Photodiagnosis and Photodynamic Therapy 39 (2022) 102996

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Choroidal vascularity index after a single dose of intravitreal dexamethasone implant in patients with refractory diabetic macular oedema

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ARTICLE INFO

Keywords:
Aflibercept
Choroidal vascularity index
Dexamethasone
Diabetic macular oedema
Enhanced depth-optical coherence tomography

ABSTRACT

Purpose: To evaluate choroidal vascularity index (CVI) after a single dose of intravitreal dexamethasone implant in refractory diabetic macular oedema (DME).
Methods: Total choroidal area, luminal area, and CVI were measured at baseline, 1st month, and at 3rd month after dexamethasone implant using binarization of enhanced depth imaging optical coherence tomography (EDI-OCT) images.
Results: A total of 25 eyes of 25 patients (mean age: 61.4 ± 8.3 years; 12 males, 13 females), were enroled in the study. All eyes had been previously treated with intravitreal aflibercept injections (mean number of injections 4.6 ± 2.5). Mean CVI was 70.3 ± 8.1 prior to intravitreal dexamethasone treatment. It was decreased to 66.1 ± 9.3 at 1 month and 63.5 ± 10.1 at 3 months after treatment. The mean CVI was significantly decreased at 3 months compared with pre-treatment measures ($p = 0.033$).
Conclusion: CVI was found to be decreased in patients who responded to intravitreal dexamethasone implant.

1. Introduction

Diabetic retinopathy (DR) is the leading cause of blindness and visual impairment in the working-age population worldwide [1]. Diabetic macular oedema (DME) is a thickening of the macula that is responsible for the highest resolution of vision. DME may occur at any stage of DR, ranging from minimal DR to severe proliferative DR. There are many factors involved in the pathophysiology of DME, including vascular endothelial growth factor (VEGF), which is known to have an important role in increasing vascular permeability in DR, and numerous inflammatory cytokines [2,3].

Mounting evidence exists that inflammation plays a significant role in the development of DME. Given the apparent role of inflammation in the pathogenesis of DME, corticosteroids have more recently been utilized for the treatment of DME. Intravitreal dexamethasone implant (Ozurdex; Allergan, Irvine, CA, USA) is a sustained-release biodegradable implant that was found to be effective for the treatment of DME. Studies showed that intravitreal injection of dexamethasone implant has proven to be a novel treatment modality for persistent DME and particularly in cases unresponsive to multiple injections of anti-VEGF agents [4,5].

The main pathological findings of diabetes develop on the retina, therefore the majority of the studies have concentrated on this part of the eye. Recent studies have shown that choroid plays a significant role in the pathological changes in DR. Fryczkowski et al. have demonstrated a drop out of microvessels in the choroid at an early stage of diabetes [6]. Researchers have reported controversial results of either increased or decreased choroidal thickness (CT) relating to disease severity or response to treatments for DME [7,8].

Although the clinical implication of changes in CT and its exact role in the pathophysiology of DME remains undetermined, we hypothesized that it would be clinically relevant to study the changes in the choroidal structure and to evaluate the potential role of choroidal vascularity index (CVI) as a clinical biomarker for treatment response.

Therefore, the aim of the current study was to evaluate CVI using binarization of EDI-OCT images in patients with aflibercept-resistant DME after intravitreal dexamethasone implant injection.

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https://doi.org/10.1016/j.pdpdt.2022.102996
Received 13 November 2021; Received in revised form 28 June 2022; Accepted 29 June 2022
Available online 2 July 2022

2. Materials and methods

This retrospective study enroled 25 eyes of 25 patients with refractory DME who were treated with intravitreal dexamethasone implant (0.7 mg Ozurdex) at the Retina Unit of University Hospital. In these patients, DME persisted for at least 6 months, despite treatment with intravitreal aflibercept injections. The last injection of aflibercept was administered at least 3 months before intravitreal dexamethasone implant treatment. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

All participants underwent an ophthalmic evaluation including the measurement of best-corrected visual acuity in logMAR units, slit-lamp biomicroscopy, fundoscopy, fluorescein angiography, and EDI-OCT imaging (Spectralis®, Heidelberg Engineering Inc., Heidelberg, Germany).

Evidence of macular ischaemia, history of any systemic disease other than diabetes, previous ocular surgery and/or laser photocoagulation, epiretinal membrane, vitreomacular traction or adhesion, glaucoma/ocular hypertension, presence of media opacities that could distort image quality were determined as exclusion criteria.

The diagnosis of DME was based on the results of OCT and fluorescein angiography. Cystoid DME was defined as the presence of intraretinal round-oval spaces with non-reflective (hyporeflective) or less frequently moderate reflective fluid in OCT sections. Mixed DME was defined as the presence of diffuse retinal thickening with cystoid spaces. Serous retinal detachment was present if the macula was elevated over a non-reflective cavity with minimal shadowing of the underlying tissues.

Refractory DME is defined as central foveal thickness (CFT) of 300 μm with persistent increased intraretinal fluid and no morphological improvement of DME on OCT despite at least 3 consecutive monthly injections of aflibercept (Eylea; Regeneron, Tarrytown, NY, USA and Bayer, Leverkusen, Germany). CFT was measured manually as the distance from the outer border of the hyper-reflective line corresponding to the retina pigment epithelium, perpendicular to the chorioscleral interface.

All dexamethasone implants were injected under sterile conditions in an outpatient operating room. The implant was inserted into the vitreous cavity through the pars plana using a single-use applicator. Patients were treated with a topical ophthalmic antibiotic for seven days after treatment.

Binarization of EDI-OCT images was performed with Image-J software (Version 1.50a; National Institutes of Health, Bethesda, MD, USA). 3000 μm wide area with the margins of 1500-μm nasal and 1500-μm temporal from the fovea was selected. Borders of the choroidal area were set manually with the Image-J ROI Manager. The image was adjusted by the Niblack auto local threshold (Fig. 1) [9]. Total choroidal area (TCA), luminal area (LA) and stromal area (SA) were measured. The choroidal vascularity index (CVI) was the ratio between LA and choroidal area.

The analysis of the data was done using IBM SPSS 28.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were defined as mean ±standard deviation for variables with normal distribution, median (min-max) for variables with non-normal distribution, and the number of cases (%) for nominal variables. Measurements applied to patients at different times points were evaluated with repeated measures ANOVA. When the difference was found, it was evaluated from which time points the difference originated with pairwise comparisons. Bonferroni adjustments for multiple comparisons were applied to all pairwise comparisons. Univariate regression analysis was used to find the statistical significance of relationships between independent and dependant variables. A p-value of <0.05 was considered statistically significant.

3. Results

A total of 25 eyes of 25 patients (mean age: 61.4 ± 8.3 years; 12 males, 13 females), all with type 2 diabetes, were enroled in the study. All eyes had persistent DME and received intravitreal aflibercept injections (mean number of injections 4.6 ± 2.5). Before administration of intravitreal dexamethasone implant, all eyes had refractory DME.

According to the OCT findings, 8 eyes with DME showed cystoid DME, and 13 eyes had mixed DME. Subretinal fluid was present in 4 eyes. Fluorescein angiography showed dye pooling within the cystic spaces with a petaloid pattern in the foveal area in all eyes. Baseline characteristics of patients are given in Table 1.

The mean central foveal thickness was 512.3 ± 119.2 μm before the intravitreal dexamethasone implantation. It was decreased to 320.3 ± 98.1 μm and 306.1 ± 89.2 μm at 1 month ($p<0.001$) and at 3 months

Table 1
Baseline characteristics of the patients.

	Eyes/patients (n)	25/25
	Mean age (years)	61.4 ± 8.3
	Male/Female (n)	12/13
	HbA1c (%)	7.8 ± 1.3
	NPDR/PDR (n)	25/0
	Mean number of anti-VEGF injections	4.6 ± 2.5
	BCVA (logMAR)	1.028±0.3
	Phakic/pseudophakic eyes	6/19
	Spherical equivalent	−0.04±1.29
	Axial length (mm)	23.67±0.7
DME type	**Cystoid**	8
	Mixed (Cystoid + diffuse)	13
	Subretinal fluid	4

DME: Diabetic macular oedema; HbA1c: hemoglobin A1c; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; VEGF: Vascular endothelial growth factor; BCVA: Best-corrected visual acuity.

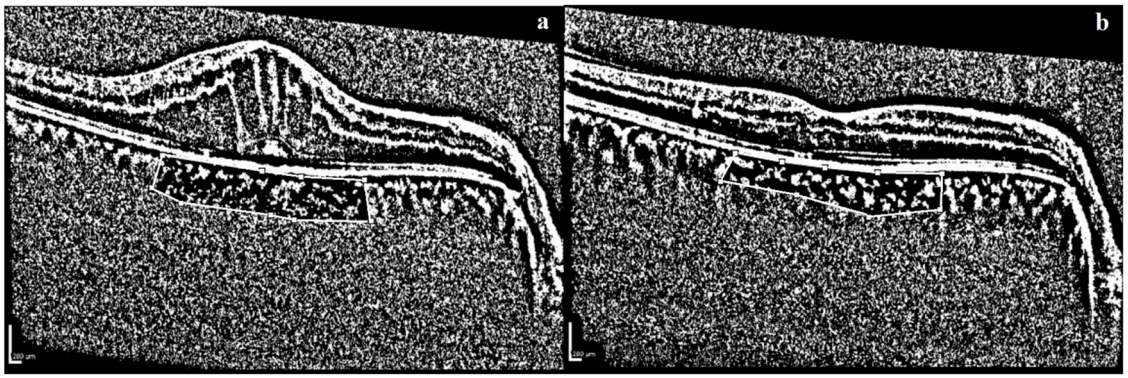

Fig. 1. a: Converted binary image of a diabetic eye with macular oedema using Image-J with the area of interest in the choroid demarcated with a white line **b:** The converted binary image of the same eye at 3rd month after intravitreal dexamethasone implant treatment.

($p<0.001$) consecutively following the treatment. All eyes revealed a significant decrease and none of them showed any worsening at 1 and 3 months.

The mean subfoveal choroidal thickness was 291.9 ± 37.2 μm before the intravitreal dexamethasone implantation and it was significantly decreased to 261.2 ± 29.1 μm at 1 month ($p<0.001$) and to 260.8 ± 28.8 μm at 3 months ($p<0.001$), consecutively.

The initial BCVA (logMAR) was 1.028±0.3 and improved to 0.89 ±0.2 at 1st month, and 0.74±0.2 at 3rd month. The improvement continued up to 3 months. The BCVA changes were statistically significant both at 1st and 3rd months when compared with pre-dexamethasone implant treatment ($p = 0.036$ and $p = 0.028$, respectively).

Prior to the intravitreal dexamethasone treatment, the mean CVI was 70.3 ± 8.1%. It was decreased to 66.1 ± 9.3% and 63.5 ± 10.1% at 1st and 3 months, consecutively. The decrease at 3 months was statistically significant ($p = 0.033$). The mean TCA was statistically significantly decreased at 3 months ($p = 0.013$). The mean LA was statistically significantly decreased at 1 and 3 months ($p = 0.034$ and $p = 0.020$, respectively). ($p = 0.013$). The mean SA was statistically significantly increased at 3 month compared to baseline ($p = 0.004$). Choroidal parameters during the follow-up period are shown in Table 2. P-values for pairwise comparisons (Bonferroni test) are given in Table 3.

The choroidal structural parameters at baseline and during the follow up were selected for the regression analysis (The independent variables were age, axial length (AL), spherical equivalent (SE), gender, HbA1c, and number of anti-VEGF injections). According to the univariate regression analysis, there were negative correlations between the baseline LA and age and HbA1c (ß: −0.429, $p = 0.032$ and ß: −0.399, $p = 0.048$, respectively) and baseline CVI and HbA1c (ß: −0.426, $p = 0.034$). At 1 month, univariate regression analysis revealed a positive correlation between the SA and HbA1c (ß: 0.480, $p = 0.015$) and negative correlations between the LA, CVI and HbA1c (ß: −0.481, $p = 0.015$ and ß: −0.499, $p = 0.011$, respectively). At 3 month, SA was positively correlated with age (ß: 0.508, $p = 0.010$) and LA and CVI were negatively correlated with age (ß: −0.513, $p = 0.009$ and ß: −0.546, $p = 0.005$, respectively). Only SA was positively correlated with age, when the changes in choroidal parameters between the baseline and at 3 month were assessed (ß: 0.437, $p = 0.029$).

None of the patients developed any serious ocular and systemic adverse events like visually significant cataracts, endophthalmitis, or retinal detachment. Two eyes (8%) had a transient elevation of intraocular pressure at 1 month, which was controlled with topical dorzolamide 2% timolol 0.5% combination.

4. Discussion

Diabetes is a metabolic disorder mainly affecting the systemic vasculature. Although the primary changes in diabetic eyes occur in the retinal vasculature, accompanying changes are also observed in the choroidal layer, an vascular tissue that supplies blood to the outer retina.

Chronic inflammation has been shown to be involved in the pathogenesis of DME. In addition to VEGF, many inflammatory cytokines have been reported to have crucial roles in the development of DME.[3] Histological studies of retina and choroid in diabetic retinopathy have shown various changes in choroidal vascular structures, as an accumulation of inflammatory cells, and focal dilation or narrowing [10,11]. Moreover, various cytokines and growth factors that promote DME can also influence choroidal vascular structures, which may account for changes in CT.

Subfoveal CT changes in patients with DME have been studied previously and the results on this subject are still controversial. This discrepancy may be due to differences in patient profiles. Kim et al. evaluated changes in CT in type 2 diabetic patients with DME using EDI-OCT [7]. They reported that subfoveal choroidal thickness was increased in eyes with DME than in those without. In contrast, Gerendas et al. measured CT by spectral-domain OCT images using automated algorithms and correlated choroidal pathology with retinal changes attributable to DME [12]. According to their results, CT was significantly decreased in eyes with DME and in nonedematous fellow eyes. Similarly, Esmaeelpour et al. reported a decrease in CT in eyes with DME [13].

Choroidal thickness is a parameter that varies substantially both in healthy and pathological conditions. It decreases from the macula to the periphery and is at its maximum subfoveal. Choroidal thickness is not a true representative of the entire choroidal vasculature as an objective biomarker. Measuring CVI can enable us to obtain more information about vascular and stromal components of the choroid.

The results of the current study showed that, in all eyes which responded to intravitreal dexamethasone implant treatment, the mean CVI at 3 months was significantly decreased compared with pre-dexamethasone treatment CVI. To the best of our knowledge, no prior study has evaluated CVI using binarization of EDI-OCT images before and after intravitreal dexamethasone injection in patients with aflibercept-resistant DME.

Tan et al. evaluated EDI-OCT scans of 38 eyes of 19 patients with diabetes and compared results with eyes of healthy controls [14]. Their results showed that there were no significant differences between patients with DM and controls in TCA, LA, SA, and CT. However, there was a significantly lower CVI in patients with DM as compared to controls. They found a significant increase in TCA, LA, SA, and CT in DR patients compared with patients without DR. Moreover, there was a significantly decreased CVI in patients with DR when compared with patients without DR. Gupta et al. characterized specific morphological and vascular features of the choroid in diabetic individuals [15]. They reported that in comparison with non-diabetic eyes, the choroidal vascular area was markedly decreased in patients with DM. Gupta et al. found that SFCT was significantly increased in eyes with DME as compared to controls.

Table 2
Comparison of choroidal structural changes during the follow-up.

	Before implant	At 1 month	At 3 month	p value (overall)
TCA (mm^2)	0.850±0.08	0.804±0.09	0.794±0.07	0.002
SA (mm^2)	0.250±0.06	0.272±0.07	0.289±0.10	0.003
LA (mm^2)	0.600±0.09	0.531±0.08	0.505±0.09	<0.001
CVI (%)	70.3 ± 8.10	66.1 ± 9.30	63.5 ± 10.10	<0.001

TCA: Total choroidal area.
SA: Stromal area.
LA: Luminal area.
CVI: Choroidal vascularity index.

Table 3
P-values for pairwise comparisons (Bonferroni test).

		Before implant	At 1 month	At 3 month
TCA (mm^2)	**Before implant**	–	0.008	0.006
	At 1 month	0.008	–	0.082
	At 3 month	0.006	0.082	–
SA (mm^2)		Before implant	At 1 month	At 3 month
	Before implant	–	0.182	0.004
	At 1 month	0.182	–	0.373
	At 3 month	0.004	0.373	–
LA (mm^2)		Before implant	At 1 month	At 3 month
	Before implant	–	0.002	<0.001
	At 1 month	0.002	–	0.065
	At 3 month	<0.001	0.065	–
CVI (%)		Before implant	At 1 month	At 3 month
	Before implant	–	0.023	<0.001
	At 1 month	0.023	–	0.151
	At 3 month	<0.001	0.151	–

TCA: Total choroidal area.
SA: Stromal area.
LA: Luminal area.
CVI: Choroidal vascularity index.

CVI was significantly decreased in DME with DR eyes compared with controls and it was significantly decreased with worsening DR. [15]. Kase et al. evaluated choroidal structures in healthy subjects and patients with or without DME. They found that DM eyes showed a significantly decreased LA/TCA ratio than control eyes, whereas there were no significant differences in CT or TCA, LA, and SA. Choroidal thickness and TCA, LA, and SA were significantly increased in the DME group than in the non-DME group [16].

Kim et al. showed that eyes with advanced DR had a significant decrease in CVI and CT over 12 months after panretinal photocoagulation (PRP) treatment [17]. Russell et al. analysed the CT and vascularity in proliferative DR after PRP. The choroid in DR eyes had a decreased CVI than in normal eyes. After PRP, the CT decreased, but the CVI remained constant, which suggested that decrease in choroidal vascularity persisted [18]. In DM patients, choroidal thinning has been found in all eyes independent of the severity of retinopathy [19]. In our study, the changes in CVI indicated a significant decreasing tendency throughout the follow-up period after intravitreal dexamethasone implantation. Conti et al. used OCT angiography imaging to evaluate choriocapillaris and retinal capillary perfusion density changes in DR following anti-VEGF treatment [20]. Compared to control, choriocapillaris and retinal capillary perfusion density were reduced in patients with DR. These changes remained similar up to 12 months in DR eyes following anti-VEGF treatment [20].

Intravitreal dexamethasone implant delivers a sustained release corticosteroid and has been proven to be an effective treatment choice for DME [21]. Corticosteroids block the production of inflammatory cytokines and VEGF, inhibit leukostasis and endothelial nitric oxide synthase, reduce tissue oedema, and decrease the release of prostaglandins and histamines. All these effects prevent vasodilation [22]. These data may explain the decrease in LA and CVI in eyes with refractory DME after intravitreal dexamethasone implant.

As mentioned above, there is a discrepancy in both CT and CVI measurements in DM patients. For the studies with decreased choroidal parameters in diabetic eyes, this could be explained by various choroid pathologies like decreased choroidal blood flow, choroidal anomalies, choriocapillaris occlusion, or vessel loss. For studies reporting increased results, this could be due to increased cytokines with a resultant increase in vascular hyperpermeability, fluid leakage, and blood flow leading to increased CT or CVI. We may assume that if the patients have a treatment-resistant DME, they can be highly expected to exhibit different retinal and choroidal vascular changes than other DM patients.

We also found that there were significiant correlations between the choroidal vascular changes and HbA1c values. Sahinoglu-Keskek et al. [23], reported that the subfoveal choroid in patients without DR was significantly thicker than that in patients with DR. They did not find any significant differences in HbA1c levels and concluded that there was no correlation between CT and HbA1c values. Torabi et al. [24]. classified diabetic patients according to the HbA1c values and found that the CT in the control group was nearly equal to that in patients with good glycemic control and was significantly more than the CT in diabetic patients with poor glycemic control. Therefore, in patients with uncontrolled DM and high levels of HbA1c, the choroid is expected to be thinner. Unsal et al. [25], revealed a weak to moderate negative correlation between the subfoveal CT and HbA1c values which is compatible with our results.

Until recently, indocyanine green angiography and Doppler or B-scan ultrasonography have been used to study choroidal circulation with particular deficiencies. Choroidal imaging using EDI-OCT systems is a non-invasive technique that allows in-vivo quantitative assessment of the choroid. It could be used to explain the vision loss, disease activity and monitor the treatment response. The binarization methods supplied objective and reproducible measurements of choroidal parameters. These parameters like CVI have provided a better understanding of the pathogenesis and in the future may also help to change treatment options. In the studies mentioned in this article that assessed CVI, there was a significant decrease in CVI with worsening of retinopathy. This reflects the stability of CVI compared with CT and makes it a more robust tool in assessing DR progression and the severity of the disease. CVI may represent choroidal vascular changes which can be a valuable tool even in DM patients with no visible DR. As CVI is a ratio, it is less likely to be affected by the factors affecting CT, making it a better tool to be used in the evaluation of choroidal pathologies.

The current study had several limitations, including the cross-sectional retrospective design, relatively small number of patients, and short duration of 3 months follow-up. Previous treatments with anti-VEGF agents might have exerted potential influence on the measurement of CT, but the potential effect of anti-VEGF on subfoveal CT may be minimal in eyes with DME, as shown in previous studies. The definition of refractory DME may vary amongst different studies and it is not a universal term. Therefore, the results of the current study may not necessarily apply to other studies with different protocols and different definitions of refractory DME.

In conclusion, CVI can be used as a biomarker for choroidal evaluation in patients with refractory DME. In the future, prospective, population-based studies with a larger sample size are needed to reveal the longitudinal effect of intravitreal dexamethasone on choroidal vasculature. Clinical applications of this new choroidal imaging technology also need further evaluations.

CRediT authorship contribution statement

Özkan Kocamiş: . **Emine Temel:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gökçen Özcan:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Nazife Aşikgarip:** . **Kemal Örnek:** Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

Funding: There are no sources of funding.

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