Non-cystic macular thickening on optical coherence tomography as an alternative to fluorescein angiography for predicting retinal vascular leakage in early stages of uveitis

Nazanin Ebrahimiadib
Tehran University of Medical Sciences
Zahra Kianzad
Tehran University of Medical Sciences
Mohammad Zarei
Tehran University of Medical Sciences
Samaneh Davoudi
Boston University School of Medicine
Hamid Riazi-Esfahani
Tehran University of Medical Sciences
Fatemeh Bazvand
Tehran University of Medical Sciences
Zahra Mahdizad (fmadizad66@gmail.com)
Tehran University of Medical Sciences
Bobeck S Modjtahedi
Southern California Permanent Medical Group

Article

Keywords: retinal vascular leakage, retinal vasculitis, uveitic macular edema

Posted Date: March 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1463697/v1

Abstract

Purpose: To evaluate the relationship between non-cystic thickening of the macula on optical coherence tomography (OCT) and retinal vascular leakage on fluorescein angiogram (FA) in patients with uveitis.

Method: A cross-sectional study of patients seen at the uveitis clinic was conducted. The correlation between OCT features and the degree of anterior chamber and anterior vitreous cell, best corrected visual acuity (BCVA), and FA findings were examined.

Results: A total of 100 exam data met inclusion criteria. There was a significant relationship between macular volume as well as central macular thickness (CMT) and the mean 3mm and 6mm perifoveal macular thickness with angiographic scores (all P values<0.0001). Regarding the colors in thickness map, colors of red and orange which is indicative of thickening were more frequently observed in the area between 1 and 3mm ring.

Conclusion: Non-cystic thickening of the macula on OCT, especially in perifoveal area, is a reliable predictor of the presence of retinal vascular leakage in patients with uveitis.

Introduction

Uveitis is an important cause of vision loss and requires complex monitoring of disease activity which relies on both physical exam and multi-modal imaging[1,2]. Early treatment of intraocular inflammation, and associated sequelae, is critical to preserving vision. The degree of uveitis activity has been correlated to macular and retinal nerve fiber layer thickness on optical coherence tomography (OCT)[1,3]. Perivascular retinal thickness on OCT is correlated with uveitis activity and has been suggested as a surrogate for large vessel leakage severity on fluorescein angiography (FA)[3]. Thomas et al found that such correlation between perivascular thickening in OCT and retinal vascular leakage in fluorescein angiography (FA) is stronger in birdshot retinochoroiditis compared to intermediate uveitis[4]. Retinal vasculitis can be difficult to diagnose on clinical exam and is an important cause of visual morbidity in uveitis patients. It has been reported that one out of 8 uveitis patients has retinal vasculitis, with most not having corresponding signs of systemic vasculitis[5,6]. The Standardization of Uveitis Nomenclature (SUN) Working Group has defined retinal vasculitis as the presence of ocular inflammation and retinal vascular changes including perivascular sheathing and vascular leakage or perivascular leakage with occlusion on FA[7]. Based on SUN definition, detection of vascular leakage in FA of patients with uveitis is not equivalent to “retinal vasculitis”, therefore the term “angiographic vascular leakage” may be the more exact terminology.

FA is an essential tool in the diagnosis, grading, and monitoring of retinal vascular leakage [6] with ultra-wide-field FA allowing for earlier detection and treatment of vasculitis, potentially resulting in better outcomes[8]. Although FA provides valuable insights into disease activity, it is time consuming, requires fluorescein sodium (which may not always be available in all areas), and carries the risk of adverse events.

Immunomodulatory therapy is often adjusted based on the severity of vascular leakage on FA; however, repeated FA can be burdensome. Identifying surrogate biomarkers on OCT may help identify which patients require FA for further assessment of retinal disease activity and also lessen the demand on FA for the assessment and monitoring of retinal vascular leakage.

To the best of our knowledge, no prior studies have evaluated the correlation of macular thickness on OCT with vascular leakage on FA in uveitis patients. This present study sought to characterize OCT features that correlate with the presence, severity, extension and location of retinal vascular leakage on FA.

Methods

Patients with active uveitis who presented to the Farabi Eye Hospital uveitis service between January and October 2019 were included in this cross-sectional study. Patients with the presence of any number of cells in anterior vitreous were eligible for inclusion. Patients with foveal atrophy, intra-retinal cyst/sub-retinal fluid or epiretinal membrane in macular OCT, glaucoma, diabetes, and cataract surgery within the past six months were excluded as were those with media opacities that precluded retinal assessment. Eyes that had reduced vision from causes not directly related to active inflammation, such as cataract or amblyopia, were not included in analyses exploring visual acuity correlations.

Institutional review board approval was attained from the Tehran University of Medical Sciences and the protocol adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients. Spectral-domain OCT (Heidelberg Engineering Inc, Heidelberg, Germany, software version 6.5.2.0), high speed 6 mm scan, and central 55° FA with seven standard fields were performed for all patients. Patients were imaged either at their presentation to the uveitis clinic or during their follow up when they were receiving immunomodulatory therapy. Follow up sessions were included as separate sets of data if they were at least three months apart.

Baseline patient characteristics including age, sex, and history of systemic disease were recorded as were clinical exam features including the presence, location, and degree of intraocular inflammation. Comprehensive ophthalmologic examinations were performed for all patients. Best-corrected visual acuity (BCVA) in LogMAR was assessed. Then concurrent FA and OCT imaging were obtained.

Macular thickness map using Early Treatment Diabetic Retinopathy (ETDRS) circles was assessed in three zones; in the central 1 mm (CMT), between 1 and 3mm ring, and between 3 and 6mm ring as was central 1mm and total macular volume. The thickness values of each nine sector of ETDRS on the topographic map were recorded (Fig. 1). The mean thickness of 4 sectors between 1 and 3mm ring was defined as perifoveal 3mm thickness and the mean thickness of 4 sectors between 3 and 6mm ring was defined as perifoveal 6mm thickness. Normative thickness maps and quantitative values for retinal thickness were used, with orange or red coloration in a sector being considered evidence of thickening. OCTs were reviewed to ensure that the segmentation lines were arranged correctly. In case of segmentation error, the image was excluded from the analysis.

Anterior chamber (AC) and anterior vitreous (AV) cells were graded by one uveitis expert (NE), blinded to the result of FA and OCT findings, on a level of 0 to 4 + based on observation of cells in a dilated pupil during slit lamp examination[9]. The size of the beam of slit lamp used for evaluation of AC cells was 1x1 mm and for AV cells was 1x0.5 mm. For the purpose of analysis, the least number of cells observed in the vitreous have being assigned a numeric value of + 0.25.

A scoring system for FA for grading of inflammatory activity was developed in our center by M.Z. for the purpose of research projects[10]. This scoring system is predominantly based on peripheral and posterior vascular leakage, on frames at least five minutes after infusion of fluorescein. The prototype of this grading is depicted in Fig. 2. Peripheral vascular leakage grading has two components of severity and extent of leakage. The severity of peripheral vascular leakage was graded as 0 (no leakage), 1 (minimal) defined as faint background leakage, 2 (mild) defined as diffuse but mild background leakage, 3 (moderate) defined as more intense leakage but the boundary between vessels is not blended, 4+ (severe) defined as great leakage which causes blending of leakage area into each other in less than half of the area of peripheral quadrant and 5 (very severe) defined as diffuse blending of leakage in more than half of the area of peripheral quadrant. The scoring should be separately done for each quadrant so that a maximal score of 5 can be attributed to each quadrant and the maximal score for all four quadrants can sum up to 20. Posterior vascular leakage has three components including retinal vascular leakage posterior to the equator, macular and optic nerve leakage. For scoring the posterior vascular leakage, macular and optic nerve leakage should not be included and its grading is as follow: 0 (none), 2 (faint background leakage), 4 (diffuse but mild background leakage), 6 (more intense leakage but the boundary

between vessels is not blended), 8 (great leakage which causes blending of leakage area into each other in less than half of the area), 10 (defined as diffuse blending of leakage in more than half of the area). The score for posterior vascular leakage can be a maximum of 10. The grading of macular leakage was based on observation of the ring of leakage and can have a maximum score of 4; 0 (no perifoveal hyperfluorescence), 1 (incomplete ring), 2 (complete ring < 1 disc diameter), 3 (complete ring 1-1.5 disc diameter), 4 (complete ring > 1.5 disc). The grading of optic disc hyperfluorescence can have a maximum score of 3 and include 0 (normal staining of scleral rim), 1 (partial staining), 2 (diffuse leakage without blurring of the disc margin), and 3 (diffuse leakage with blurring of the disc margin).

Scoring was performed while the expert was blinded to the result of OCT findings and slit lamp examination.

Statistical Analysis

Descriptive statistics were calculated as the mean, median and standard deviation. Associations between macular thickness and volume with angiographic scores were estimated using a generalized estimation equation (GEE) approach that accounted for relatedness and repeated measures. In addition, the correlation between OCT parameters and cells in the anterior vitreous, anterior chamber, and BCVA were investigated. Comparison of relations was evaluated by interaction analysis within GEE. For multiple comparisons, Bonferroni's method was applied. All statistical analyses were performed with the SPSS software (IBM Corp., released 2016; IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.). P values ≤ 0.05 were considered significant.

Results

A total of 100 exam data of 43 patients met inclusion criteria. Forty-one patients had bilateral retinal vascular leakage in FA. The follow up data of 8 patients were also included; two eyes of one patient at one year follow up, 6 eyes of 3 patients at the 6th month follow up time and 8 eyes of 4 patients at the 3rd month. Baseline characteristics are summarized in Table 1. three eyes with significant cataract, one eye with substantial posterior synechiae, and two with amblyopia were excluded from vision analyses. Three patients (4 eyes) had a history of cataract surgery greater than six months before study enrollment.

Table 1
Demographic and Clinical characteristics of the study population

Number of patients (eyes, data)	**43(87)**
Age	
years ± SD (range)	21 ± 14 (6–64)
Gender	
Male	24
Female	19
Lens Status	
Pseudophakic	2 patients (2 eyes)
Aphakic	1 patient (2 eyes)
Laterality of uveitis	
Unilateral	2
Bilateral	41
Type of uveitis (patients)	
Intermediate	12
Posterior	31
Grading of Cells	
AC; mean (range)	0.08(0–1)
AV mean (range)	0.6(0–3)
Best Corrected Visual Acuity	
decimal (range)	9/10 (5/10–10/10)
LogMAR; mean (SD)	0.1 (0.2)
Diagnosis	
Undefined	35 patients
TB	2
JIA	1
Behcet's disease	2
Psoriasis	1
AS	2

AC, Anterior chamber; AV, Anterior vitreous; BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; TB, Tuberculosis; JIA, Juvenile Idiopathic Arthritis; AS, Ankylosing spondylitis.

Eight patients with bilateral uveitis had a history of systemic disease: tuberculosis (2 patients), Behcet's disease (2 patients), HLA-B27 + ankylosing spondylitis (2 patients), Juvenile idiopathic arthritis (one patient) and psoriasis (one patient).

The mean CMT was 297.25 ± 34.44μm (min = 227 and max = 397). Mean perifoveal 3 mm thickness was 371.55 ± 25.60μm and mean 6 mm perifoveal thickness was 333.49 ± 23.81μm. The mean total macular volume was 9.63 ± 0.65 mm^3 and the mean central macular volume was 0.23 ± 0.02 mm^3.

The mean peripheral and posterior vascular leakage scores were 7.79 ± 4.75 (median = 8, range: 0–19) and 2.71 ± 2.19 (median = 2, range: 0–10), respectively. The mean macular and optic disc leakage scores were 0.69 ± 0.83 (median = 1, range: 0–4) and 1.25 ± 1.03 (median = 1, range: 0–3) Table 2 demonstrates the correlations among OCT measures and FA, clinical exam, and BCVA.

Table 2
the correlation (p values and correlation coefficients) of macular parameters using OCT with angiographic and examination findings

	Angiographic findings				**Examination findings**		
Inflammation indices/Macular indices on OCT	Macular leakage score (0.69 ± 0.83)	Optic disc leakage score (1.25 ± 1.03)	Posterior vascular leakage score (2.41 ± 4.96)	Peripheral vascular leakage score (2.76 ± 1.88)	AC inflammation (0.08 ± 0.23)	AV inflammation (0.57 ± 0.65)	BCVA (0.10LogMAR)
CMT (297.25 ± 34.44μm)	< 0.001 R = 0.40	0.001 R = 0.36	0.000 R = 0.63	< 0.001 R = 0.69	0.35	0.26	0.74
Perifoveal 3mm thickness (371.55 ± 25.60μm)	0.000 R = 0.40	0.001 R = 0.34	< 0.001 R = 0.61	0.000 R = 0.65	0.62	0.68	0.41
Perifoveal 6mm thickness (333.49 ± 23.81μm)	< 0.001 R = 0.49	0.000 R = 0.49	< 0.001 R = 0.71	0.000 R = 0.76	0.87	0.34	0.65
Central macular volume (0.23 ± 0.02 mm^3)	< 0.001 R = 0.38	0.002 R = 0.33	0.000 R = 0.61	< 0.001 R = 0.67	0.39	0.34	0.80
Total macular volume (9.63 ± 0.65 mm^3)	0.000 R = 0.48	< 0.001 R = 0.46	0.000 R = 0.70	< 0.001 R = 0.75	0.92	0.28	0.97
* mean values in parentheses R = Correlation Coefficient							

There was a significant correlation between CMT and peripheral vascular leakage on FA (Fig. 3). CMT additionally correlated with the macular, optic disc and posterior leakage scores. There were statistically significant correlations between 3mm and 6mm perifoveal thickness and angiographic peripheral vascular leakage (Fig. 3).

There was also a significant relationship between central and total macular volume with peripheralas well as posterior leakage scores. Regression analysis demonstrated that every unit increase in the score of peripheral vascular leakage was associated with an average increase of 5.8 and 132.6 mm^3 in the total and central macular volume, respectively.

A subgroup analysis was done for patients with peripheral vascular leakage who doesn't have leakage in the posterior and macula. In this group of patients, peripheral vascular leakage score was significantly correlated with BCVA and AC and AV inflammation (p = 0.002, p = 0.028 and p = 0.003, respectively) Regression analysis showed that after adjusting for angiographic macular and posterior leakage, the mean CMT, 3mm and 6mm perifoveal thickness were still significantly correlated with peripheral leakage score (p = 0.02, p = 0.02 and p = 0.05, respectively).

Reviewing the normative thickness map revealed that in the area between 1- and 3-mm circle, an average of 3.5 sectors had the red or orange color; and in the area between 3- and 6-mm circle, an average of one sector with these colors was present. In the area between 1- and 3-mm circle, 96 (96%) eyes were found to have at least one sector of red or orange color and 63 (63%) eyes showed to have all four sectors with these colors. In the area between 3- and 6-mm circle, only three (3%) eyes had all sectors in red or orange sectors and 43 (43%) eyes were free of any sectors with such coloration.

Comparing the R values between different OCT parameters and angiographic scores, showed that the correlation of perifoveal thickness 6 mm with score of peripheral vascular leakage (R = 0.76; P < 0.001) is stronger than the correlation of CMT with this angiographic score(R = 0.69; P = 0.078)[11], although both p values were significant.

Discussion

The management of uveitis patients relies on in-depth history taking, physical exam, and imaging. The findings presented herein demonstrate that non-cystic or spongiform macular thickening is strongly correlated with the presence, severity, and extent of retinal vascular leakage on FA.

In uveitis, FA gives valuable information regarding the presence, extent and severity of retinal vascular leakage which cannot be obtained by examination especially in the absence of other suggestive signs such as cystoid macular edema. Regarding FA findings, there is no standardized scoring system. Therefore, we defined a scoring system which reflected our daily practice with FA of patients with uveitis[10]. With the progression of inflammation, the vascular leakage in peripheral becomes more extensive involving more quadrants and/or extends towards the posterior pole. Additionally, the intensity of leakage in periphery and posterior pole is a sign of severity of uveitis. Taking into account all these items, we defined our scoring system by grading these parameters. We found that the level of retinal thickening in the fovea and perifoveal area in OCT while the foveal contour is still preserved, can reliably predict the gradings in our FA scoring system. To validate the importance of peripheral vascular leakage in causing macular thickening, we performed a subgroup analysis with those lacking vascular leakage in posterior and macular area while peripheral leakage was present. Analysis showed that peripheral vascular leakage in isolation, have a significant correlation with thickening in OCT. Therefore, attention to the small thickenings in OCT map, may help monitoring the disease activity and reduce ordering FA which is invasive and time-consuming.

We also found that regarding the colors in the thickness map, the area between 1- and 3-mm circle is more frequently show red or orange color changes which are indicative of thickening, while the central macula and the area between 3- and 6-mm circle still preserve a color near the normal range. Therefore, attention to a doughnut between 1- and 3-mm circle can more readily guide us to the presence of peripheral vascular leakage.

Two previous studies investigated the correlation between perivascular thickening in OCT and retinal vascular leakage in FA and found it a useful noninvasive biomarker of inflammatory activity in birdshot retinochoroiditis[3,4]. However, these studies did not describe the severity, extension and location of retinal vascular leakage on FA and did not investigate the

correlation of these parameters with OCT indices. We developed such scoring and demonstrated that with increasing the level of angiographic score, the level of macular thickening on OCT increases.

Increases in the volume of Muller cells are the first histopathologic findings in macular edema and correspond to spongiform macular edema on OCT. When cellular dysfunction occurs, fluid first accumulates inside retinal cells resulting in tissue swelling without cystic changes. As swelling progresses, cystic changes eventually form within the macula[12]. Prior studies have reported the presence of subclinical macular edema in uveitis patients including those with JIA patients or patients with anterior uveitis [13,14]. As the development of cystoid macular edema and its magnitude obviously reflect the activity of uveitis most of the times, we included cases before development of macular edema or after resolution of macular edema. These are the cases in which the diagnosis of the presence of retinal vascular leakage is mostly dependent on performing an FA.

Patients in this study had thickening on OCT with preserved foveal contours and without cystoid macular edema. As such, they were in relatively earlier or milder stages of macular inflammation. Visual acuity and AV inflammation were not correlated with macular OCT parameters. This may be due to the fact that CMT that predicts visual acuity was near normal in our patients. Also, the score of AV cells in our cases were all small with a mean score of 0.5. All angiographic scores were significantly correlated with foveal and perifoveal thickness and volume. In fact, in a circle farther from the fovea, the correlation becomes stronger with inflammation indicators.

Although there is no standard scale for the measurement of vitreous cells, we graded the cells based on the method used in Multicenter Uveitis Steroid Treatment Trial[9]. We found a lower grade of inflammation in AC compared to AV. This may be because most cases in this series had posterior segment inflammation as their predominant feature. Also, administration of topical corticosteroids can suppress AC inflammation more than AV. Macular changes on OCT may help determine which patients with AV cells would benefit from a FA. Additionally, it is commonly difficult for clinicians to determine if AV cells are from intermediate uveitis or spill over cells from the AC. In these equivocal cases, macular changes on OCT may help point clinicians towards which cases of uveitis are predominantly posterior in nature.

This study demonstrates that non-cystic thickening on macular OCT, especially perifoveal area, strongly corresponds to retinal vascular leakage. Color maps on OCT can help highlight macular thickening and indicate the presence of retinal vascular leakage. A significant correlation was seen between peripheral vascular leakage and OCT changes, even in the absence of posterior vascular leakage on FA. This may be from inflammatory mediators which include intra-cellular inflammation. One of the limitations of the current study is lack of interobserver evaluation for scoring FA, however, in another study from our center, this scoring system was shown to have a high interclass correlation coefficient of 0.986[10]. Larger and prospective studies are necessary to support this correlation and determine which OCT features correspond to changes in retinal vascular leakage over time, especially with regards to treatment response. In addition, including uveitis patients with cystic macular edema in another study would be useful to evaluate the validity of our findings in this subcategory of patients

Declarations

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

NE conceived of the presented idea, developed the theory and was the major contributor in writing the manuscript. ZK performed the data acquisition and analysis and helped in manuscript revision. MZ, RE, SD, FB and BM revised the draft. ZM helped in analysis, drafting and interpretation of data.

Competing interests

The authors declare that they have no competing interests.

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Figures

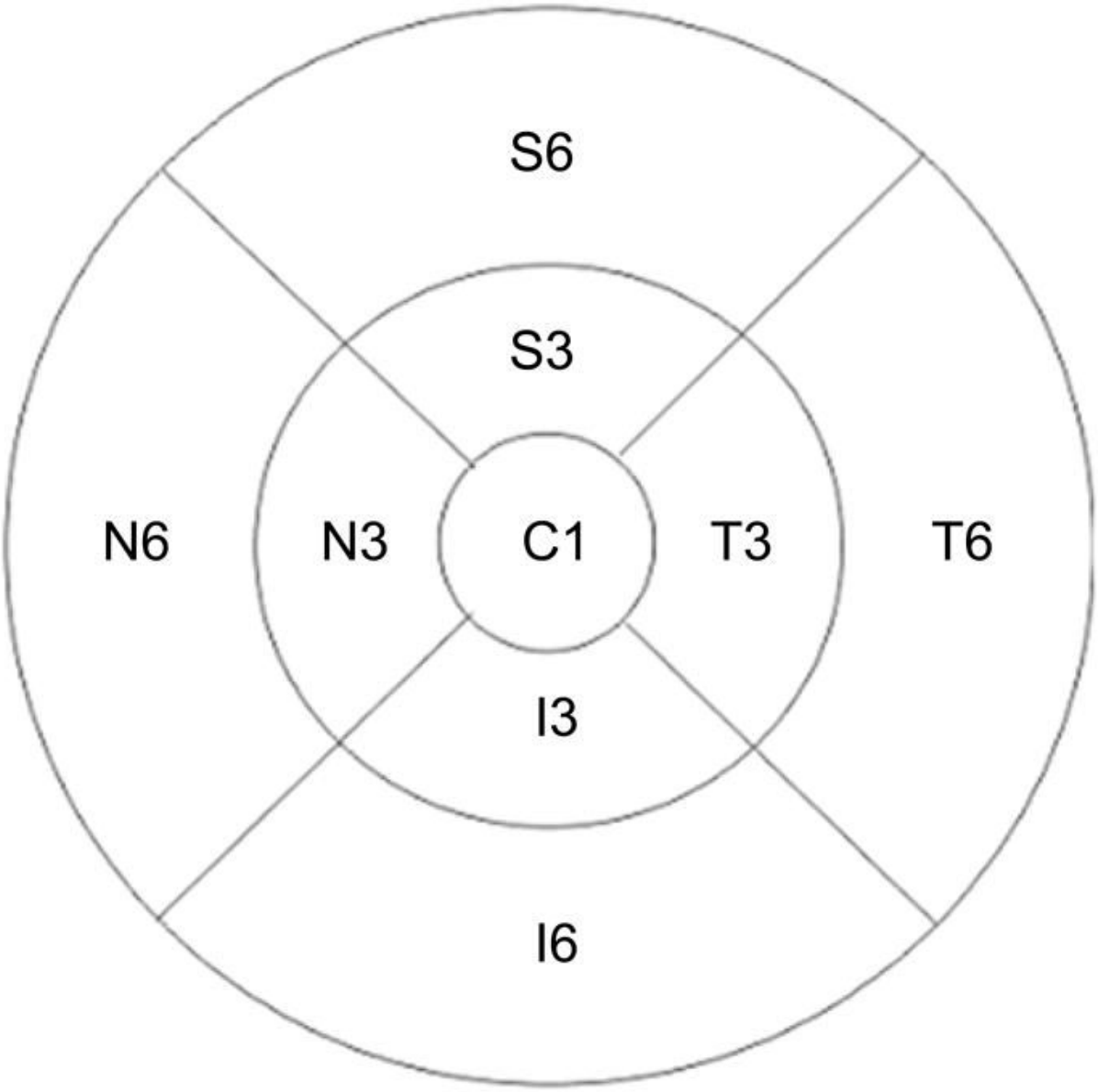

Figure 1

Early Treatment of Diabetic Retinopathy Study (ETDRS) macular map. First ring=1mm, second ring=3mm, third ring=6mm. C1:center, S:superior, I: inferior, N:nasal, T:Temporal.

Figure 2

examples of FA scoring system for grading of inflammatory acitivity. The first row shows the optic disc Hyperfluorescence grading, 0 to 3 (from left to the right; 0: normal, 1: partial staining of the disc, 2: diffuse leakage without blurring of the disc margin, 3: diffuse leakage and blurring of the disc margin.) The second row shows macular leakage grading, 0 to 4 (from left to the right; 0: no perifoveal hyperfluorescence, 1: incomplete ring of leakage, 2: complete (360°) leakage but less than 1 disc diameter (DD) wide, 3: complete (360°) leakage of 1 to 1.5 DD wide, 4: complete (360°) leakage of more than 1.5 DD wide) The third row shows posterior vascular leakage grading, 0 to 10 macular hyperfluorescence was not included (from left to the right; 0: none, 2: increased visibility of the smallest capillaries or scattered faint capillary leakage, 4: diffuse mild capillary leakage, 6: more intense diffuse leakage with

clear distinction between adjacent vascular domains, 8: greater leakage with blending of adjacent leaking domains into each other in less than half of the area of the posterior view (excluding macular hyperfluorescence), 10: greater leakage with blending of adjacent leaking domains into each other in more than half of the area of the posterior view) The fourth row shows the peripheral vascular leakage grading, 0 to 4 (from left to the right; 0: none, 1: increased visibility of the smallest capillaries or scattered faint capillary leakage, 2: diffuse mild capillary leakage, 3: more intense diffuse leakage with clear distinction between adjacent vascular domains, 4: greater leakage with blending of adjacent leaking domains into each other in less than half of the area of the peripheral quadrant, 5: greater leakage with blending of adjacent leaking domains into each other in more than half of the area of the quadrant).

Figure 3

scatterplot showing the correlation between peripheral vascular leakage score and CMT (**a**) as well as perifoveal 3mm (**b**) and 6mm (c) thickness.