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Vitreous Levels of Autophagy Activation Biomarkers in Patients with Rhegmatogenous Retinal Detachment

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Abstract

Background/Aims: Autophagy mechanisms in experimental models of retinal detachment have a role in photoreceptor damage as the main cause of visual loss in rhegmatogenous retinal detachment (RRD). The study aimed to analyse the levels of the autophagy biomarkers: human Bcl-2 interacting protein 1 (Beclin-1) and autophagy-related protein 5 (ATG5) in the vitreous of patients with RRD and to investigate their relationship with the clinical features of the disease.

Methods: Sixty-four patients with RRD were enrolled. The control group comprised 20 patients with an idiopathic full-thickness macular hole. In a study group, the duration of symptoms, extent of RRD, macular involvement, number of retinal breaks, and presence of proliferative vitreoretinopathy were analysed.

Results: The vitreous levels of Beclin-1 were significantly higher in the study group (0.548–2.024 ng/ml, median: 1.104 ng/ml) than in the controls (0–0.705 ng/ml, median: 0.255 ng/ml; p<0.001), whereas ATG5 levels showed no differences (p=0.266). Beclin-1 and ATG5 levels demonstrated no correlation with the extent of RRD, number of retinal breaks, or involvement of the macula; however, the vitreous expression of these proteins significantly decreased with the duration of RRD; r=-0.626199, p<0.001 and r=-0.686180, p<0.001, respectively. The vitreous ATG5 levels were negatively correlated with proliferative vitreoretinopathy, grade C, compared to eyes without this complication (p=0.0175).

Conclusion: The study demonstrated increased vitreous levels of Beclin-1 in eyes with RRD compared with controls. The results also showed that Beclin-1 and ATG5 levels decreased with the duration of RRD, indicating that autophagy mechanisms weakened during the course of prolonged RRD. This may explain why most patients with RRD do not recover their visual acuity despite successful surgery.

Keywords: Rhegmatogenous retinal detachment; Vitreous; Autophagy; Beclin-1; ATG5

Abbreviations: Beclin 1: BCL-2 interacting protein 1; RRD: Rhegmatogenous Retinal Detachment; FTMH: Full-Thickness Macular Hole; RPE: Retinal Pigment Epithelium; PPV: Pars Plana Vitrectomy; ATG5: Autophagy-Related Protein 5; OCT: Optical Coherence Tomography; ELISA: Enzyme-Linked Immunosorbent Assay; BCVA: Best Corrected Visual Acuity; IOP: Intraocular Pressure; PVR: Proliferative Vitreoretinopathy; AMD: Age-Related Macular Degeneration; LC3-II: Microtubule-Associated Protein 1 Light Chain 3; LC3-I: Microtubule-Associated Protein 1A/1B-Light Chain 3

Introduction

Detachment of photoreceptors from the Retinal Pigment Epithelium (RPE) is a characteristic clinical feature of Retinal Detachment (RD) [1]. Several types of RD exist: rhegmatogenous, exudative, tractional, and combined tractional-rhegmatogenous; however, the former is the most common form [1]. The incidence of Rhegmatogenous Retinal Detachment (RRD) varies geographically, but is generally estimated to be approximately 12.17 (10.51–14.09) per 100,000 population per year and based on recent studies, an increasing trend for RRD incidence worldwide is observed [2,3]. Factors such as age, high myopia, previous intraocular surgery, ocular trauma, RD in the contralateral eye, and positive family history increase the risk of RRD [3-6]. The duration of macular detachment before surgery is an important prognostic factor regarding the final visual recovery. Clinical observations show that many eyes with 'macula-off' RRD, despite successful postoperative retina reattachment, demonstrate deterioration of vision [7,8]. Clinical experience has demonstrated that vision restoration can be achieved if the retina is reattached within 1 week [7,8]. Experimental studies have demonstrated the existence of cellular defence mechanisms against photoreceptor death during RD [9-11].The activation of autophagy during the early period after photoreceptor separation from the RPE cell layer has been previously documented [9-11]. Autophagy is a natural cellular recycling system that is activated by various factors that occur during RRD, including nutrient deprivation, energy limitation, and oxidative stress [10]. Autophagy maintains cellular homeostasis and inhibits cell death; however, experimental studies have indicated that autophagy occurs only in the early stages of the disease [9-11]. In prolonged RRD,

reduced activation of the autophagy pathway and a shift from cell survival to death has been observed [9]. Autophagy occurs in several stages: 1) initiation (formation of a pre-autophagosomal structure), 2). nucleation (formation of phagophores), and 3) elongation (engulfment of the cytoplasm by damaged organelles or proteins), 4) maturation and fusion (formation of an autophagosome, which fuses with a lysosome), and degradation of the enclosed material by lysosome enzymes [12].

Bcl-2 interacting protein 1 (Beclin-1) and autophagy-related Protein 5 (ATG5) are key regulators of autophagy. Among the more than 40 autophagy-related proteins, Beclin-1 was the first autophagy effector identified to play a central role in initiating autophagy through autophagosome formation [13,14]. ATG5 is recruited later during the autophagy activation cascade and plays a crucial role in autophagosome expansion (elongation phase) [15]. Both of these proteins are important in the progression of autophagy and have been studied as potential biomarkers and therapeutic targets for some systemic diseases [16,17]. There are many publications on autophagy mechanisms in experimental models of RD, indicating that its role in photoreceptor damage is the main cause of visual loss in RRD [9-11,18-20]. To the best of our knowledge, there has been only one clinical study on autophagy protein expression in patients with primary RRD [21]. Therefore, this study aimed to assess the presence of the autophagy biomarkers Beclin-1 and ATG5 in the vitreous of patients with RRD. We also aimed to evaluate the associations between the vitreous levels of these autophagy proteins and age, sex, refraction, lens status, duration of RRD symptoms, and clinical features of the disease, including the extent of RRD, number of retinal breaks, presence and stage of Proliferative Vitreoretinopathy (PVR), and macular involvement.

Materials and Methods

Participants and study design

The study provided double-centre data and had a case-control design. The study group comprised 64 patients (64 eyes) with primary RRD qualified for Pars Plana Vitrectomy (PPV) between April 2023 and April 2025 in the Clinic of Ophthalmology and Ocular Oncology, Jagiellonian University Medical College in Krakow, Poland, and the Clinic of Ophthalmology of Medical University of Silesia, Faculty of Medical Sciences in Zabrze, Poland. The control group comprises 20 individuals with idiopathic Full-Thickness Macular Hole (FTMH). The exclusion criteria were other concomitant ocular diseases (glaucoma, uveitis, intraocular tumours, Age-related Macular Degeneration (AMD), diabetic retinopathy, or other retinal diseases) or systemic comorbidities possibly involving autophagy in the pathogenesis of diabetes, cardiovascular diseases, renal disorders, autoimmune diseases, neurodegenerative disorders, and malignancies. Current and former smokers were excluded. Participants with prior vitrectomy or recurrent RRD were excluded.

The RRD duration was based on the onset of visual field defects (loss of the peripheral or central visual field), as reported by the patient. Baseline ophthalmic examinations included Best Corrected Visual Acuity (BCVA) assessment, tonometry, anterior segment examination, dilated indirect fundoscopic examination, B-scan ultrasonography (Ellex Eye Cubed A and B-scan Module, Version 3, Germany), and Optical Coherence Tomography (OCT) (Topcon 3D OCT 2000, Japan) in eyes with RRD in which

scanning of the macula was possible. In controls with FTMH, ophthalmic examinations included all the procedures described earlier. The study protocol was approved by the Bioethics Committee of the Jagiellonian University Medical College (approval no.1072.6120.66.2022) and the Ethics Committee of the Medical University of Silesia (approval no. PCN/CBN/0052/KB1/22). This study was conducted in accordance with the tenets of the Declaration of Helsinki, and all patients provided written informed consent to participate in the study.

Sample collection

As autophagy activity showed diurnal fluctuations in all participants, the vitreous specimen was collected at the same time between 8:00 and 11:00 AM during the 25G PPV (Consellation Vision System, Alcon Inc., Texas, USA). If the patient was scheduled for combined phacoemulsification and PPV, vitreous collection was performed before cataract surgery. The procedure was initiated with a closed infusion line to avoid vitreous dilution. A 5-cc sterile syringe was connected to the aspiration line of the cutter for manual aspiration of the vitreous. After reducing the cut rate to 600 cpm, the vitreous sample was aspirated from the mid-vitreous to the attached syringe. Usually, 0.5 to 1.0 ml of the undiluted vitreous was aspirated into a syringe. Then immediately, all samples of vitreous were collected in sterile Eppendorf tubes in aliquots and stored at -80 °C until analysis. Then, the infusion line was opened to the fluid to Increase Intraocular Pressure (IOP), and vitrectomy was performed.

Laboratory tests

All laboratory tests were performed at the Bioengineering and Cell Imaging Laboratory of the Centre for the Development of Therapies for Civilisation and Age-Related Diseases at Jagiellonian University Medical College. Human Beclin-1 and ATG5 levels were evaluated using a Human ATG5 Enzyme-Linked Immunosorbent Assay (ELISA) Kit (ELK Biotechnology, USA; cat. number ELK7439) and a Human BECN1 ELISA Kit (ELK Biotechnology, USA; cat. number ELK3491). Briefly, the collected specimens were thawed and centrifuged at 2,000 rpm for 5 min and transferred to ELISA reaction plates for analysis according to the manufacturer's protocol. The absorbance was measured using a Cytation 5 microplate reader (Agilent BioTek, USA), and the results were calculated using a standard curve and expressed in ng/ml.

Statistical analysis

Numerical variables were presented as medians, along with the first and third quartiles (Q1–Q3) due to a lack of normal distribution, as confirmed by the Kolmogorov–Smirnov test. Numerical variables were compared between the two groups using the Mann–Whitney U test. Categorical variables were reported as numbers and percentages and were analysed using the $\chi 2$ test or Fisher's exact test. Associations between numerical variables were assessed using Spearman's rank correlation coefficient (R). Statistical significance was set at $p<0.05$. All statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 28 (IBM Corp., 2023) or R Core Team (2013). R: Language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Results

Demographic and clinical characteristics of patients with RRD and controls

The study group included 64 patients (64 eyes) with RRD: 33 males (51.6%) and 31 females (48.4%) aged 56 -71 years, median: 65.1 years. The control group

consisted of five males (25%) and 15 females (75%) aged 65–73 years, median: 69.5 years. Statistically significant differences were observed in age and sex distributions among the analysed groups. RRD was more frequent in younger patients and in males, whereas FTMH was more often diagnosed in older individuals, and females were more often affected by this macular disease. No statistically significant differences were observed between the study and control groups regarding the prevalence of refractive errors. None of the patients with RRD had any other concomitant ocular pathologies, except for moderate senile cataracts. A history of prostatic hyperplasia, vertebral column degenerative disc disease, cardiac arrhythmia, and deafness was reported in nine patients; however, no other systemic comorbidities were present in the analysed group of patients. In the control group, no other chronic ocular or systemic diseases that potentially involve autophagy mechanisms in their pathogenesis were present.

The duration of ocular symptoms in the RRD group ranged from 2 to 360 days (median: 14 days). The preoperative BCVA ranged from light perception to 0.8 by the Snellen charts. IOP ranged from 8 to13 mmHg (median: 11 mmHg) in the affected eye. In the control group, the IOP in eyes with FTMH ranged from 15 to 20 mmHg (median: 17 mmHg). Furthermore, 33(51.6%) patients were phakic, whereas 31 (48.4%) had pseudophakia in eyes with RRD. In phakic eyes, the lens was clear in 16 cases (25%), and moderate cataracts were diagnosed in 17 cases (26.6 %). In all cases, indirect fundoscopy revealed RRD with an extent ranging from 2 to12 clock hours (median: 4.5 clock hours). In 50 (59.2%) patients, the 'macula-off' RRD was diagnosed. Fifty-three eyes (67.2%) showed varying degrees of PVR. The detailed clinical characteristics of the patients and eyes in the RRD and control groups are presented in **Table 1.**

Table 1: Detailed demographic and clinical characteristics of patients with Rhegmatogenous Retinal Detachment (RRD) and a control group.

Parameter	**Patients (RRD)**	**Controls (FTMH)**	**P - value**
	N=64	**N=20**	
Demographic characteristics			
Age, years (range, median)	56 – 71 (65.1)	65-73 (69.5)	0.025*
Sex, n (%)			
Males	33 (51.6)	5 (25)	0.038*
Females	31 (48.4)	15 (75)	
Clinical characteristics			

BCVA, Snellen, n (%)			
1.0 – 0.7	9 (14.1)	0 (0)	
0.6 – 0.3	12 (18.8)	5 (25)	0.001*
0.2 – 0.05	11 (17.1)	14 (70)	
0.05 - light perception	32 (50)	1(5)	
Tonometry, mmHg (range, median)	8 -13 (11)	15-20 (17)	0.001*
Lens			
Phakic eyes	33 (51.6)	12 (60)	
Clear lens	16 (25)	2 (10)	0.02*
Moderate age-related cataract	17 (26.6)	10 (50)	
Pseudophakic eyes	31 (48.4)	8 (40)	
Refractive error (number, %)			
Myopia < -6.0D	12 (18.8)	4 (20)	0.001*
Myopia ≥ -6.0D	14 (21.9)	1 (5)	
FTMH (diameter, µm) (range, median)	-	250-550 (455.2)	-

RRD			
Duration of symptoms (days) (range, median)	2-360 (14)	-	-
Extent of RRD, n (%)			
1 – 3 clock hours	6 (7.1)		
4 - 6 clock hours	27 (32.1)		
7 – 9 clock hours	12 (14.3)		
10 -12 clock hours	18 (21.4)		
'Macula-off' (number of patients, %)	50 (59.2)		
Retinal breaks (range, median)	1 -12 (2.2)		
PVR (number, %)			
A	15 (23.4)		
B	18 (28.2)		
C	10 (15.6)		

*p value – significant statistically

RRD - rhegmatogenous retinal detachment, FTMH – full thickness macular hole, PVR – proliferative vitreoretinopathy

Comparison of Beclin-1 and ATG5 vitreous expression in the RRD group and the control group

The vitreous levels of autophagy biomarker Beclin-1 were significantly higher in a study group (0.548–2.024 ng/ml, median: 1.104 ng/ml) than in controls

(0–0.705, median: 0.255 ng/ml); p<0.001, whereas ATG5 levels showed no differences in both analysed groups (p=0.266), and ranged from 1.103–2.119 ng/ml, median: 1.59 ng/ml and 1.071–1.741 ng/ml, median: 1.40 ng/ml, respectively **(Figure 1).**

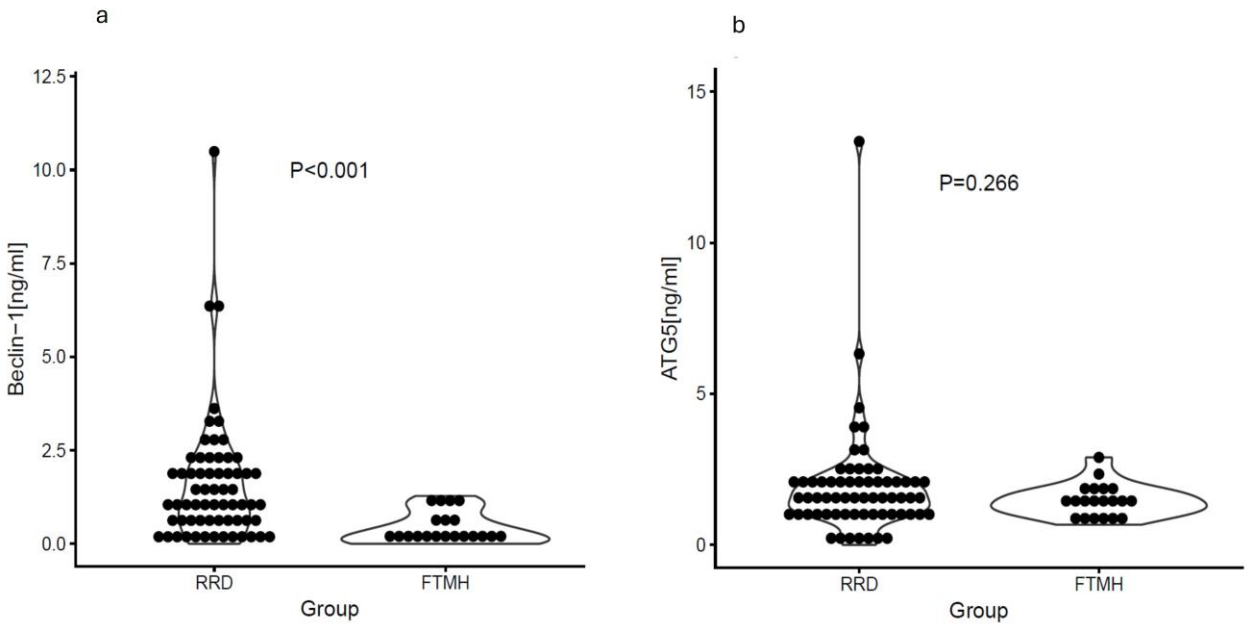

Figure 1: Vitreous levels of Beclin-1 (a) and ATG5 (b) in patients with rhegmatogenous retinal detachment (RRD) and full thickness macular hole (FTMH).

Analysis of the vitreous levels of Beclin-1 and ATG5 in the RRD group also showed a statistically significant positive correlation between the expression of these two proteins; r=0.628, p<0.001.

Comparison of Beclin-1 and ATG5 vitreous expression in the RRD group and clinical features of the disease

Vitreous levels of Beclin-1 and ATG5 were negatively correlated with the duration of RRD, and the expression of these autophagy proteins was significantly decreased with prolonged RRD **(Figure 2).** Additionally, significantly higher levels of Beclin-1 and ATG5 were observed in patients with an RRD duration of 7 days or less than in patients with an RRD duration of more than 7 days **(Figure 3).**

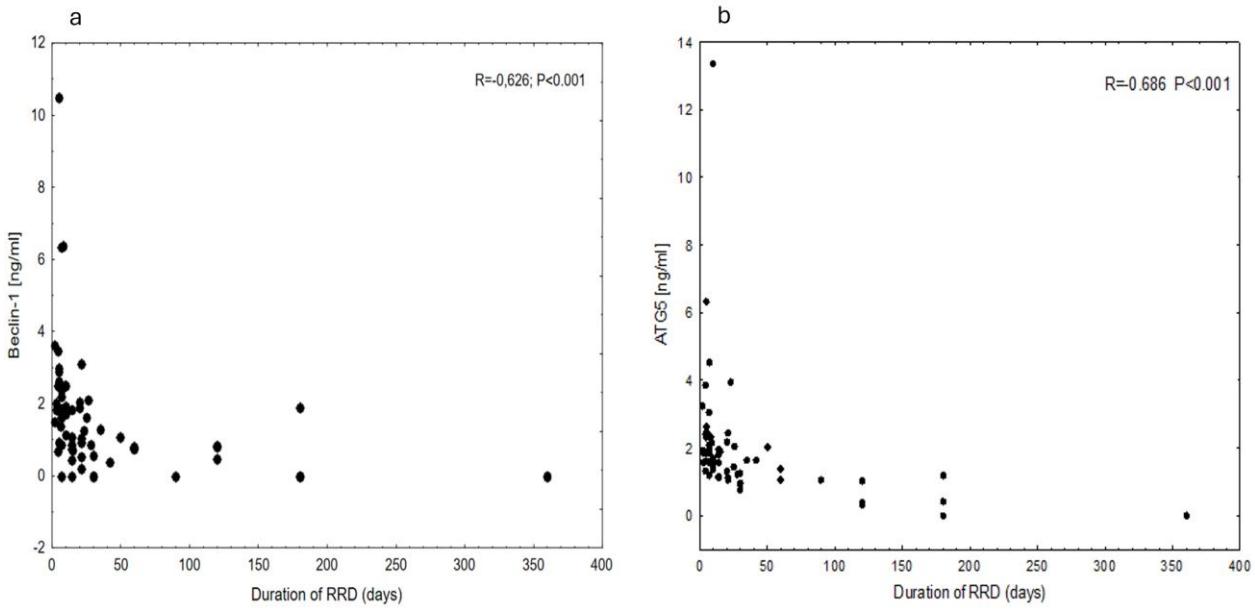

Figure 2: Comparison between vitreous expression of Beclin-1 (a) and ATG5 (b) and the duration of rhegmatogenous retinal detachment (RRD) symptoms.

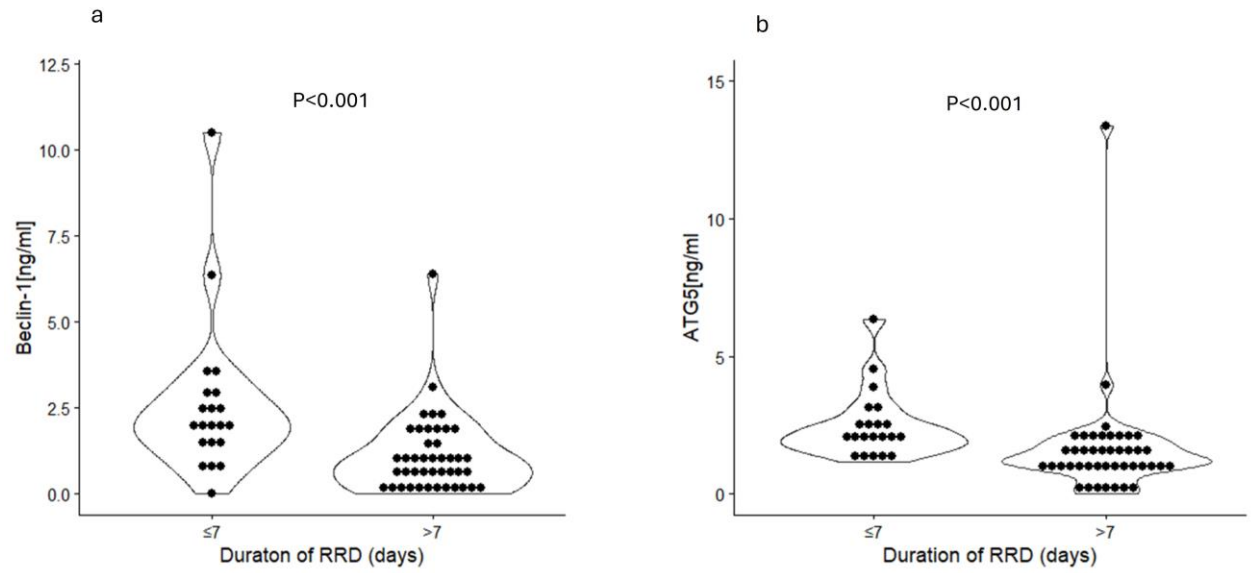

Figure 3: Correlations between vitreous levels of Beclin-1 (a) and ATG5 (a) according to the duration of Rhegmatogenous Retinal Detachment (RRD) symptoms determined as ≤ 7 days and > 7 days.

The results demonstrated no differences in vitreous levels of Beclin-1 and ATG5 regarding RRD area (p=0.25 and p=0.07, respectively) **(Table 2)**. No statistically significant differences were observed between vitreous expression of Beclin-1 and ATG5 and the number of retinal breaks (p=0.809 and p=0.962, respectively) and 'macula-off' vs. 'macula-on' RRD, either **(Table 2).** However, the vitreous ATG5 levels were lower in eyes with PVR grade C than in those without this severe complication (range:

1,155–2,077 ng/ml (median: 1,838 ng/ml) and 0,329-1,536 ng/ml (median: 0.748 ng/ml), respectively (p=0.0175) **(Table 2).** Additionally, refractive error (myopia <-6.0D vs. ≥-6.0D) and lens status showed no relationship with Beclin-1 and ATG5 vitreous levels, either **(Table 2).**

Table 2: Correlation between vitreous expression of Beclin-1 and ATG5 and gender, macula involvement, retinal detachment extent, number of retinal breaks, presence of Proliferative Vitreoretinopathy (PVR) and refraction in analyzed group of patients.

z	Beclin-1		ATG5	
Variable	**Median (Q1-Q3)**	**P-value**	**Median (Q1-Q3)**	**P-value**
Sex				
Male	1.5665 (1.064-2.077)		1.0685 (0.277-1.885)	
Female	1.5145 (1.175-1.973)	0.982	0.747 (0.182-1.700)	0.281
Macula involvement				
'Macula-off'	1.5665 (1.072-2.178)		1.104 (0.474-1.929)	
'Macula-on'	1.763 (1.176-2.077)	0.5	1.256 (0.736-2.502)	0.547
Retinal detachment extent (clock hours)				
1-3	1.644 (1.378-1.954)		1.8485 (1.123-2.498)	
4-6	1.838 (1.15-2.077)		0.858 (0.700-1.829)	
7-9	1.911 (1.212-2.391)		1.90 (0.8654-2.332)	
10-12	1.146 (0.432-1.624)	0.075	0.964 (0-1.800)	0.249
PVR				
0	1.854 (1.558-2.385)		1.829 (0.909-2.2021)	
A	1.838 (1.155-2.077)		0.903 (0.566-2.057)	
B	1.151 (1.017-2.321)		1.081 (0.171-1.80)	
C	0.748 (0.329-1.536)	0.0175*	0.73 (0-1.885)	0.1151
Myopia				
< - 6.0D	1.5785 (1.066-2.031)		0.9665 (0.324-1.8755)	
≥ -6.0D	1.452 (1.112-1.800)	0.665	0.852 (0-1.800)	0.545
Lens status				
Clear	0.855 (0.394-2.057)		1.8295 (1.243-2.178)	
Moderate cataract	0.537 (0-1.095)		1.5145 (1.082-1.985)	
Pseudophakia	1.085 (0.171-1.885)	0.26	1.582 (1.045-2.077)	0.43

*p value – statistically significant

RRD - rhegmatogenous retinal detachment, PVR – proliferative vitreoretinopathy

Comparison of Beclin-1 and ATG5 vitreous expression with patients' age and sex in both groups

Overall, analysis of the expression of Beclin-1 and ATG5 in the RRD and control groups showed that the vitreous levels of these proteins decreased with age, and this correlation was statistically significant (r=-0.241264, p=0.027 and r=-0.231171, p=0.034, respectively). No differences were observed in the vitreous levels of Beclin-1 and ATG5 according to patient sex **(Table 2).**

Discussion

The retina, containing light-sensitive photoreceptor cells, is one of the most metabolically active tissues in the human body, with the highest oxygen consumption index **[22].** The function of photoreceptors, the highly specialised cells, depends on the integrity with the most external layer of retina–RPE. Under normal physiological conditions, the retina and RPE are connected, and RPE is crucial for maintaining photoreceptor metabolism and protecting against oxidative stress **[22,23].** The RPE plays an important role in maintaining retinal homeostasis; however, this deteriorates with ageing and in the course of the disease. Alterations of autophagy processes are implicated in the pathogenesis of some ocular diseases, such as AMD, cataract, glaucoma, and diabetic retinopathy **[24].** Autophagy dysfunction in AMD is among the best studied **[25-29].** Additionally, our previous study on the serum expression of key autophagy proteins in patients with exudative AMD documented significantly reduced serum levels of Beclin-1 in the advanced stages of exudative AMD and discovered that lower serum Beclin-1 levels were present in older individuals and were more evident in patients with AMD than in controls. These findings suggest that circulating Beclin-1 decreases with age and is downregulated in patients with exudative AMD, indicating a decline in autophagy during the course of the disease **[30].** Similar to AMD, after RD, photoreceptor cells experience hypoxia and a lack of nutrients, which trigger a defence mechanism called autophagy, the process by which cells recycle damaged components **[31].** Experimental studies have indicated that in the early stages of RD, the induction of autophagy protects photoreceptors from apoptotic cell death, whereas in prolonged RD, a reduction in the activation of autophagy leads to cell death **[18-20,32].** These observations suggest that, in the early stages of RD, autophagy activation serves as a mechanism for enhancing photoreceptor survival **[33].** As demonstrated in experimental studies, prolonged RD leads to the weakening of the autophagy protective mechanism, local inflammation, cell stress, and photoreceptor death **[9-11,18-20,32].** This may explain why, despite retinal reattachment after surgery, patients with prolonged RRD do not experience vision recovery **[19,20].** Chinesky et al. demonstrated in an experimental RD model in rats that at 1 week post-detachment, there was a reduction in the activation of autophagy, resulting in a shift from cell survival to cell death, a factor responsible for vision loss in patients with RD **[32].** The authors showed that the autophagy biomarkers ATG5 and microtubule-associated protein 1 light chain 3(LC3-II) undergo upregulation within 1 day after detachment, peaking at approximately 1–3 days and

then decreasing at 7 days. This inactivation of autophagy correlates with the clinical observations that RD involving the macula needs to be repaired within 1 week to preserve central vision [7,8]. The results of this experimental study are consistent with our observations; the post-hoc analysis revealed that in patients with RRD lasted for approximately 7 days (≤7 days), higher vitreous levels of Beclin-1 and ATG5 than in those with prolonged RRD (>7 days) were observed, indicating a reduction in the activation of autophagy with the duration of RRD. However, the overall analysis of the entire group of patients with RRD showed that the vitreous levels of Beclin-1 were higher than those in the control group, whereas ATG5 showed no differences between these two groups. Our findings are inconsistent with those reported by Huang et al., who, for the first time analysed Beclin-1, microtubule-associated protein 1A/1B-light chain 3(LC3-I) and LC3-II expression in the vitreous of patients with RRD. The authors observed a lower expression of Beclin-1 and LC3-I in patients with RRD than in controls, whereas LC3-II levels were not different from those in the control group [21]. However, the control group was not homogeneous and included patients with FTMH and epiretinal membranes. In our study, the control group consisted only of patients with FTMH, which usually affects individuals aged >60 years, whereas RRD was diagnosed in younger patients. Therefore, it cannot be excluded that the lower expression of autophagy proteins in the control group was related to age, because these patients were older than those in the RRD group. Autophagy declines with ageing, and various age-dependent functional and molecular changes may impact its activity [33-35]. Huang et al. [21] showed no correlation between macular involvement or the extent of RRD and the vitreous expression of Beclin-1, and these observations are in accordance with our findings.

Notably, our study is the first to report a negative correlation between the vitreous expression of the autophagy protein ATG5 and the presence of PVR, indicating that weakened autophagy may promote the development of this severe and common complication of prolonged RRD. Our study had some limitations. First, we analysed only two autophagy biomarkers, Beclin-1 and ATG5, in the vitreous of patients with RRD. Thus, extending this research and analyse the vitreous expression of other autophagy proteins during the course of RRD is advisable. Second, because of bioethical limitations, we did not assess Beclin-1 and ATG5 levels in the vitreous of healthy eyes; thus, we do not know the normal range of expression of these proteins in vitreous fluids. As we considered eyes with FTMH to have close to normal vitreous (no RD, no glial proliferation), we used vitreous samples from patients with FTMH as controls in our study. This study is the first clinical to document significantly reduced vitreous levels of Beclin-1 and ATG5 in prolonged RRD compared to eyes with RRD lasting up to 7 days, which indicates that autophagy mechanisms weaken with disease duration. Our clinical observations are in accordance with the results of experimental studies indicating photoreceptor cell death in prolonged RRD, which may explain why, despite successful anatomical results after surgery, most patients with RRD have low visual acuity.

Conclusion

Autophagy dysfunction plays a crucial role in RRD pathology; thus, further studies involving other autophagy proteins in a larger group of patients are required to validate these observations which may be

helpful in investigating new potential therapies that protect against photoreceptor damage and improve vision restoration.

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