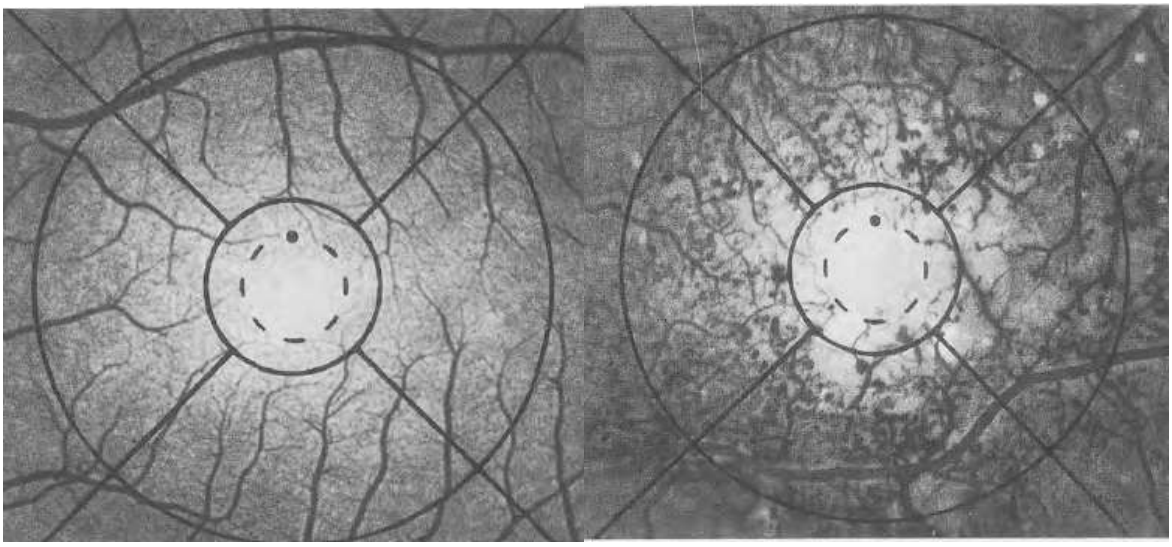

**Figure 1: Standard ETDRS photographs showing a normal capillary bed *(left)* and severe capillary loss in the central subfield and the inner temporal subfield *(right)* (ETDRS 1991a).**

The recent emergence of optical coherence tomography angiography (OCTA) enabled the visualization of vasculature using three-dimentional cross-sectional images in the central macula. Thus, the superficial and deep capillary plexuses, as well as the choriocapillaris can be studied (Jia et al. 2012, 2015). In addition, vascular abnormalities may be visualized and quantified (Ishibazawa et al. 2015).

Several studies have addressed the correlation between DMI and visual acuity, stage of DR, and OCT findings using FFA only (Conrath et al. 2005, Yeung et al. 2009, Sim et al. 2013a, 2013b). With the emergence of OCTA, more research is directed towards using OCTA for such correlations.

# REVIEW OF LITERATURE

## Vascular Anatomy of the Macula

The first knowledge about the macular vascular arrangement came from histological studies of primate retinae. The primate macula was found to have 2-4 capillary plexuses within the inner retina (Henkind 1967b) [Figure 2]. An additional layer, the radial peripapillary capillary plexus (RPCP) was visualized by Henkind et al. on Indian Ink preparations of the peripapillary retina (Henkind 1967b) [Figure 3, Figure 4].

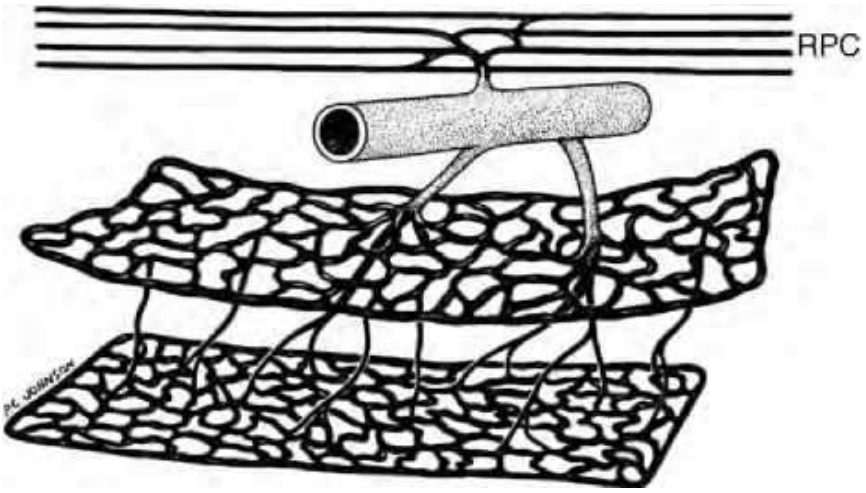


**Figure 2: Schematic representation of the retinal vasculature showing the respective positions, distribution, and morphological characteristics of the different retinal vascular networks. The retinal vessels give rise to the RPCP by superior branches, and the SCP by inferior branches. The SCP then branches into the outer retinal layers to form the deeper capillary plexuses. (Henkind 1969)**

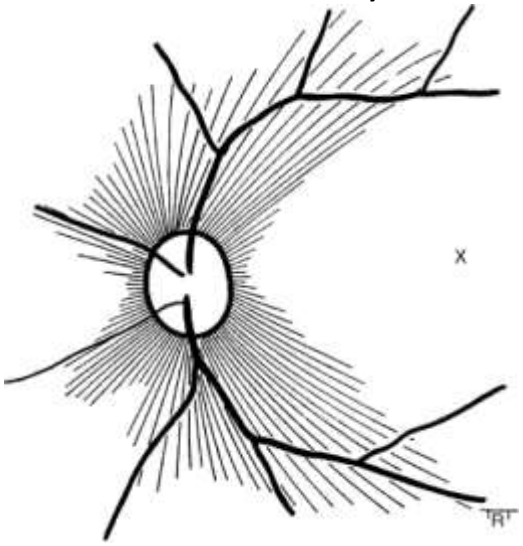


**Figure 3: Diagramatic representation of the RPCP (Henkind 1967b)**

**Figure 4: Microscopic Appearance of RPCP Radial peripapillary capillaries in Indian Ink preparation of infero-temporal peripapillary region. (Henkind 1967b)**

The capillary plexuses of the retina have been visualized and quantified in retinal specimens using confocal microscopy [Figure 5] (Chan et al. 2012, Tan et al. 2012).

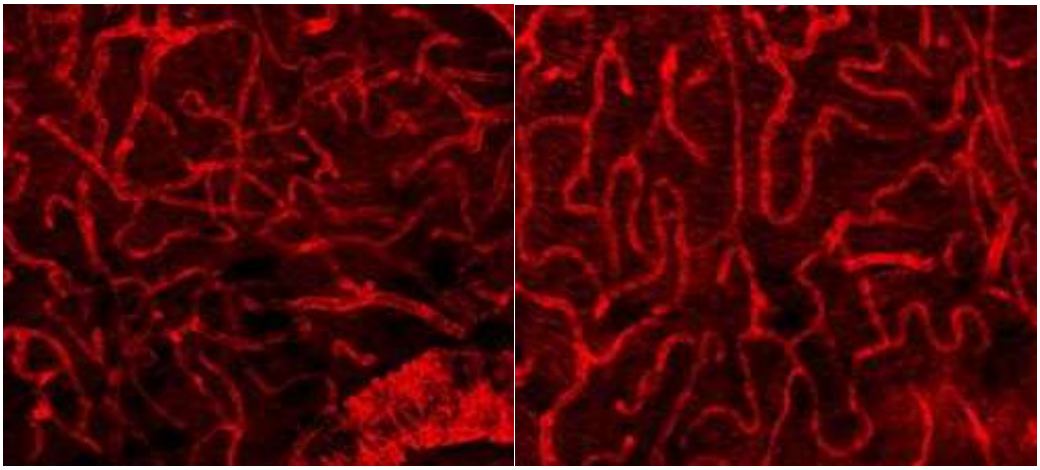

**Figure 5: Confocal Microscopy**
**The superficial (left) and deep (right) capillary plexi captured using confocal microscopy. (Chan et al. 2012)**

Multiple attempts have been made for in vivo visualization of the retinal capillary layers. These include power Doppler optical coherence angiography (Kurokawa et al. 2012) and adaptive optics confocal scanning laser ophthalmoscopy (AO-cSLO) [Figure 6] (Chui et al. 2012, Chan et al. 2015). However, these methods are not widely available and are not practical for use in the clinical setting (Campbell et al. 2017).

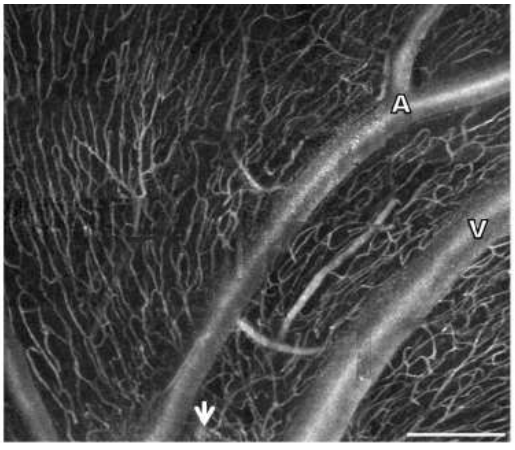


**Figure 6: AoSLO image of the RPCP**
**Image obtained using AoSLO of the RPCP in the region superotemporal to the optic disc. An artery and a vein are indicated by 'A' and 'V' respectively. The arrow points to the upper border of the optic disc.**
**(Chui et al. 2012)**

FFA has been very useful in diagnosing numerous maculopathies including DME due to its high sensitivity in detecting evidence of breakdown of the blood-retinal barrier. Unfortunately, it only provides two-dimensional images which are not depth resolved in order to view and study the retinal vasculature at each layer. Therefore, it can only clearly visualize the more superficial retinal vessels [Figure 7] (Weinhaus et al. 1995).

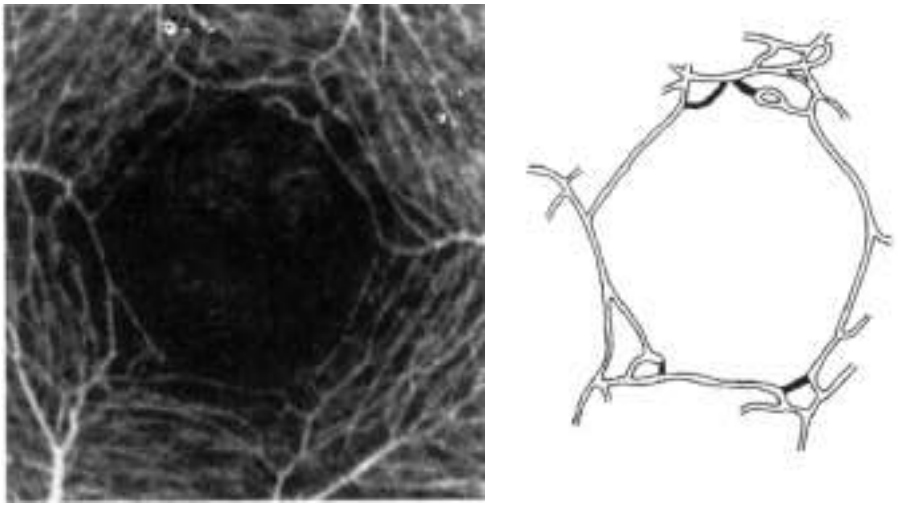

**Figure 7: FFA versus Tissue Examination**
**FFA of central macular circulation *(left)*. Drawing of the terminal capillary ring as it appears on FFA *(right)*. The black bold lines indicate vessels detected on tissue examination but not visualized by FFA. (Weinhaus et al. 1995)**

The advent of optical coherence tomography angiography has enabled the visualization of the macular vascular plexuses within the inner retina at their corresponding levels (Campbell et al. 2017) confirming previously documented histological findings. These plexuses were classified as follows [Figure 8]:

- the superficial vascular plexus (SVP) at the level of the RNFL and the ganglion cell layer (GCL). This plexus arises from the central retinal artery (CRA) and consists of arterioles, capillaries, then venules (Provis 2001, de Carlo et al. 2015).
- the intermediate capillary plexus (ICP) above the inner nuclear layer (INL) (Provis 2001, de Carlo et al. 2015), and
- the deep capillary plexus (DCP) occupying the interfaces between the inner plexiform layer (IPL) and the INL and between the INL and the outer plexiform layer (OPL). These two plexuses arise from anastomotic vessels of the SCP [Figure 2] (Provis 2001, de Carlo et al. 2015).

- the radial peripapillary capillary plexus (RPCP) is found only in the peripapillary region within the RNFL. It supplies the thick RNFL in this area. The capillaries run parallel to the nerve fiber axons (Henkind 1967b).

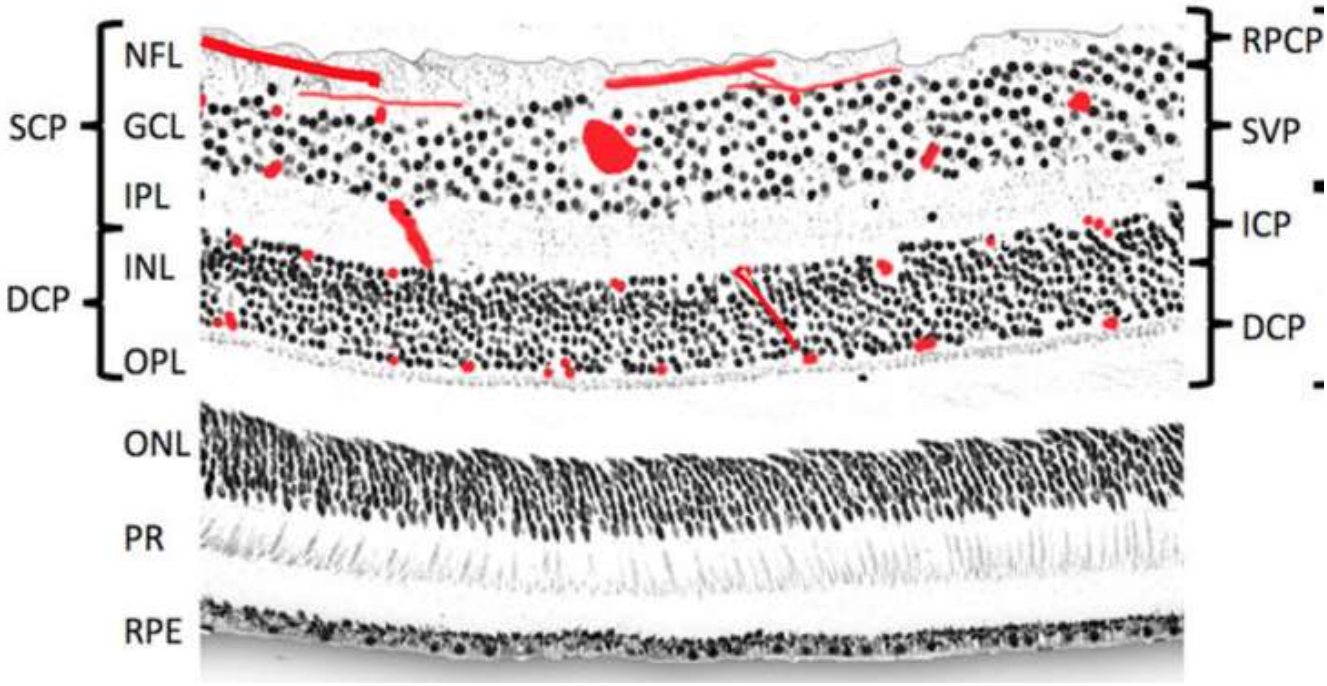


**Figure 8: Histology of Inner Retinal Circulation**
**A diagramatic representation of a histological section in the retina showing the capillaries (in red). The retinal layers are labelled on the left of the diagram. The capillary plexuses are labelled on the right of the diagram. (Campbell et al. 2017)**

## Angiographic anatomy of the FAZ

There is high variability in the size of the FAZ at each layer on OCTA in both normal and diseased individuals (Samara et al. 2015, Shahlaee et al. 2016) [Figure 9]. Samara et al. found the mean FAZ area in the SCP in normal individuals to be 0.266 $mm^2$ ± 0.097 $mm^2$ with values ranging from 0.071 $mm^2$ to 0.527 $mm^2$. In the DCP, the mean FAZ area was 0.495 $mm^2$ ± 0.227 $mm^2$ with a range from 0.160 $mm^2$ to 0.795 $mm^2$ (Samara et al. 2015). Iafe et al. reported the mean FAZ area to be 0.289 ± 0.108 $mm^2$ in the SCP and 0.614 ± 0.200 $mm^2$ in the DCP (Iafe et al. 2016). The FAZ area in the DCP was significantly larger than in the SCP (Samara et al. 2015, Iafe et al. 2016).

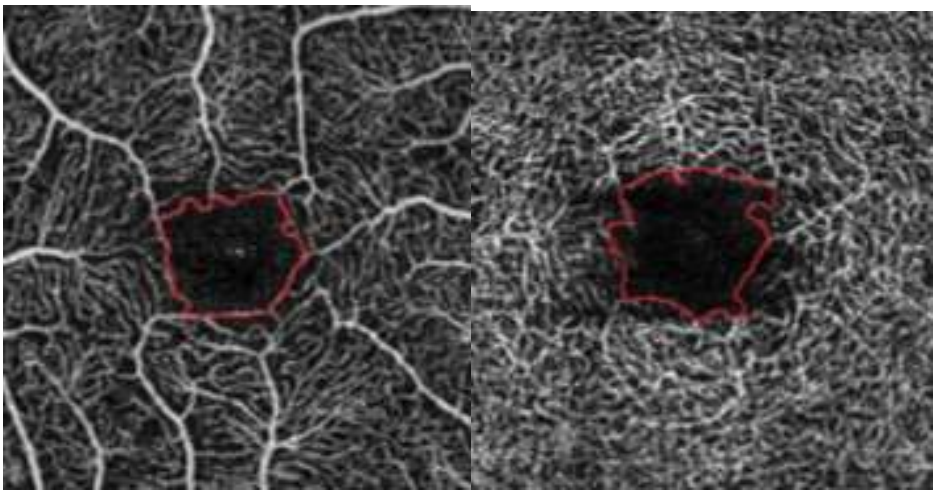

**Figure 9: FAZ Area**
**Manual tracing of the FAZ borders in the OCTA images of the SCP (left) and the DCP (right) using ImageJ software. Note the radial branching pattern of vessels in the SCP compared to the more irregular vascular orientations in the DCP (Samara et al. 2015).**

A significant reduction in FAZ area with age has been reported (Iafe et al. 2016). Moreover, the FAZ in the SCP images was more well-defined and easier to measure than in the DCP. This was attributed to projection artifact and to the different vascular structure at each layer. The SCP consisted of main vessels and their branches while the DCP was described as "a denser and more complex distribution of fine capillaries with multifocal spoke-like orientations surrounding the fovea" [Figure 9] (Iafe et al. 2016).

## Pathophysiology of Diabetic Macular Ischemia

Diabetic vasculopathy affects the intra-retinal capillary plexuses leading to ischemic changes which include:

- FAZ enlargement and irregularity
- Areas of capillary drop-out
- Vessel attenuation

These changes result in an increase in growth factors such as vascular endothelial growth factor (VEGF) which leads to formation of neovascular membranes and DME. Although DME is the commonest cause of visual loss in patients with DR, associated DMI may lead to extensive visual loss that does not correspond to the associated edema (Coscas et al. 2016). This fact suggests a relation between DMI and visual prognosis.

## Fundus Fluorescein Angiography

FFA has been useful in retinal imaging ever since its release in 1961 (Novotny and Alvis 1961). The introduction of the ETDRS grading system (followed by more simplified grading systems) made it the gold-standard in diagnosing and grading all aspects of diabetic macular ischemia (DMI) until today (ETDRS 1991a).

FFA is useful in evaluating the functional integrity of the retinal vasculature (Salz and Witkin 2015). It can detect FAZ enlargement in cases of DMI as well as areas of capillary drop-out due to retinal ischemia. Associated DME would be seen as areas of leakage due to loss of the integrity of the blood-retinal barrier. Other changes such as microaneurysms (MAs), new vessels, intraretinal microvascular abnormalities (IRMA), and cotton wool spots can also be detected to aid in the grading of diabetic retinal disease [Figure 10, Figure 11] (Salz and Witkin 2015).

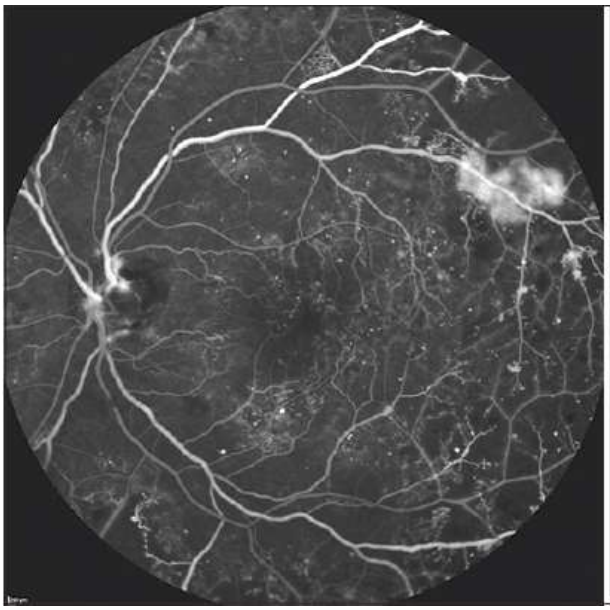

**Figure 10: FFA of DR**
**FFA image centered on the fovea showing multiple MAs as well as IRMA and leaking new vessels at the superior temporal arcade in a case with diabetic retinopathy. (Salz and Witkin 2015)**

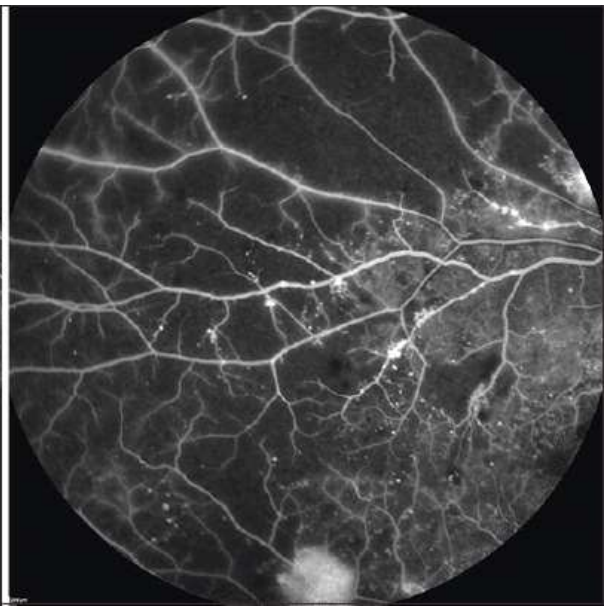

**Figure 11: FFA of DR**
**Peripheral fundus image showing capillary drop out in a case with diabetic retinopathy. (Salz and Witkin 2015)**

The ETDRS proposed a grading system to evaluate the FAZ contour in eyes with DMI using FFA images such that grade 0 is normal, grade 1 is questionable, grade 2 is disruption of less than half of the FAZ circumference, grade 3 is disruption of more than half of the FAZ circumference, grade 4 is complete destruction of the FAZ outline, and grade 8 is ungradable (ETDRS 1991a).

However, it has a number of limitations. FFA is an invasive procedure which requires the injection of dye. For this reason, it is relatively time-consuming requiring at least ten minutes to complete. The dye itself has a host of complications which range from the very mild skin and urine discoloration, through to nausea and vomiting, up to the rare but potentially fatal myocardial infarction and anaphylactic shock. These potential issues limit the use of FFA in renal and pregnant patients as well as children. Also, the procedure cannot be repeated on the same day (Yannuzzi et al. 1986, Salz and Witkin 2015).

In addition, images acquired by FFA have a number of setbacks. Although, leakage and pooling of dye through a defective blood-retinal barrier in diseased vessels allows functional assessment of vascular integrity, however, this extravascular dye leads to blurring of the image making it only possible to