Disorganization of the inner retinal layers in diabetic macular edema: systematic review

Desorganização das camadas internas da retina sem edema macular diabético: uma revisão sistemática

Andreas Di-Luciano[1], Wai-Ching Lam[2], Laurent Velasque[3], Eduardo Kenstelman[4], Rodrigo M. Torres[5], Rosa Alvarado-Villacorta[6], Manish Nagpal[7]

[1] Flying Eye Hospital, Orbis International, New York, United States.
[2] Deparment of Ophthalmology LKS Faculty of Medicine University Hong Kong, Hong Kong
[3] Centre Retine Gallien Bordeaux, France
[4] HOlhos São Gonçalo, Rio de Janeiro, Brazil
[5] ROMAT Creator center, Colonia Avellaneda, Entre Ríos, Argentina.
[6] Research Unit, Clinica Vista, Lima, Peru
[7] Retina foundation, Gujarat, India

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Corresponding author:
Andreas Di-Luciano
520 8th Avenue, 12th Floor
New York, NY 10018
Email: andreasdilu@gmail.com

Institution:
Flying Eye Hospital, Orbis International, New York, United States.

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ABSTRACT

The objective of this article was to review the disorganization of inner retinal layers as a biomarker in diabetic macular edema. A systematic search was conducted in PubMed®/MEDLINE®, Cochrane and Embase until August 2021. The keywords used were: "disorganization of inner retinal layers (DRIL)", "diabetic macular edema (DME)" and "biomarkers". No restrictions were imposed on the types of study to be included. The studies selected for eligibility were those that included the diagnosis of diabetic macular edema (center involved, resolved), that were well documented with spectral domain optical coherence tomography, that included disorganization of inner retinal layers as one of the reported alterations, with a follow-up of at least 3 months, and those in which the best corrected visual acuity was evaluated pre and post. There were no limitations regarding the type of treatment established. References of identified studies were searched for additional relevant articles. Articles not published in peer review journals were excluded. All studies were evaluated by two investigators independently. When one of them was in doubt, it was assessed by a third evaluator. A total of seven studies were included. Four were retrospective, longitudinal cohort study and three cross-sectional observational. Regarding the population studied, 61.5% were men and 38.4% were women, most of them had diabetes mellitus type 2 (85.8%). Regarding the stage of diabetes, the percentage of patients with mild nonproliferative diabetic retinopathy was 28.2%, with moderate nonproliferative diabetic retinopathy was 28.5%, with severe nonproliferative diabetic retinopathy was 15.9% and with nonproliferative diabetic retinopathy was 27.4%. In 100% of the studies, the diagnosis of diabetic macular edema in the center involved was included by spectral domain optical coherence tomography (Heidelberg). In all the studies, the presence of disorganization of inner retinal layers was recorded and its association with best corrected visual acuity was evaluated. The measurement was carried out using the LogMAR scale. In all the studies, the presence or absence of disorganization of inner retinal layers was associated with the best corrected worse/better final visual acuity using $p < 0.05$ as a statical significance. The disorganization of inner retinal layers as a biomarker and their presence have shown to be important predictors of visual acuity in the future in patients with diabetic macular edema. Histopathological studies are required to understand its mechanism of action.

RESUMO

O objetivo deste artigo foi revisar sobre a desorganização das camadas internas da retina como biomarcador no edema macular diabético. Uma busca sistemática foi realizada no PubMed®/MEDLINE®, Cochrane e Embase até agosto de 2021. As palavras-chave utilizadas foram "disorganization of inner retinal layers (DRIL)", "diabetic macular edema (DME)" e "biomarkers". Não foram impostas restrições quanto aos tipos de estudo a serem incluídos. Os estudos selecionados para elegibilidade foram aqueles que incluíram o diagnóstico de edema macular diabético (centro envolvido, resolvido), que foram bem documentados com tomografia de coerência óptica de domínio espectral, que incluíram a desorganização das camadas internas da retina como uma das alterações relatadas, com acompanhamento de pelo menos 3 meses, e aqueles em que a melhor acuidade visual corrigida foi avaliada pré e pós. Não houve limitações quanto ao tipo de tratamento estabelecido. Referências de estudos identificados foram pesquisadas para artigos relevantes adicionais. Foram excluídos os artigos não publicados em revistas de revisão por pares. Todos os estudos foram avaliados por dois investigadores de forma independente. Quando havia dúvida com algum deles, a mesma era avaliada por um terceiro avaliador. Um total de sete estudos foram incluídos. Quatro eram estudos de coorte

retrospectivos longitudinais e três eram observacionais transversais. Em relação à população estudada, a proporção de homens foi de 61,5% e de mulheres, 38,4%, a maioria com diabetes mellitus tipo 2 (85,8%). Em relação ao estágio do diabetes, o percentual de pacientes com retinopatia diabética não proliferativa leve foi de 28,2%, retinopatia diabética não proliferativa moderada foi de 28,5%, de retinopatia diabética não proliferativa grave foi de 15,9% e de retinopatia diabética não proliferativa foi de 27,4%. Em 100% dos estudos, o diagnóstico de edema macular diabético no centro envolvido foi incluído pela tomografia de coerência óptica de domínio espectral (Heidelberg). Em todos os estudos, foi registrada a presença de desorganização das camadas internas da retina e avaliada sua associação com a melhor acuidade visual corrigida. A medição foi realizada usando a escala LogMAR. Em todos os estudos, a presença ou ausência de desorganização das camadas internas da retina foi associada a pior/melhor acuidade visual final melhor corrigida usando $p<0,05$ como significância estática. A desorganização das camadas internas da retina como biomarcador e sua presença têm se mostrado importantes como preditor da acuidade visual no futuro em pacientes com edema macular diabético. Estudos histopatológicos são necessários para entender seu mecanismo de ação.

INTRODUCTION

Diabetic mellitus (DM) is a global epidemic with significant morbidity and mortality. Diabetic retinopathy (DR) is a major complication of DM and a leading cause of vision loss in middle-aged working adults.[1] Diabetic macular edema (DME) is the most common cause of vision loss in DR.[2] Standard treatment for DME involves repetitive, invasive intraocular injections, which place heavy burdens on the patient, physician, and health care reimbursement.[3] Despite advances in treatment, there are no reliable methods to determine which individuals with DME will gain or lose vision.[4] Attempts have been made to analyze biomarkers to see the anatomical and functional response to the treatments available to date. Among the parameters studied to evaluate visual results there are: glycemic control, retinopathy severity, presence of DME, and extent of retinal thickness. All of them have been associated but cannot be future visual predictors and cannot be individualized to each patient.[4] The same occurs with circulatory, genetic, aqueous humor and vitreous humor biomarkers.[5] With the technological advance in imaging diagnosis, new biomarkers have been studied.

Optical coherence tomography (OCT) has been an indispensable tool to evaluate response to treatment in patients with DME. Optical coherence tomography is a rapid, non-invasive imaging modality that uses light waves to render a cross-sectional view of the retina in vivo. It creates high-resolution images of retinal morphology, allowing for volumetric quantification of retinal and choroidal thickness (CT) and DME.[4-6]

In 2012, Soliman et al., using spectral domain optical coherence tomography (SD-OCT), found that the disorganization of the inner retinal layer (DRIL) was correlated with current visual acuity (VA) in patients with existing or resolved center-involved DME.[6]

In 2014 Sun et al. studied the DRIL and found that the DRIL in the 1-mm foveal area was associated with VA, and that the change in DRIL predicts future change in VA.[4] Based on the findings of Sun et al., DRIL has been evaluated together with other anatomical characteristics by OCT, evaluating anatomical and visual response in patients receiving anti-VEGF or intravitreal corticosteroids.[7-10] Identifying imaging findings and biomarkers capable of predicting risks of development and progression of DR is important to screen, monitor, and treat patients.[5] For this reason, we conducted a systematic review to evaluate all the existing information on DRIL in DME as a non-invasive biomarker.

SEARCH STRATEGY AND STUDY SELECTION

Two investigators performed an electronic search, following the recommendations of Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) (Figure 1). An electronic search without date or language restrictions was carried out in the following databases: PubMed®/MEDLINE®, Scopus and Embase for articles published until August 2021. The keywords used were: "disorganization of inner retinal layers (DRIL)", "diabetic macular edema (DME)" and "biomarkers". No restrictions were imposed on the types of study to be included. The studies selected for eligibility were those that included the diagnosis of DME (center involved, resolved), that were well documented with SD-OCT, that included DRIL as one of the reported alterations, with a follow-up of at least 3 months and whose best corrected VA (BCVA) was pre and post evaluated. There were no limitations regarding the type of treatment established. References of identified studies were searched for additional relevant articles. Articles not published in peer review journals were excluded. All studies were evaluated by two investigators independently. When one of them was in doubt, it was assessed by a third evaluator, it was assessed by a third evaluator.

Operational definitions

Center involved DME was defined as SD-OCT central subfield thickness (CST), ≥320µm for men and ≥305µm for women.[11]

Resolved DME was defined as SD-OCT CST <320µm for men or <305µm for women.[11]

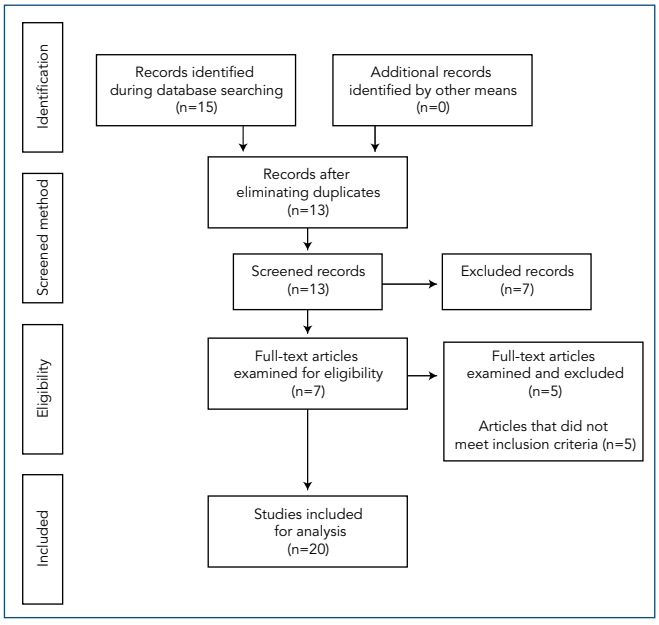

Figure 1. Flowchart: Inclusion criteria regarding systematic review based on PRISMA recommendations.

Disorganization of inner retinal layers was defined (measured by SD-OCT) as the horizontal extent in microns for which any boundaries between the ganglion cell-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer could not be identified.[3]

Data extraction and analysis

The documents found in the search were exported to the EndNote software (version x9.3.3, Clarivate Analytics, 2020, Philadelphia, US) to eliminate duplicates, and subsequently imported into the Microsoft Excel 2019 program (Version 16.0.13426.20270, 32 bits, Microsoft Corporation, Redmond, Washington, US). Two authors independently screened and assessed the studies for eligibility, with discrepancies resolved after discussion. According to the Oxford Center for Evidence-Based Medicine Levels of Evidence, the methodological quality of the studies was graded. Data included first author, year of publication, number of eyes, gender, type of diabetes, stage of the DR, follow-up (months), diagnosis, type of OCT, treatments used, pre and post BCVA, and the biomarkers found associated with gain or loss of vision were recorded on a standardized data collection sheet. Descriptive statistics were performed using mean and standard deviation (SD) for continuous variables, and numbers (n) and percentages (%) for categorical data, using the Stata software version 15.1 (StataCorp. 2015, Texas, United States).

RESULTS

Seven studies were included in the analysis. Regarding the characteristics of the studies included (Table 1), three studies were conducted in the United States, one was multicentered, one in the United Kingdom, one Japan and one in Turkey. Four were retrospective, longitudinal cohort study and three were cross-sectional observational studies.

All demographic information including number of eyes, gender, type of diabetes, stage of DR was found in four of seven studies. Regarding gender, which was specified in five of seven studies, the proportion of men was 61.5% and there were 38.4% women. The type of diabetes was specified in five of seven studies, and type 2 DM was found in 85.8% of the participants and type 1 DM in 14.1%. Regarding the stage of diabetes, it was recorded in five of eight studies, being fully detailed in four of seven. The percentage of patients with mild nonproliferative diabetic retinopathy (NPDR) was 28.2%, with moderate NPDR was 28.5%, with severe NPDR was 15.9% and with proliferative diabetic retinopathy (PDR) was 27.4%.

Table1. Characteristics of the studies included in the review

	Increasing/presence of DRIL	Decreasing/absence of DRIL	DRIL and other associations
Sun et al.[3]	Greater horizontal DRIL extent, worse baseline VA (per 100µm; p<0.001) Extent, worse VA during 8 month follow-up (per 100µm; p<0.001)	At least 250 µm at 4 months, no eyes had VA decline of at least 1 line at 8 months 77.7% had VA improvement of at least 1 line	NA
Sun et al.[5]	Greater extent, worse VA during 12 month follow-up (p<0.0001)	Better VA and fewer foveal scans with DRIL (p<0.0001)	NA
Das et al.[7]	For each 100µm in the average global DRIL, decrease in the mean VA of 4.6 letters	Better final VA in absent of DRIL (9.8 letters, p<0.001)	OR of having DRIL was greater in eyes with disrupted ELM (OR: 4.4; p=0.003, EZ (OR: 2.7; p=0.03), presence of ERM (OR: 2.8; p=0.03) and increase in RTF (OR: 2.2; p< 0.001)
Zur et al.[8]	NA	Better final VA in absent of DRIL at the baseline (LogMAR VA, 0.50 versus 0.47; p=0.03)	DRIL at baseline and (OR: 8.8; p< 0.001) intraretinal cyst (OR: 17.8, p<0.001) were predictive for DRIL at 12 months
Eraslan et al.[9]	Eyes with DRIL worse final BVCA (logMAR VA, 0.1 versus 0.35; p<0.0001)	NA	NA
Radwan et al.[12]	Eyes with DRIL at baseline had poorer initial VA versus eyes lacking DRIL at baseline (logMAR VA, 0.5 versus 0.24; p=0.008)	The greatest vision improvement at 8 months was noticed in eyes with no baseline DRIL	DRIL length and DRIL extent are higher in non DME resolvers
Lee 2019[13]	Eyes with DRIL worsen final BVCA	NA	Intraretinal fluid is associated with DRIL (p< 0.001)

DRIL: disorganization of inner retinal layers; VA: visual acuity; NA: not available; DME: diabetic macular edema; OR: odd ratio; ELM: external limiting membrane; EZ: ellipsoid zone; ERM: epiretinal membrane; RTF: retinal thickness at the fovea; BVCA: best corrected visual acuity.

Table 2. Analysis of the presence/ absence of DRIL in visual acuity

Characteristics of the studies included in the review															
Author	Year	Country	Type of study	Number of eyes	Diagnosis	Imaging	Follow-up	Gender	Type DM	Stage DM	IVI	Laser	Corticoids	DRIL	DRIL associated with worse final BVCA
Sun et al.[3]	2014	United States	RLC	120	DME-CI	SD-OCT	8	Men: 49 Women: 47	DM1: 34 DM2: 62	NPDR mild: 24 Moderate: 38 Severe: 24 PDR: 34	+	+	-	+	+
Sun et al.[5]	2015	United States	RLC	43	DME-CI	SD-OCT	12	Men: 39 Women: 19	DM1: 21 DM2: 37	NPDR mild: 22 Moderate: 21 Severe: 16 PDR: 21	-	-	-	+	+
Das et al.[7]	2018	United Kingdom	CO	100	DME-CI	SD-OCT	4	Men: 70 Women: 30	DM1: 17 DM2: 63	NPDR mild: 53 Moderate: 37 Severe: 0 PDR: 10	+	-	-	+	+
Zur et al.[8]	2019	Multicenter	CO	177	DME-N DME-R	SD-OCT	12	Men: 100 Women: 77	DM1: 0 DM2: 177	NPDR: 86 PDR: 91	+	-	-	+	+
Eraslan et al.[9]	2020	Turkey	RLC	296	DME	SD-OCT	19.61±9.31	NA	NA	NA	+	-	-	+	+
Radwan et al.[12]	2015	United States	CO	32	DME-CI	SD-OCT	8	Men: 27 Women: 5	DM1: 0 DM2: 32	NA	-	+	-	+	+
Lee 2019[13]	2019	Japan	RLC	65	DME-CI	SD-OCT	13.9 ± 1.8	NA	DM1: 0 DM2: 65	NPDR mild: 4 Moderate: 8 Severe: 18 PDR: 35	+	-	-	+	+

DM: diabetes mellitus; IVI: intravitreal injection; DRIL: disorganization of the inner retinal layers; BVCA: best corrected visual acuity; RLC: retrospective longitudinal cohort; DME-CI: Center involved diabetic macular edema; SD-OCT: spectral domain optical coherence tomography; NPDR: nonproliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; CO: cross-sectional observational case series; DME-N: Naive diabetic macular edema; DME-R: refractory macular edema.

In 100% of the studies the diagnosis of center involved diabetic macular edema (DME-CI) was included by SD-OCT (Heidelberg). In the totality of the studies, the imaging technique was detailed and performed by an experienced ophthalmologist. The diagnosis of DME-CI according to our operational definition was recorded in five of seven studies and the definition of DRIL was made according to the description of Sun et al. in all the studies.[4] Regarding the history of previous treatments, this information was possible to obtain in six of seven studies. The treatments described were: intravitreal injections in 62.5%, macular laser in 12.5%, PRP in 25%, corticosteroids (DEX-I) in 25% and combined treatment in 12.5%.

In all the studies, the presence of DRIL was recorded and its association with BVCA was evaluated (Table 2). The BVCA was registered in all the studies. The measurement was carried out using the LogMAR scale. In all the studies, the presence of DRIL was associated with a worse final BVCA using $p < 0.05$ as a statical significance.

DISCUSSION

The literature analysis enables us to highlight the importance of DRIL as a biomarker of DME. Numerous studies have discovered a variety of biomarkers for patients with DME, but what is worth mentioning is that reliability differs. Many of them are obtained invasively and not all of them are eligible to predict the effectiveness of the treatment that is ultimately the main objective.[14] When looking for a biomarker, it is extremely important that it be easily obtained, that it is measurable over time, that it is obtained non-invasively and that it is capable of predicting a response over time in order to evaluate the response to treatment reliably and efficiently. Disorganization of the inner retinal layers has been considered a robust biomarker in DME.[3,4] The presence of DRIL has been shown to be associated with VA and is a predictor of VA in the future. The exact mechanism by which DRIL affects VA has not been fully demonstrated and the need for histological studies becomes important.[3] Nevertheless, studies have shown that edema causes an interruption of the visual pathway due to the inability of the axons of the bipolar cells because their elasticity has exceeded.[15] Disorganization of the inner retinal layers could represent disorganization or destruction of cells within inner retinal layers, including bipolar, amacrine, or horizontal cells, and possibly indicates a disruption of pathways that transmit visual information from the photoreceptors to the ganglion cells.[3] Studies using OCT-A in resolved DME have shown that in patients with DRIL, the loss of the superficial (SCP) and deep plexuses (DCP) is greater. This has also been explained due to the relationship between the thickness of the retinal layers and the degree of ischemia of the capillary plexuses.[16] Other studies have shown that, in the presence of foveal DRIL, the vessel density (VD) at the SCP and DCP is lower, and it is associated with worse VA. This highlights the role of retinal vascular ischemia in the pathogenesis of DRIL.[17]

The characteristics and importance of DRIL has been evaluated using SD-OCT. Sun et al have shown that centrally located DRIL was correlated with VA in eyes with DME-CI.[3] In DME-CI, VA change over time was best associated with DRIL change over time, showing a dynamic association of DRIL morphology in these patients.[12]

On the other hand, the location of the central DRIL is not solely important since it was found that its horizontal extension was also involved as a predictor of VA in the future.[3] Radwan and et al found that greater horizontal DRIL extent was associated with worse baseline VA.[12] Das et al demonstrated the association between the horizontal extent of the DRIL and VA, finding that, for every 100µm increase in DRIL, there is a negative impact of approximately 6 letters (ETDRS score).[7] DRIL by itself does not explain the findings in VA since this biomarker is strongly associated with other alterations such as the interruption of the external limiting membrane (ELM) and ellipsoid zone (EZ) layers.[7]

Artificial intelligent (AI) based in deep learning algorithm in the actual "Big-Data" era allows us to construct useful therapeutic protocols for managing retinal diseases.[18-20] Biomarkers are part of the necessary information to feed the AI data networks. The results presented in this systematic review shows that DRIL can be one of those biomarkers. Although information relies on an OCT image acquisition, processed and medical human interpretation, some concerns must be described. In the present study, all the imaging comes from the same OCT device. This is good for our purpose, avoiding differences in this aspect, however there are more OCT devices in the market, and it will be necessary to confirm our present results with more OCT equipment. Also, it is difficult to confirm the clinical use of our results until an AI software is available for obtaining an objective and reproducible imaging interpretation, avoiding the potential human mistakes that could arise doing manually retinal OCT measurements, where a few microns means a big difference between normal and pathological.

In conclusion, DRIL as a biomarker and its presence has been shown to be an important predictor of VA in the future in patients with DME. Histopathological studies are required to understand its mechanism of action.

REFERENCES

1. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology. 2018;125(10):1608-22.
2. Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Ophthalmol. 2014;132(11):1334-40.
3. Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132(11):1309-16.
4. Sun JK, Radwan SH, Soliman AZ, Lammer J, Lin MM, Prager SG, et al. Neural retinal disorganization as a robust marker of visual acuity in current and resolved diabetic macular edema. Diabetes. 2015;64(7):2560-70.
5. Kwan CC, Fawzi AA. Imaging and biomarkers in diabetic macular edema and diabetic retinopathy. Curr Diab Rep. 2019;19(10):95.
6. Soliman AZ, Radwan SH, Prager SG, Kwak H, Silva PS, Aiello LP, et al. Spectral domain optical coherence tomography parameters associated with visual acuity in patients with resolved center-involved diabetic macular edema. Invest Ophthalmol Vis Sci. 2012; 53(14):1338. [ARVO Annual Meeting Abstract].
7. Das R, Spence G, Hogg RE, Stevenson M, Chakravarthy U. Disorganization of inner retina and outer retinal morphology in diabetic macular edema. JAMA Ophthalmol. 2018;136(2):202-8.
8. Zur D, Iglicki M, Sala-Puigdollers A, Chhablani J, Lupidi M, Fraser-Bell S, et al.; International Retina Group (IRG). Disorganization of retinal inner layers as a biomarker in patients with diabetic macular oedema treated with dexamethasone implant. Acta Ophthalmol. 2020;98(2):e217-23.
9. Eraslan S, Yıldırım Ö, Dursun Ö, Dinç E, Orekici Temel G. Relationship between final visual acuity and optical coherence tomography findings in patients with diabetic macular edema undergoing anti-VEGF therapy. Turk J Ophthalmol. 2020;50(3):163-8.
10. Vujosevic S, Toma C, Villani E, Muraca A, Torti E, Florimbi G, et al. Diabetic macular edema with neuroretinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. Acta Diabetol. 2020;57(3):287-96.
11. Chalam KV, Bressler SB, Edwards AR, Berger BB, Bressler NM, Glassman AR, et al.; Diabetic Retinopathy Clinical Research Network. Retinal thickness in people with diabetes and minimal or no diabetic retinopathy: Heidelberg Spectralis optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(13):8154-61.
12. Radwan SH, Soliman AZ, Tokarev J, Zhang L, van Kuijk FJ, Koozekanani DD. Association of disorganization of retinal inner layers with vision after resolution of center-involved diabetic macular edema. JAMA Ophthalmol. 2015;133(7):820-5.
13. Lee H, Kang KE, Chung H, Kim HC. Three-dimensional analysis of morphologic changes and visual outcomes in diabetic macular edema. Jpn J Ophthalmol. 2019;63(3):234-42.
14. Budzinskaya MV, Fursova AZ, Pedanova EK. Spetsificheskie biomarkery otveta na antiangiogennuyu terapiyu [Specific biomarkers of response to antiangiogenic therapy]. Vestn Oftalmol. 2020;136(2):117-24.
15. Pelosini L, Hull CC, Boyce JF, McHugh D, Stanford MR, Marshall J. Optical coherence tomography may be used to predict visual acuity in patients with macular edema. Invest Ophthalmol Vis Sci. 2011;52(5):2741-8.
16. Sarraf D, Rahimy E, Fawzi AA, Sohn E, Barbazetto I, Zacks DN, et al. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. JAMA Ophthalmol. 2013;131(10):1275-87.
17. Cennamo G, Montorio D, Fossataro F, Fossataro C, Tranfa F. Evaluation of vessel density in disorganization of retinal inner layers after resolved diabetic macular edema using optical coherence tomography angiography. PLoS One. 2021;16(1):e0244789.
18. Islam MM, Poly TN, Walther BA, Yang HC, Li YJ. Artificial intelligence in ophthalmology: a meta-analysis of deep learning models for retinal vessels segmentation. J Clin Med. 2020;9(4):1018.
19. Waldstein SM, Vogl WD, Bogunovic H, Sadeghipour A, Riedl S, Schmidt-Erfurth U. Characterization of drusen and hyperreflective foci as biomarkers for disease progression in age-related macular degeneration using artificial intelligence in optical coherence tomography. JAMA Ophthalmol. 2020;138(7):740-7.
20. Sorrentino FS, Jurman G, De Nadai K, Campa C, Furlanello C, Parmeggiani F. Application of artificial intelligence in targeting retinal diseases. Curr Drug Targets. 2020;21(12):1208-15.