The Evaluation of Fundus Autofluorescence as A Prognostic Factor for Post Injection Visual Improvement in Diabetic Macular Edema

Thesis

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By

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ABSTRACT

Purpose: To detect fundus autofluorescence patterns in cases of diabetic macular edema prior to and following intravitreal injections of bevacizumab and to determine if these changes correlate with visual acuity and serve as prognostic factors

Design: randomized, prospective interventional study

Methods: forty eyes with non-ischemic cystoid or diffuse edema underwent SW-FAF imaging with a cSLO prior to and after three intravitreal injections of bevacizumab and pattern of hyperautofluorescence was determined (number and total area of hyperautofluorescent spots). SD OCT was done to determine the CFT, integrity of the IS/OS junction and detect other visually significant findings. The primary outcome was to determine the changes in FAF and the secondary outcome was determining whether there is an association between baseline and post injection visual acuity and FAF findings.

Results: 35 cases (87.5%) had abnormal foveal hyperautofluorescence: four showed a single spot of hyperautofluorescence (11.4%) and 31 showed multiple spots (88.6%). Pre injection the mean BCVA was best for those with no then multiple then single spots and post injection, the BCVA was best for those with multiple spots then no spots then single spots, but the differences were non significant. The total area of hyperautofluorescent spots was significantly greater for single than multiple spots both pre and post injection. On subdivision of cases into groups according to the change in their BCVA, in 23 cases the visual acuity improved, 15 remained the same and 2 cases deteriorated. The improved viusal acuity group had lower CFT, less hyperautofluorescent spots and a slightly greater total area of hyperautofluorescence but the differences were not significant.

Conclusion: there are certain FAF patterns in DME, but they cannot be definitively correlated with vision or prognosis following therapy.

Key Words: Fundus autofluorescence, diabetic macular edema, OCT, anti-VEGF therapy, bevacizumab

List of Abbreviations

AF	:	Autofluorescence
AMD	:	Age related macular degeneration
BCVA	:	Best corrected visual acuity
BRB	:	Blood retinal barrier
CFT	:	Central foveal thickness
CMT	:	Central macular thickness
CNVM	:	Choroidal neovascular membrane
CSCR	:	Central Serous chorioretinopathy
cSLO	:	Confocal scanning laser ophthalmoscopy
CSME	:	Clinically significant macular edema
DME	:	Diabetic macular edema
ELM	:	External limiting membrane
ETDRS	:	Early treatment diabetic retinopathy study
FAF	:	Fundus autofluorescence
FAZ	:	Foveal avascular zone
Fc	:	Fragment crystallizable
FFA	:	Fundus fluorescein angiography
GA	:	Geographic atrophy
GCL	:	Ganglion cell layer
HRA	:	Heidelberg retinal angiograph
ILM	:	Internal limiting membrane
INL	:	Inner nuclear layer
IPL	:	Inner plexiform layer
IRMA	:	Intraretinal microvasular abnormalities
IS/OS	:	Internal segment/ outer segment
MP	:	Macular pigments
MPOD	:	Macular pigment optical density
NFL	:	Nerve fiber layer
NIR	:	Near infrared

NPDR	:	Non proliferative diabetic retinopathy
NSD	:	Neurosensory detachment
OCT	:	Optical coherence tomography
ONL	:	Outer nuclear layer
OPL	:	Outer plexiform layer of Henle
PVD	:	Posterior vitreous detachment
RPE	:	Retinal pigment epithelium
RVO	:	Retinal vein occlusion
SD	:	Spectral domain
SW	:	Short wavelength
VEGF	:	Vascular endothelial growth factor

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INTRODUCTION

Diabetes mellitus, in the year 2014 affected 9% of adults 18 years and older worldwide. This percentage continues to increase and it is estimated that diabetes will affect 366 million people by the year 2030 [(1)]. Despite advances in the treatment of diabetic retinopathy, macular edema remains the leading cause of blindness in the diabetic population. Macular edema affects up to fourteen percent of all diabetic patients [(2)].

The pathogenesis of macular edema is multi-factorial, mainly resulting from breakdown of the blood retinal barrier (BRB). The mechanism of BRB breakdown results from loss of pericytes and endothelial cells and increased permeability of the surface membranes of retinal vessels and retinal pigment epithelium cells [(3)]. This disruption leads to abnormal inflow of fluid into the neurosensory retina, which on accumulation exceeds the outflow and collects in the intraretinal layers of the macula [(3)].

The cause of visual loss in diabetic macular edema (DME) is not entirely clear and there is little information in the literature about the effect on local visual function of the specific lesions found in diabetic retinopathy[(4)].

The functional impact of DME is usually determined by the quantification of best-corrected visual acuity, which is influenced by many factors, not only by macular thickness. Thus, for a given degree of maculopathy, a wide range of visual acuities may be observed [(5)].

Various treatments, such as focal/grid laser photocoagulation, intra-vitreal injection of anti-vascular endothelial factor (VEGF) agents or triamcinolone acetonide and vitrectomy have been reported for the resolution of DME. In many cases this leads to an improvement in visual acuity, while in others (despite the complete resolution of macular edema) the visual outcome remains poor [6].

Use of spectral domain optical coherence tomography (SD OCT) is the gold standard for diagnosis and follow-up of DME in clinical practice. However, it has failed to become an indicator for visual function or prognosis, as it shows only moderate correlation with best corrected visual acuity [7].

On the other-hand, the role of fluorescein angiography in diabetic macular edema remains mostly in the assessment of macular perfusion and not an indicator of macular function [8].

Fundus autofluorescence (FAF) is not a new technique for in vivo imaging, which is most likely affected by the lipofuscin content in the retinal pigment epithelium [6].

Fundus autofluorescence of diabetic macular edema was shown to be associated with increased autofluorescence in the macular area, which could result from lateral displacement and reduction in the density of macular pigments, decreasing the blockage of the autofluorescence signal from the retinal pigment epithelium (RPE) [9].

Areas of increased autofluorescence have been found to correlate with visual prognosis. Increased level of FAF was associated with functional and structural impairment of the macula in patients with DME. Vision in patients with multilobulated FAF pattern was worse than in patients with single-lobulated FAF [10].

Fundus autofluorescence is a rapid and noninvasive technique yet to be routinely used in the evaluation of diabetic macular edema. It may allow correlation of structural and functional parameters and subsequently the identification of new DME patterns, which may be responsible for different responses to local treatments. Therefore, therapeutic regimens based on OCT macular thickness or fluorescein angiography leakage alone may be not as efficient as expected, giving rise to the role of FAF in more appropriate tailoring of DME treatment.

AIM OF WORK

The aim of this study is to determine the changes in fundus autofluorescence patterns in patients with diabetic macular edema before and after intravitreal injection of bevacizumab. This will then allow detection of any association between visual acuity and fundus autofluorescence findings in DME and if there is a correlation between the FAF patterns and the patient's response to intravitreal therapy. This will help determine whether fundus autofluorescence, a noninvasive investigation, is an appropriate means of follow-up of DME and if it is more functionally sensitive than OCT determined changes in macular thickness.

CHAPTER I

Diabetic Macular Edema: Pathogenesis and Clinical Manifestations

The macula and specifically the fovea are the pivotal regions for vision in the retina. It is defined anatomically as the portion of the posterior retina that contains xanthophyll pigments and two or more layers of ganglion cells. It lies approximately 4 mm temporal and 0.8mm inferior to the center of the optic disc and is 5.5 mm in diameter. It is subdivided into several zones (Fig. 1). The fovea is the central depression approximately one disc diameter (1.5mm) and its central floor is the foveola (0.35mm). The umbo is a small depression at the center of the foveola. The fovea is surrounded by the parafoveal region, which is surrounded by an outer 1.5mm of perifoveal region [11].

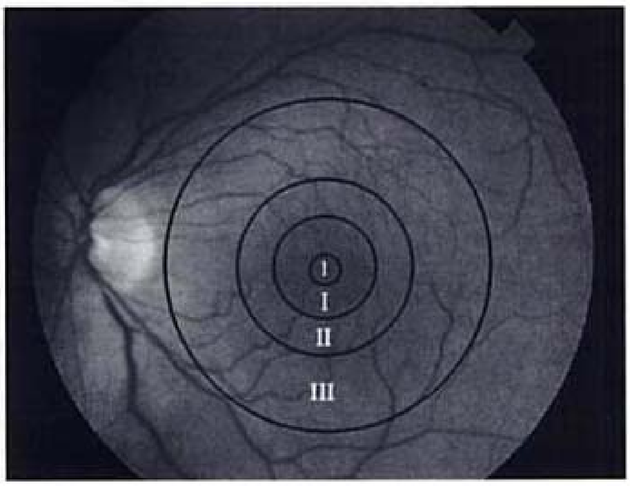

Fig.1: Topographic Anatomy of the macula. Subdivided into zones: I. Fovea with central foveola (1), II. Parafovea, III. Perifovea [11].

Many studies have been carried out to determine the normal variants of macular thickness. ***Wakitani et al*.,** used optical coherence tomography