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Original Article

The Comparison of Intracystic Hyperreflectivity in Different Macular Edema Etiologies. Is It a New Optical Coherence Tomography Biomarker?

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Abstract

Objectives: To detect the difference in internal hyperreflectivity of macular cystoid spaces in diabetic retinopathy (DR), exudative (wet) age-related macular degeneration (wet AMD), branch retinal vein occlusion (BRVO).

Methods: The medical records of the consecutive patients who were followed up from Prof. Dr. Cemil Taşçıoğlu City Hospital, from 01 April 2023 to 01 June 2023, in the retina department, have been included in this study. The mean gray value (GV) and max-min GV parameters of the cystoid spaces which were detected in the spectral domain optical coherence tomography (OCT) scans, were measured by using the ImageJ program (National Institutes of Health, Bethesda, Maryland, USA). The established diagnosis, baseline best corrected visual acuities (BCVA), OCT biomarkers such as serous macular detachment, hard exudate, hyperreflective foci and central macular thicknesses were also noted. The parameters were compared to each other regarding the different pathologies.

Results: The mean-max GV of cystoid spaces and the mean-max GV of cystoid/vitreous ratio were found to be highest in the DR, followed by BRVO, and lowest in wet AMD ($p<0.001$ and $p<0.001$; respectively). Correlation analyses revealed a positive correlation between OCT biomarkers and intracystic hyperreflectivity (ICH) ($p<0.001$, respectively). Besides, the max GV cystoid/vitreous ratio is positively correlated with the BCVA ($p<0.046$; $p=0.04$, respectively).

Conclusion: This pilot study investigates ICH in macular edema of various etiologies. The ICH was highest in the DR group, followed by the BRVO group, and lowest in the AMD group. It has been observed that there is a high correlation between ICH and OCT biomarkers. Findings support the hypothesis that ICH may reflect underlying inflammatory processes and contribute to individualized treatment approaches in retinal vascular pathologies.

Keywords: Branch retinal vein occlusion, diabetic maculopathy, diabetic retinopathy, intracystic hyperreflectivity, optical coherence tomography

Introduction

Macular edema accompanies various pathologies and is characterized by complaints of decreased vision. The main reason for the deterioration of vision in patients with DR, BRVO, and wet AMD is fluid accumulation in the macular region, which is very important in making treatment decisions (1-3).

Intraretinal fluid-containing cavities which are called cystoid spaces, pseudocysts, or at times inappropriate cysts, can arise from impairment of the inner blood-retina barrier (BRB), associated with an insufficiency in the metabolism of the Muller cells (4). Trauma, vascular, or inflammatory ocular diseases can cause disruption of the BRB and enable the fluid

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to pass to the retinal interstitium. Besides that, the localization of the cysts varies depending on whether the source is the inner BRB or the outer BRB because of the diffusion barrier function of the inner and outer plexiform layers (2).

Increased vascular hyperpermeability, disruption of BRB, and imbalance between osmotic-hydrostatic pressure in retinal vasculature caused by various underlying diseases such as DR and BRVO are the leading causes of this formation (2,5). Additionally, emerging hypoxia, oxidative stress, increased vascular leukostasis, and loss of pericytes contribute to the worsening of this situation simultaneously. One of the most prominent theories regarding the pathophysiology is the theory of increased inflammation, which holds that elevated levels of proinflammatory cytokines cause damage to BRB, vascular endothelial dysfunction, and increased vascular permeability. It has been shown in many studies that systemic and local proinflammatory cytokines such as VEGF, TNF-alfa, MCP-1, IL-6, and IL-8 are significantly increased in macular edema due to DR and BRVO (6,7). In addition to this, intraretinal fluids may arise from the choroidal vasculature due to the disruption of Bruch's membrane in wet AMD (8).

With the introduction of OCT in clinical practice, ophthalmologists can recognize the structural features of macular edema. By courtesy of this, several OCT biomarkers have been identified for many diseases, particularly for DR, such as intraretinal cyst (IRC), disorganization of retinal inner layers (DRIL), external limiting membrane (ELM)/ellipsoid zone (EZ) integrity, retinal hyperreflective foci (HRF), and serous macular detachment (SMD) (9). It has been shown in various studies that these biomarkers, detected by macula OCT, can be used to determine the type of intravitreal injection and that some of these biomarkers regress with an intravitreal steroid injection due to their anti-inflammatory effect (7,10,11).

The presence of intracystic hyperreflectivity is another finding detected by OCT in patients with CME. The contents of some cysts were found to be more hyperreflective compared to other cysts on OCT, and this condition was previously named a solid cyst (12). Various theories have been put forward regarding the content of cysts with this reflectivity, and it has been suggested that they may be blood, inflammatory end products or macrophages, and these theories have been tried to be confirmed by multi-modal imaging (13,14). However, none of these possible theories has yet been proven conclusive.

There are a few reports about intracystic hyperreflectivity in the literature but they all define the hyperreflective cyst with the help of trained individuals and compared with other findings, accompanied by the presence or absence of intracystic hyperreflectivity in a selected single disease, such as DME or BRVO. However, there are no reports regarding the distribution and measurement of cystic hypereflectivity in different macular edema etiologies. The aim of the current study was to investigate whether intracystic hyperreflectivity varies in different cystic edema etiologies, in order to highlight the pathogenesis of this clinical entity. With this purpose, we measure the intracystic hyperreflectiveness in DR, BRVO, and wet AMD patients to define the association between this value and the grade of inflammation; also find out the benefit of the cyst internal hyperreflectivity in predicting prognosis in such macular edema and to introduce intracystic hyperreflectivity as a new OCT biomarker.

Methods

The study was carried out in accordance with the tenets of the Declaration of Helsinki and ethical approval was obtained from the Institutional Ethical Board of Prof. Dr. Cemil Taşcıoğlu City Hospital in İstanbul (date: 19.02.2024, no: 24). Written informed consent was taken from all individual participants.

In our study, we studied the medical records of 172 eyes of 152 patients who were followed up from 01 April 2023 to 01 June 2023 in the retina department of Prof. Dr. Cemil Taşcıoğlu City Hospital. All consecutive patients admitted to our clinic between 01 April 2023 and 01 June 2023, who have been suffering from macular edema due to one of the following diseases: DR, BRVO, wet AMD, were included. All patients with these features within the specified date ranges were considered to have passed the preliminary criteria for the study. After that, diagnosis, age, and BCVA were noted from patients' files and macula OCT images captured by using SD-OCT (HRA-Spectralis, Heidelberg Engineering-Germany) were collected. Phacic patients, patients with files containing inadequate data, previous vitrectomy history, low-quality OCT images (Q score lower than 20) due to corneal opacity or vitreous opacity, macular edema without cyst formation in OCT images, patients with macular ischemia detected by FFA, and patients with two different etiologies simultaneously causing macular edema were excluded from the study.

Initially, OCT biomarkers such as SMD, hard exudate, number of HRF in macular OCT sections were evaluated and noted by two independent specialists before hyperreflectivity measurements. The presence of HRF was graded according to the range of the number of HRF detected in OCT sections (1-10; 11-20, ≥21). Central macular thickness (CMT) of each patient was also recorded. Subsequently, 128-bit images, which were selected so that the cyst appearance was in the 3x3 mm area of the central macula, were obtained (Shown in Fig. 1). For quantitative measurement of hyperreflectivity in cysts, images of the foveal median section -obtained in raster scan mode- were imported to Image J software. After that, the largest cysts' borders were manually selected with the help of the tools integrated into Image J by two separate ophthalmology specialists independently (Shown in Fig. 2a and Fig. 2b). Interobserver variability was evaluated by comparing the two observers' measurements statistically (p=0.287, p=0.361, respectively, Student's t-test).

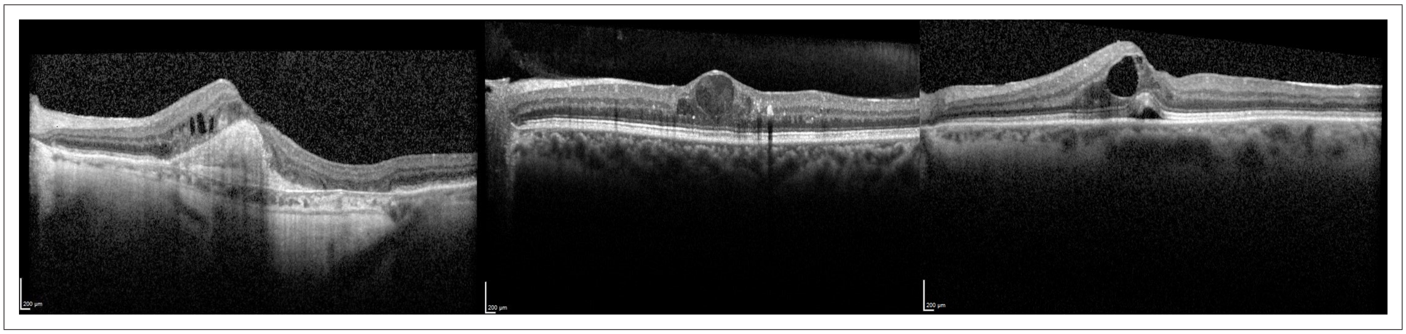

Figure 1. Example of cystoid spaces in macula without intracystic hyperreflective material in wet age-related macular degeneration (left side), cyst with intracystic hyperreflective material in diabetic macular edema (middle) and cystoid space appearance in branch retinal vein occlusion.

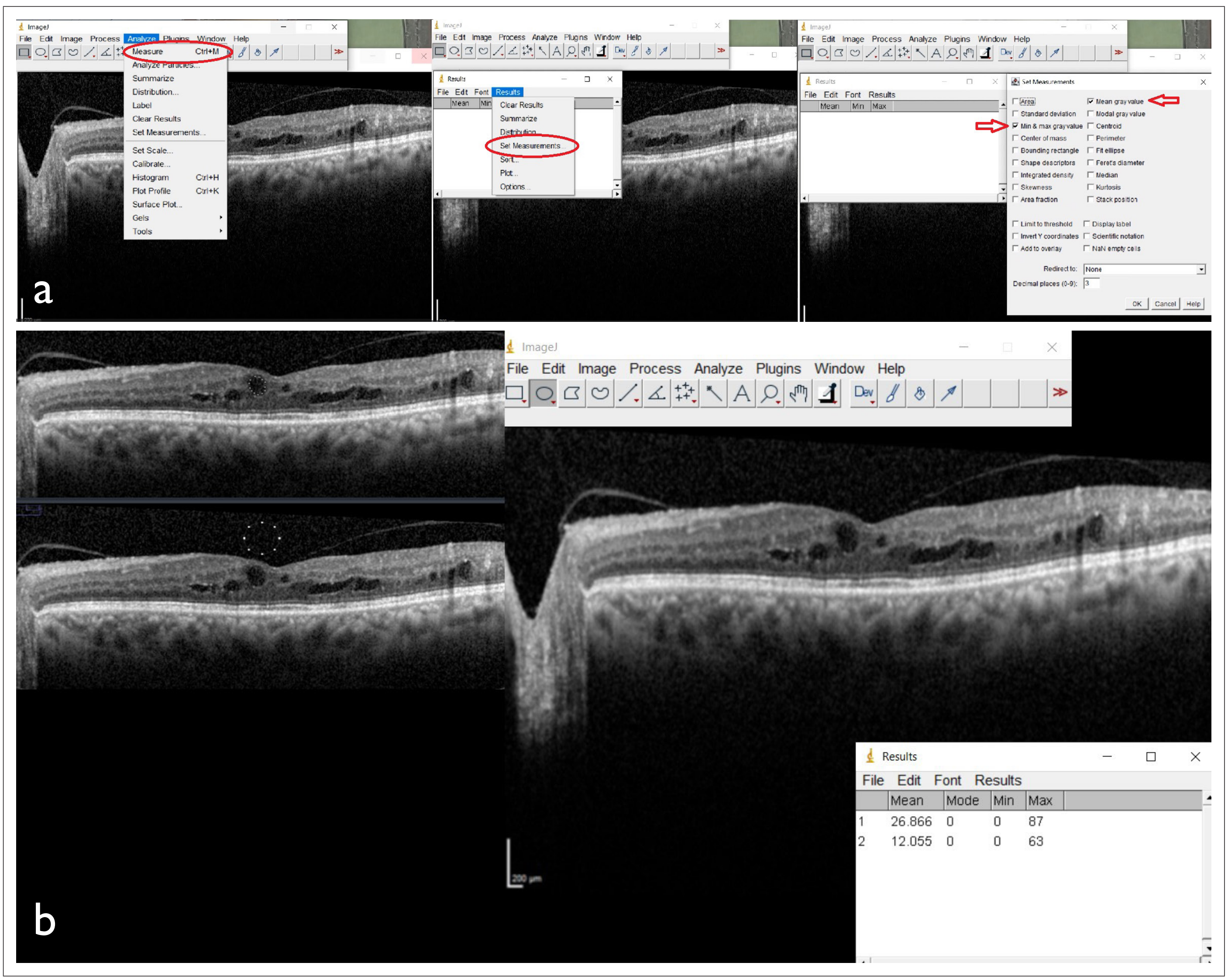

Figure 2. (a) Parameter selection settings before the measurements, **(b)** Example of cyst border and randomly chosen vitreous area manually selection and gray value measurements with the help of the tools integrated into Image J software.

Intraobserver variability was assessed by looking at the coefficient of variance (% CV). CV was calculated by using the following formula: CV=SD/mean *100. The first observer's CV was 14%-15%, and the second observer's CV was 12%-14%.

The mean level of gray value, mode level of gray value, maximum level of gray value, and minimum level of gray value were measured inside the cysts. For each pixel, the program assigns a nominal gray value from its own scale in bit type, and as this value increases, the color of the pixel approaches white, and as this value decreases, it approaches black.

Considering that it will be a reference point against contrast and brightness differences that occur at the time of examination, all of these measurements were performed for the prefoveal vitreous area adjacent to the selected cyst which was identified in each patient's OCT images. The results of two different measurements that the specialists made were averaged for all values and noted. Afterward, intracystic values were compared to values of the selected vitreous region, and "Ratio mean gray value (RATmeanGV)", "Ratio maximum gray value (RATmaxGV)", "Ratio minimum gray value (RATminGV)" were calculated, and comparisons were made for each of these calculations.

These calculations and measurements were recorded by using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY, USA) program for statistical analysis. The variables were investigated using histograms and probability plots, and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. One-way ANOVA was used to compare these parameters. Kruskal-Wallis tests were conducted for those variables that were not normally distributed. The Levene test was used to assess the homogeneity of the variances. An overall p-value of less than p<0.05 was considered to show a statistically significant result. When an overall significance was observed, pairwise post-hoc tests were performed using Tukey's test. We performed Spearman and Pearson tests for the correlation analysis, depending on whether it was normally distributed or not.

Results

In this study, 172 eyes of 152 patients meeting these criteria were classified according to diagnoses: 40 eyes in the wet AMD group, 88 eyes in the DR group, and 44 eyes in the BRVO group. There were 83 (%48) male and 89 (%52) female patients. The mean age was 66.0 ±8.0 for the DR group, 78.4 ±8.4 for the wet AMD group, and 64.9±10.6 for the BRVO group. The CMT was measured as 376.1±96 for the DR group, 430.6±270.8 for the BRVO group, and 408.5±179.4 for the wet AMD group. All the demographic findings, in addition to the central macular thickness, are summarized in Table 1. Mean durations of macular edema were 10.43±8.07 months for the wet AMD group, 8.87±6.50 months for the DR group and 7.85±5.56 months for the BRVO group. The average of previous injection numbers was 5.95±3.78 for the wet AMD group, 4.26±2.66 for the DR group and 3.56±1.70 for the BRVO group. The mean time since the last intravitreal intraocular injection was 1.80±0.79 months for the AMD group, 2.05±0.91 months for the DM group, and 2.36±1.33 months for the BRVO group.

As expected, it was determined that there was no statistically significant difference between the groups in the maximum gray value (IVmaxGV), minimum gray value (IVminGV), or mean gray value (IVmeanGV) measurements of the selected vitreous area, which was taken as the reference point in each OCT section (Table 2).

As a result of the measurements, the mean gray value of intracystic space (ICmeanGV) was significantly higher in the DR group (57.43±28.97) than in the other groups and followed by the BRVO group (45.98±34.57), at the very least in the wet AMD group (36.28±19.19, p<0.001). The DR group (112.68±36.61) had the highest maximum gray value of intracystic space (ICmaxGV), followed by the BRVO group (100.73±38.79) and finally the wet AMD (82.55±31.72) group (p<0.001). Similarly, RATmaxGV was found to be highest in the DR group (1.59±0.73), second highest in

Table 1. All demographic findings and central macular thickness

Diagnosis	Age	BCVA (logMAR)	CMT
DR	66.0 ±8.0	0.5±0.5	376.1±96
BRVO	64.9±10.6	1.0±0,7	430.6±207.8
wet AMD	78.4 ±8.4	1.1±0.5	408.5±179.4
p	<0.001	0.23	<0.001

DR: Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration; BCVA: Best corrected visual acuity; CMT: Central macular thickness.

Table 2. Gray value measurements of selected vitreal areas as a reference point

Measurement	DR	BRVO	wet AMD	p
IVmeanGV	20.9±10.1	20.4±6.6	22.6±12.28	0.85
IVmaxGV	77.2±25.5	77.3±19.3	79.4±29	0.98
IVminGV	0	0	0	

IVmeanGV: Intravitreal mean gray value; IVmaxGV: Intravitreal maximum gray value; IVminGV: Intravitreal minimum gray value; DR: Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration.

the BRVO group (1.39±0.78), and lowest in the wet AMD group (1.08±0.35) and these findings are statistically significant (p<0.001). Likewise, the RATmeanGV value was again found to be highest in the DR group (3.26±2.16), followed by the BRVO (2.66±2.75) and the wet AMD (1.85±1.33) groups, respectively. Afterward, statistical analyses show, in the DR group, a significant positive correlation between the BCVA and RATmeanGV-RATmaxGV. (RATmeanGV p<0.001 CC: 0.3, RATmaxGV p:0.046 CC: 0.2) For the BRVO group; RATmaxGV has to be found significantly positively correlated with BCVA. (p=0.04, CC: 0.5) In all measurements, ICminGV, IVminGV, and RATminGV were not significant between groups (Table 3).

Table 3. Intracystic gray values and comparison results of intracystic measurements to values of the selected vitreous region

Measurement	DR group	BRVO group	wet AMD	p
ICmeanGV	57.4±29	46±34.6	36.3±19.2	<0.001*
ICmaxGV	112.7±36.6	100.7±38.8	82.5±31.7	<0.001*
ICminGV	0	0	0	
RATmeanGV	3.3±2.1	2.7±2.7	1.8±1.3	<0.001*
RATmaxGV	1.6±0.7	1.4±0.8	1.08±0.3	<0.001*
RATminGV	0	0	0	

ICmeanGV: Intracystic mean gray value; ICmaxGV: Intracystic maximum gray value; ICminGV: Intracystic minimal gray value; RATmeanGV: Ratio mean gray value; RATmaxGV: Ratio maximum gray value; DR: Diabetic Retinopathy; BRVO: Branch Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration.

Table 4. Results of correlation analysis between gray value measurements and OCT biomarkers

	SMD	Hard exudate	HRF
ICmeanGV	p<0.001 r: 0.320	p<0.001 r: 0.442	p<0.001 r: 0.641
ICmaxGV	p<0.001 r: 0.335	p<0.001 r: 0.407	p<0.001 r: 0.550
ICminGV	p<0.001 r: 0.287	p<0.001 r: 0.427	p<0.001 r: 0.554
RATmeanGV	p<0.001 r: 0.289	p<0.001 r: 0.421	p<0.001 r: 0.591
RATmaxGV	p<0.001 r: 0.364	p<0.001 r: 0.471	p<0.001 r: 0.601
IVmeanGV	p: 0.691 r: -0.031	p: 0.776 r: -0.022	p:0.824 r: -0.017
IVmaxGV	p: 0.395 r: -0.065	p: 0.381 r: -0.067	p: 0.464 r: -0.061

SMD: Serous Macular Detachment; HRF: Hyperreflective foci; ICmeanGV: Intracystic mean gray value; ICmaxGV: Intracystic maximum gray value; ICminGV: Intracystic minimal gray value; RATmeanGV: Ratio mean gray value; RATmaxGV: Ratio maximum gray value; IVmeanGV: Intravitreal mean gray value; IVmaxGV: Intravitreal max gray value.

Correlation analyses between gray value measurements and OCT biomarkers have shown that ICmeanGV, ICmaxGV, ICminGV value was statistically significantly correlated in a positive manner with the presence of SMD, hard exudate and the number of HRF. On the contrary, it was observed that there was no statistically significant correlation between threshold measurements, IVmeanGV and IVmaxGV, and biomarkers. Correlation coefficients and p-value between these groups have been summarized in Table 4.

Discussion

The current study is a pilot study that measured intracystic hyperreflectivity in cystoid spaces in different pathologies and found that the intracystic hyperreflectivity was highest in DR, followed by BRVO, and lowest in wet AMD. Additionally, our study first to assess a high positive correlation between defined OCT biomarkers and elevated intracystic reflectivity. Therefore, we hypothesize that intracystic hyperreflectivity correlates with and indicates the inflammatory status.

In OCT images, fluid accumulations within the retina are generally defined as cystoid spaces located between different layers of the retina. The imbalance between fluid mechanisms can be explained by increased transudation and exudate in terms of inflow and by the deterioration in Müller cells and retina pigment epithelium (RPE) functions at the cellular level in terms of outflow. When the diseases we examined in our study are compared, the edema pathogenesis that comes to the fore in DME and BRVO is mostly cytotoxic edema (intracellular swelling) and vasogenic edema, but on the other hand, in wet AMD, the main mechanism is vasogenic edema due to increased vascular permeability in neovascularization (2,4,6,7). Berlin et al. (15) stated that hyperreflective cystoid spaces in OCT images of AMD patients can contain higher amounts of exudative materials such as lipids, proteins, and blood components, suggesting that increased reflectivity is caused by surface lipids, high-molecular-weight cellular components, and transport lipoproteins. In our study, although the intracystic reflectivity parameters (ICmeanGV, ICmaxGV, RATmaxGV) were lowest in AMD eyes, this can be attributed to the degenerative and serous nature of the cystoid spaces typically seen in AMD, which are less protein-rich and contain fewer cellular residues. Conversely, in DME and BRVO, the breakdown of the blood–retina barrier and cytotoxic edema can result in an acute vascular leakage and the accumulation of proteinaceous, lipid-rich, and cellular material, explaining the higher reflectivity measured in these groups. We believe that, although this hyperreflective pattern may also be observed in certain AMD cases, its overall prevalence is much lower compared to DME and BRVO, and this difference in frequency likely accounts for the higher mean reflectivity values detected in DR and BRVO groups. Therefore, we believe that the mechanism proposed by Berlin et al. (15) should not be restricted solely to AMD but may also apply to the DR and RVO groups, where similar exudative and inflammatory mechanisms are more dominant. We advocate the idea that the sources of these materials are the acute extravasation of large molecules from compromised vessels in early disease stages, and the cytoplasmic remnants of degenerated retinal cells subjected to chronic mechanical stretching from recurrent cytotoxic edema during later stages.

Quan-Yong Yi et al. (16) indicated that by comparing diseases caused by macular edema, such as central retinal vein occlusion (CRVO), BRVO, wet AMD, and DR with each other based on inflammatory cytokine levels in aqueous humor, DME patients had the highest level of inflammation, after CRVO patients. According to our study, hyperreflectivity values of inner cystoid spaces were higher in DR patients among the other etiologies included in this comparison. To our knowledge, our study is the first in the literature to detect nominally and compare the hyperreflectivity of the cystoid spaces in various diseases caused by macular edema. These findings strongly suggest that internal hyperreflectivity of cystoid spaces was correlated with disease inflammation levels.

Optical coherence tomography is indispensable for distinguishing the basis of structure in macular edema and also for detecting the evaluation of edema after treatment (3,17,18). Thanks to these opportunities, relationships between the disease courses and the treatment modality could be determined; in this way, several biomarkers associated with inflammation were identified (10,19). Several studies show that in these biomarkers' presence, there is an increased necessity for a repeated intravitreal anti-vascular endothelial growth factor (Anti-VEGF) and steroid injection, Moreover, for diabetic macular edema (DME) patients intracystic hyperreflective material emerged in approximately in 7. month of evaluation of macular edema appearance in their OCT and the patients who had this indication has more persistent DME appearance in their follow-up. Additionally, patients who had ICHRM had received an increased number of intravitreal injections and in these patients, findings such as EZ-ELM defects and inner segment-outer segment junction layer disruption were more common than in patients without intracystic hyperreflective material (ICHRM). Because of this interrelation, after hyperreflective material resolution, final visual acuity has been found to decrease further than in patients with low-reflective cysts (15). According to this study, we hypothesize that the ICHM is a new OCT biomarker that appears in the early stages of DME pathogenesis. In chronic stages, cysts transform into cystoid degeneration and this may explain the correlation between ICHRM and BCVA in our study.

Possible theories run about the cyst's containing material and pathophysiology which causes a hyperreflective appearance in OCT (13,20-21). Most prominent ones defend the idea that cysts containing blood, inflammation end products, or fibrinoid material increase the reflectivity of cysts; however, the definitive answer is still unclear. Besides, Kashani et al. (22) have mentioned in their study that fibrin or exudative material located within and around the cysts can cause a high level of reflectance in OCT and optic coherence tomography angiography (OCTA) images. Our study demonstrates that the diseases have the same order in the level of Aquos inflammation and reflectivity measurements such as ICmeanGV, ICmaxGV, RATmaxGV, and RATmeanGV. In addition, our study has shown that there is a statistically positive correlation between the ICmeanGV, ICmaxGV, ICminGV, RATmeanGV and RATmaxGV values, which indicate an increase in intracystic reflectivity and OCT biomarkers that have been determined to be correlated with increased inflammation by other studies. Hence, these findings strongly suggest that the contents located within the cystoid spaces are more likely to be inflammation-related, such as inflammation and product or fibrinoid material, rather than red blood cell (RBC) or low-weighted serum proteins.

It is important to note that our study has limitations. Initially, these findings obtained one cyst of each section which was manually selected, and in the future, automatic selection of all cysts in macular OCT images by artificial intelligence improves the validity of measurements. Secondly, our study may have been a low level of evidence base. The hyperreflective material inside cysts can be RBCs or lipids. Also, our study shows the correlation between baseline BCVA and ICHRM hence, it would be more accurate to evaluate the changes during long-term follow-up in order to predict the prognosis of the ICHRM sign. Our results should be supported by studies with higher evidence investigating the relationship between cytokines in the anterior chamber and intracystic hyperreflectivity. In the future, exact materials can be identified in histopathological in vitro studies with animal models.

Nowadays, multiple treatment modalities have been used against macular edema. These include, most prominently, intravitreal anti-VEGF injection, intravitreal steroid implants, and laser photocoagulation. There are a variety of different strategies and methods to bring patients and these treatments together. However, some patients with macular edema do not respond well and persist with these first-line treatments. In DME patients, refractory or persistent macular edema prevalence estimates up to %50 and patients are referred to a different therapeutic option (23). As the time between choosing the right agent and non-response to the given treatments increases, irreversible damage occurs to the macula and vision decreases permanently. Therefore, we believe that it is important to identify new generation OCT biomarkers, such as ICHRM, to show their response to the agents used in treatment and their effects on prognosis; to ensure that the right patient is administered the appropriate treatment agent earlier.

Conclusion

Our study reveals that intracystic hyperreflectivity was highest in the DR group, followed by BRVO patients and lastly wet AMD patients. As has been determined, this ranking appears to be correlated with the degree of inflammation of the diseases. Furthermore, this study has shown a high positive correlation between intracystic reflectivity and OCT biomarkers. Considering this, in a disease with high inflammation levels, the intracystic hyperreflectivity value increases and from our perspective, intracystic hyperreflectivity should be positioned as a new inflammatory OCT biomarker. Overall, considering that inflammation is one of the main factors in the formation of DME. Patients with OCT biomarkers like ICHRM, because of the effect due to the high inflammation burden, can respond favorably to intravitreal steroid therapy with anti-VEGF treatment. Hence, earlier and more effective results can be obtained at macular edema resolution.

Disclosures

Ethics Committee Approval: This study was approved by the Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Date: 19.02.2024, Number: 24) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from all patients.

Conflict of Interest: None declared.

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