Molecular Vision 2018; 24:252-260 <http://www.molvis.org/molvis/v24/252>
Received 11 November 2017 | Accepted 23 March 2018 | Published 26 March 2018

Vitreous levels of apolipoprotein A1 and retinol binding protein 4 in human rhegmatogenous retinal detachment associated with choroidal detachment

Nannan Ding, Shasha Luo, Jinjin Yu, Ying Zhou, Zhifeng Wu

(The first two authors contributed equally to this work.)

Department of Ophthalmology, Nanjing Medical University Affiliated Wuxi Second Hospital, Wuxi, China

Purpose: This study aims to quantify the concentration of apolipoprotein A1 (APOA1) and retinol binding protein (RBP4) expressed in the vitreous humors of patients with rhegmatogenous retinal detachment associated with choroidal detachment (RRDCD), rhegmatogenous retinal detachment (RRD), and idiopathic epimacular membrane (IEM). This study also aims to investigate the potential role of APOA1 and RBP4 as biomarkers of RRDCD.
Methods: Enzyme-linked immunosorbent assay (ELISA) kits were used to obtain levels of APOA1 and RBP4 from the vitreous humor samples of 76 primary patients. These patients included 23 patients with RRDCD, 28 patients with RRD, and 24 patients with IEM. All patients were undergoing planned pars plana vitrectomy. The differences between the concentrations of the molecular biomarkers among different patient groups were analyzed using the Mann–Whitney U-test for nonparametric values and independent samples *t*-test or one-way ANOVA analysis for parametric data. The relationship between the molecular biomarkers, grades of proliferative vitreoretinopathy (PVR), and quadrants of retinal detachment were analyzed using nonparametric Spearman's rank correlation analysis.
Results: The vitreous concentrations of APOA1 and RBP4 were statistically significantly higher in the RRDCD group compared to the RRD and IEM groups. Patients with severe PVR demonstrated a higher concentration of APOA1 and RBP4 compared to those with mild PVR, but this finding was not statistically significant. There was a statistically significant positive correlation between APOA1 and RBP4 in the RRDCD and RRD groups. Nonparametric Spearman's rank correlation analysis revealed that levels of APOA1 and RBP4 increased statistically significantly with an increasing number of detached retinal quadrants in the RRDCD and RRD groups.
Conclusions: The findings of this study allude to the potential of APOA1 and RBP4 as specific biomarkers of RRDCD. The findings of this study may contribute to increased understanding regarding the role of APOA1 and RBP4 in RRDCD.

Rhegmatogenous retinal detachment associated with choroidal detachment (RRDCD) is a complex type of rhegmatogenous retinal detachment (RRD) characterized by rapid progression and poor prognosis. RRDCD manifests as RRD with the addition of low intraocular pressure (IOP), severe uveal inflammation [1]. Ultrasound biomicroscopy (UBM) and B-type ultrasonography are able to observe retinal detachment, as well as choroidal and ciliary detachment. The reattachment rate of RRDCD is poor and is usually a result of severe proliferative vitreoretinopathy (PVR). Preoperative systemic or topical application of glucocorticoids may reduce the ocular inflammatory response and increase the rate of retinal reattachment [2,3]. The incidence of RRDCD in primary RRD has been reported as 2.5–19.62% in Chinese cohorts [4-6], and 2–4.5% in Western populations [7,8]. The risk factors of RRDCD include aphakia, pseudophakia, a macular hole, a high degree of myopia, and old age [5,9]; a study recently reported that a larger extent of retinal detachment, high myopia, and low IOP were independent risk factors of RRDCD [6]. China is a country with a high incidence of myopia and an increasing number of elderly individuals. These reasons may be contributing factors in explaining the higher incidence of RRDCD in China when compared to Western countries.

The exact pathogenesis of RRDCD has not been fully illustrated. Seelenfreund et al. [8] put forth hypotony secondary to retinal detachment as a key instigator of events. Hypotony elicits choroidal vasodilatation that leads to the infiltration of protein-rich exudate into the suprachoroidal space, finally resulting in choroidal and/or ciliary detachment. In contrast, Jarrett et al. [1] hypothesized that ocular inflammation secondary to retinal detachment was instead the major event. Inflammation increases the permeability of choroidal capillaries that leads to protein-rich exudate infiltrating into the suprachoroidal space which finally results

Correspondence to: Zhifeng Wu, Department of Ophthalmology, Nanjing Medical University Affiliated Wuxi Second Hospital, Wuxi, China, No. 68, Zhongshan Road, Wuxi 214002, China; Phone: +86 0510-68562771; FAX: +86510-68562052; email: zhifengwu2013@126.com

choroidal and/or ciliary detachment. All these hypotheses are involved in the broken-down blood–retinal barrier and protein-rich exudate infiltrating into the subretinal and suprachoroidal space.

We successfully demonstrated in a previous study that apolipoprotein A1 (APOA1) and retinol binding protein (RBP4) are more highly concentrated in the vitreous humor of patients with RRDCD than in those with RRD [10]; this may be a reflection of the severity of the blood–retinal barrier breakdown or retinal dysfunction. APOA1 is a plasma protein that is a major component of high-density lipoprotein (HDL) and is a negative acute phase protein. However, RBP4 is a liver-synthesized adipokine that plays a role as a transport protein responsible for ferrying lipid-soluble vitamins. It has been reported that RBP4 may contribute to retinal dysfunction and degeneration [11,12].

This study quantified the concentrations of APOA1 and RBP4 in the vitreous humor of patients with RRDCD, patients with RRD, and patients with idiopathic epiretinal membrane (IEM) and examined the correlations between these biomarkers and clinical parameters. The aim of the study was to analyze biologic processes to improve our understanding of the etiopathogenesis of RRDCD and investigate the potential ability of APOA1 and RBP4 as biomarkers of RRDCD.

METHODS

The study was designed as a prospective study and performed at the Department of Ophthalmology of Nanjing Medical University in affiliation with the Wuxi Second Hospital. This study adhered to the tenets of the Helsinki agreement and the ARVO statement. Besides, the study was approved by the ethics committee of Nanjing Medical University in affiliation with the Wuxi Second Hospital. Written informed consent was obtained from all patients after a detailed discussion of the study procedures.

Study population: This study recruited 75 patients from the Department of Ophthalmology of Nanjing Medical University. The cohort consisted of 23 patients with primary RRDCD, 28 patients with primary RRD, and 24 patients with IEM. The main exclusion criteria included those with secondary or recurrent RRD, RRDCD, or IEM, a previous complication of endophthalmitis, and a history of eye surgery within the previous 6 months. Those with a history of vitreous hemorrhage were also excluded, as the increased amount of vitreous proteins may have been a confounding factor. The age, gender, duration of detachments and PVR grades were matched between groups. All enrolled subjects underwent a comprehensive and systematic eye examination by two experienced senior ophthalmologists. The number of detached quadrants and PVR grades were evaluated in the patients with RRDCD and the patients with RRD. The PVR grades were scored according to the 1983 International Classification of PVR [13].

Vitreous samples collection: Undiluted vitreous fluids were collected from patients before they underwent primary pars plana vitrectomy. Vitreous samples were taken through a three-port 25-gauge transconjunctival suture-less vitrectomy system (TSV25G; Alcon Constellation; Alcon Laboratories, Fort Worth, TX) and were suctioned directly into a 5 ml syringe. Visualization was aided with a non-contact wide-angle viewing system (Resight; Carl Zeiss Meditec AG, Jena, Germany). The undiluted vitreous samples were immediately transferred into microcentrifuge tubes and placed on ice. Each sample was centrifuged at 1360 ×*g* for 10 min at 4 °C. The supernatant was harvested from these samples and stored at −80 °C before analysis.

Measurement of APOA1 and RBP4: Double antibody enzyme-linked immunosorbent assay (ELISA) kits were used to measure APOA1 (Boster Biologic Technology, Wuhan, Hubei, China) and RBP4 (Boster Biologic Technology) concentrations in pg/ml (sensitivity of APOA1 Kit: 3.12 pg/ml, sensitivity of RBP4 Kit: 0.78 ng/ml). All procedures were performed according to the manufacturer's instructions. The standard solution was gradually diluted to obtain a standard curve. Vitreous samples were randomly added to the polystyrene microplate wells and incubated for 90 min at 37 °C. The liquid was subsequently removed. Without rinsing the wells, biotin-labeled anti-human APOA1 antibody was added and incubated for a further 60 min at 37 °C. After this, all wells were washed three times with 1X wash buffer. Subsequently, avidin-biotin-peroxidase complex (ABC) was added and incubated for 30 min at 37 °C. Tetramethylbenzidine (TMB) chromogenic solution was then added to the wells and incubated for 25 min, with precautions taken to prevent light exposure. The ABC and TMB solutions were warmed to 37 °C for 30 min before addition. Finally, Stop Solution was added to each well to end the reactions. The optical density (OD) of each well was measured using a microplate reader set to 450 nm.

Statistical analysis: All analyses were performed with SPSS 20.0 statistical software (Chicago, IL), and diagrams were drawn with GraphPad Prism 6.0 (La Jolla, CA). Abnormally distributed data were analyzed using the non-parametric Mann–Whitney U test. The chi-square test was performed for clinical variables such as sex. Correlations between molecular biomarkers and clinical parameters were explored with Pearson correlation analysis (for normally distributed

Table 1. Clinical characteristics of the study population.

Clinical parameters	RRCD n=23	RRD n=28	IEM n=24	P
Sex, n (%)				
Males	10(30.3%)	14(42.4%)	9(27.3%)	0.663
Females	13(31.0%)	14(33.3%)	15(35.7%)	
Age, y	61.4±9.09	61.3±6.74	63.8±3.50	0.348
Duration of detachments, d				
Median (range)	8(7–14)	10(7–13)	-	0.279
PVR grade				
Mild, A, B	5	10	-	0.276
Heavy, C, D	18	18	-	
IOP mmHg Median (range)	7.60 (6.9–8.2)	13.1(10.5 −14.7)	-	0.001

p Value was calculated by Mann–Whitney U test or Chi-square test. RRDCD: Rhegmatogenous retinal detachment associated with choroidal detachment; RRD: Rhegmatogenous retinal detachment; PVR: Proliferative vitreoretinopathy; A–D: The grade of PVR; IOP: Intraocular pressure; N: Numbers; Y: Years; D: Days.

data) and Spearman's nonparametric test (for abnormally distributed data). A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and clinical parameters: Table 1 shows the demographic and clinical data of the patients enrolled in the study (23 patients with RRDCD, 28 patients with RRD, and 24 patients with IEM). There were no statistically significant baseline differences in sex, age, duration of retinal detachment, and grade of PVR between the groups ($p>0.05$). In addition, the IOP was statistically significantly lower in patients with RRDCD than in patients with RRD ($p<0.001$).

The concentrations of APOA1 and RBP4 in the vitreous of the patient groups: The concentration of APOA1 was 1240 (904-1654) ng/ml in the vitreous samples from patients with RRDCD, 622(437-1038) ng/ml in the vitreous samples from patients with RRD and 299 (171-395) ng/ml in the vitreous samples from patients with IEM. The Kruskal–Wallis test showed statistically significant differences in the APOA1 concentration between the groups ($p<0.05$). Figure 1A depicts scatter plots of the APOA1 concentrations.

The concentration of RBP4 was 1547 (862-2863) ng/ml in the vitreous samples from patients with RRDCD, 391(281-496) ng/ml in the vitreous samples from patients with RRD, and 162(110-205) ng/ml in the vitreous samples from patients with IEM. The Kruskal–Wallis test showed statistically significant differences in the RBP4 concentrations between groups ($p<0.05$). Figure 1B depicts scatter plots of the RBP4 concentrations.

Grades of PVR and vitreous humor concentrations of APOA1 and RBP4: PVR grades A and B were defined as mild PVR, whereas PVR grades C and D were defined as heavy PVR. Analysis with the Mann–Whitney U test showed that there were no statistically significant correlations found between the APOA1 and RBP4 levels and different grades of PVR in the RRDCD and RRD groups (Table 2 and Table 3).

The relationship between the concentrations of APOA1 and RBP4 in the vitreous and the extent of retinal detachment: As shown in Figure 2, in the RRDCD group, Pearson correlation analysis revealed a statistically significant positive correlation between APOA1 and the extent of retinal detachment ($R=0.426$, $p=0.043$). Analysis with Spearman's rank correlation test also revealed a statistically significant positive correlation between RBP4 and the extent of retinal detachment ($R=0.574$, $p=0.004$).

Similar results were obtained in the RRD group (Figure 3). Pearson correlation analysis revealed a statistically significant positive correlation between APOA1 and the extent of retinal detachment ($R=0.426$, $p=0.024$), whereas Spearman rank correlation test revealed a statistically significant positive correlation between RBP4 and the extent of retinal detachment ($R=0.397$, $p=0.036$).

Correlation between APOA1 and RBP4 in each group: Spearman's non-parametric test was used to determine whether there was a correlation present between APOA1 and RBP4

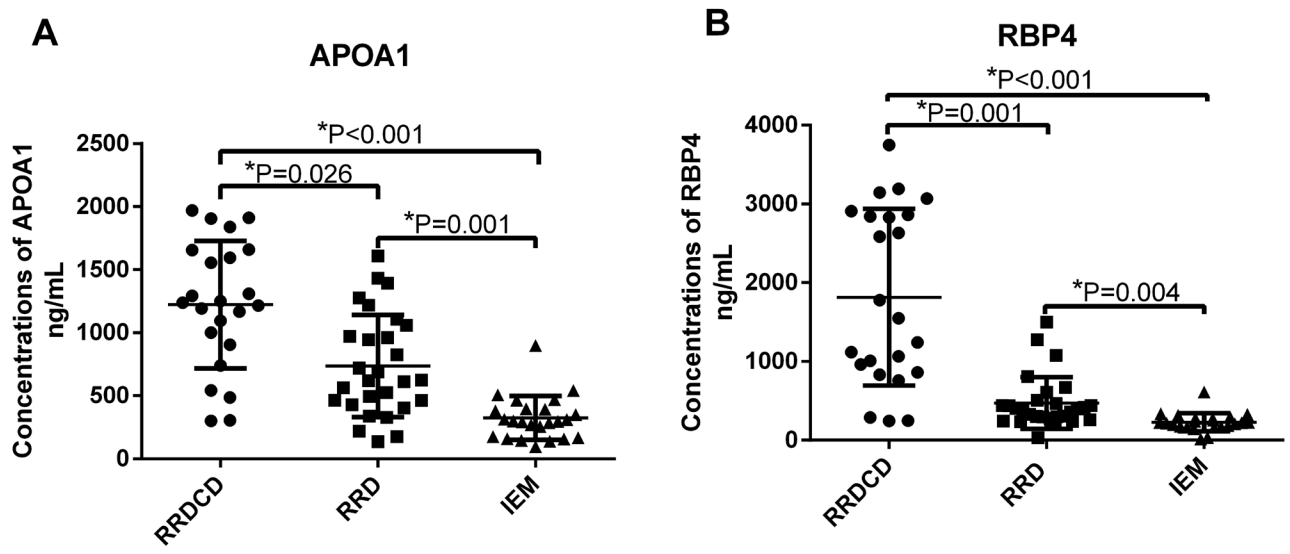

Figure 1. Scatter plots of concentration of APOA1 and RBP4. Scatter plots of concentrations of APOA1 (**A**) and RBP4 (**B**). The difference in the APOA1 and RBP4 concentrations between groups was statistically significant ($p<0.001$). Pairwise comparison among groups also showed that the difference in the APOA1 and RBP4 concentrations was statistically significant ($p<0.05$).

Table 2. The association between APOA1 and RBP4 levels and different grades of PVR in RRDCD.

PVR grades	N	ng/ml, medians and quartiles	
		APOA1	RBP4
Mild (A, B)	5	1095(514–1300)	1243(561–2065)
Heavy (C, D)	18	1245(977–1704)	2205(938–2948)
P		0.257	0.290

P value was calculated by Mann–Whitney U test. RRDCD: Rhegmatogenous retinal detachment associated with choroidal detachment; RRD: Rhegmatogenous retinal detachment; PVR: Proliferative vitreoretinopathy; **A**–**D**: The grade of PVR; APOA1: Apolipoprotein A1; RBP4: Retinol binding protein 4.

Table 3. The association between APOA1 and RBP4 levels and different grades of PVR in RRD.

PVR grades	N	ng/ml, medians and quartiles	
		APOA1	RBP4
Mild (A, B)	10	529.(402–759)	391(253–424)
Heavy (C, D)	18	773(422–1149)	399(290–705)
P		0.208	0.332

P value was calculated by Mann–Whitney U test. RRDCD: Rhegmatogenous retinal detachment associated with choroidal detachment; RRD: Rhegmatogenous retinal detachment; PVR: Proliferative vitreoretinopathy; **A**–**D**: The grade of PVR; APOA1: Apolipoprotein A1; RBP4: Retinol binding protein 4.

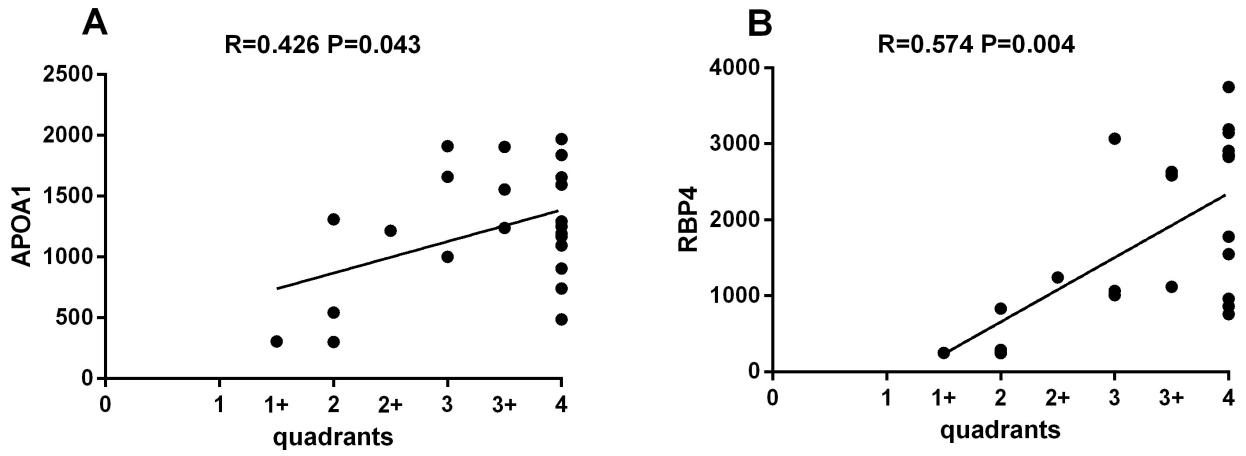

Figure 2. The relationship between the concentrations of APOA1 (R=0.426, p=0.043) and RBP4 (R=0.574, p=0.004) in the vitreous and the extent of retinal detachment in patients with RRDCD.

in each group. Statistically significantly positive correlations were identified between APOA1 and RBP4 (R=0.594, p=0.003) in the RRDCD group (Figure 4A) and between APOA1 and RBP4(R=0.708, p<0.001) in the RRD group (Figure 4B).

DISCUSSION

In this study, ELISA was used to determine the levels of APOA1 and RBP4 in the vitreous humor of patients with RRDCD, patients with RRD, and patients with IEM. Relevant clinical parameters, such as PVR grade and the extent of retinal detachment, were also measured. Further analysis was performed to investigate possible correlations between the molecular biomarkers and clinical parameters. The study results were successful in documenting a correlation between the levels of the molecular biomarkers (APOA1 and RBP4) and RRDCD. This finding strongly supports data we reported in previous studies.

APOA1 is a relatively large protein with 243 amino acid residues. It is a major protein component of vasoprotective HDL [14] and apolipoprotein E (Apo-E) [15]. Tserentsoodol et al. [16] postulated that APOA1-containing HDL facilitated

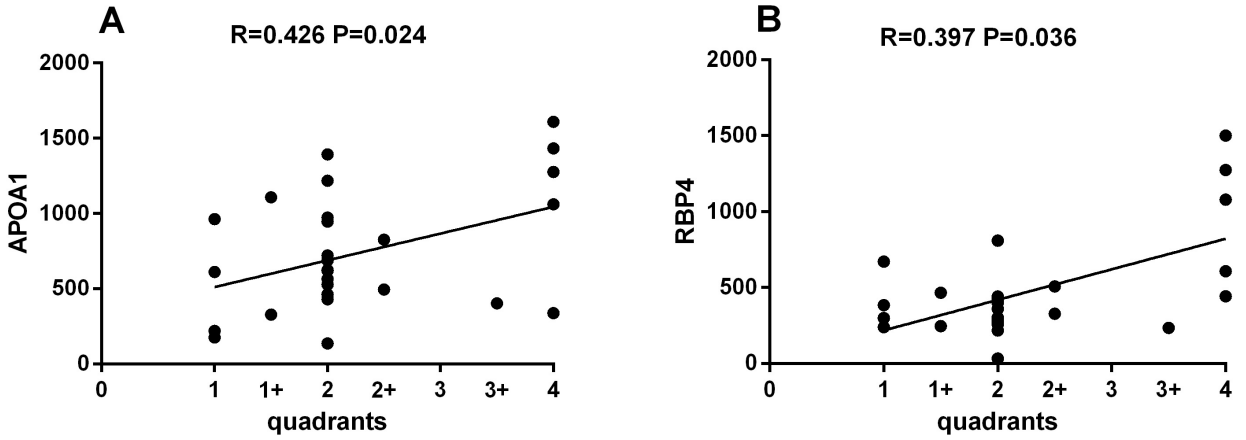

Figure 3. The relationship between the concentrations of APOA1 (R=0.426, p=0.024) and RBP4 (R=0.397, p=0.036) in the vitreous and the extent of retinal detachment in patients with RRD.

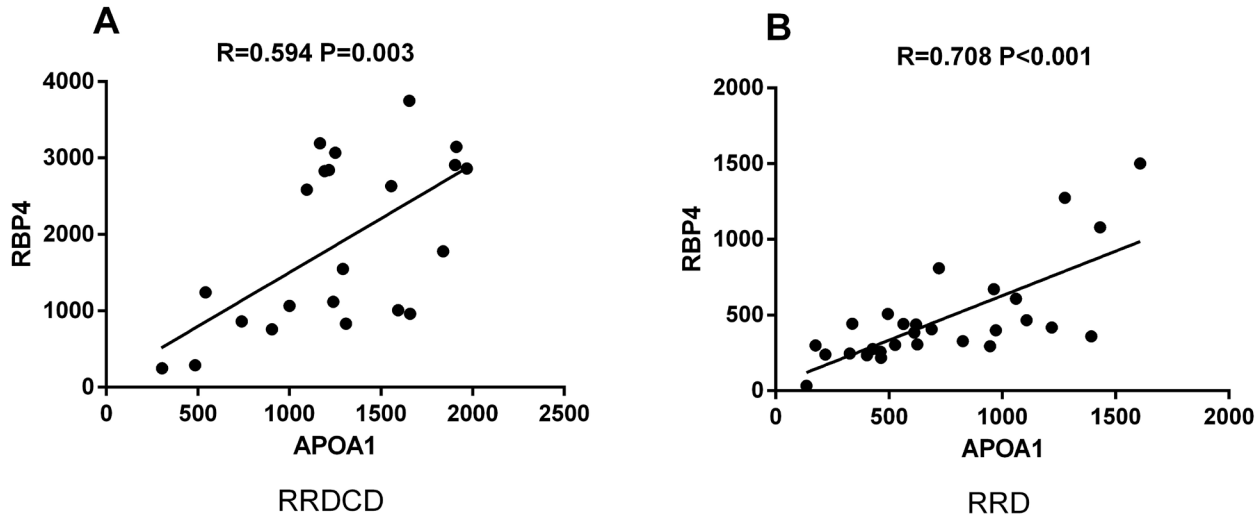

Figure 4. Correlation between APOA1 and RBP4 in each group. APOA1/RBP4 (R=0.594, p=0.003) in the RRDCD group (**A**) and APOA1/RBP4 (R=0.708, p<0.001) in the RRD group (**B**). These results confirm the presence of statistically significant positive correlations between APOA1 and RBP4 in the RRDCD and RRD groups.

lipid transport within the retina by removing deleterious oxidized lipids. Many recent studies have explored the relationship between lipid levels and the role of lipid in the pathogenesis of diabetic retinopathy (DR). Simó et al. [17] documented a higher level of APOA1 in the vitreous humor of patients with DR. Interestingly, the same authors also found a higher level of APOA1 mRNA in the RPE compared to the neuropathic epithelial layer. This indicates that the RPE serves as the main source of APOA1 in the eye. This study assumes that the DR environment can stimulate the expression of APOA1, as APOA1 is an effective scavenger for oxidative reactants [18]. Simó et al. [19] also hypothesized that increased production of retinal APOA1 is a protective compensatory mechanism against DR. Patients with DR with lower production of retinal APOA1, therefore, are more likely to experience retinal lipid deposition and higher rates of formation of hard exudates.

APOA1 is also a recognized negative acute phase protein, therefore possessing anti-inflammatory effects. Studies have shown that APOA1 is capable of inhibiting neutrophil activation and degranulation during the inflammatory response [20]. Liao et al. [21] demonstrated via in vitro experiments that APOA1 was able to inhibit activated neutrophils from adhering to fibronectin, inhibit neutrophil oxidation, reduce neutrophil degranulation, as well as reduce neutrophil killing.

The study results revealed that APOA1 was found at the highest concentrations in the RRDCD group, followed by the RRD group, and was the lowest in the IEM group. There were also statistically significant increases in the concentrations of APOA1 in the RRDCD and RRD with each increase in the number of affected retinal quadrants. With these results, we can conclude that APOA1 is a significant biomarker in RRDCD and that the levels of APOA1 correlate positively with the severity of RRDCD.

We have two inferences regarding the different APOA1 levels found in each of the three groups. First, APOA1 levels may differ due to the varying degrees of choroidal vascular leakage found in each group. As discussed previously, APOA1 is a plasma protein that is able to cross capillary membranes in the event of increased choroidal vessel permeability. Thus, we can infer that APOA1 levels may reflect the degree of choroidal vascular leakage, which, in turn, correlates with the severity of RRDCD

Second, APOA1 levels may differ due to inherent differences in retinal capability of producing APOA1. The pathophysiologic process of RRDCD is different from that of age-related macular degeneration (AMD) and DR, with RRDCD lacking the involvement of lipid deposits, such as drusen or hard exudates. Consequently, APOA1 may have a less decisive role in the pathogenesis of RRDCD. Increased APOA1 levels may instead reflect a compensatory anti-inflammatory response against severe uveitis, a known clinical manifestation of RRDCD.

RBP4 is a secretory retinol binding protein that belongs to the retinol-binding protein family. The RBP4 was first described in 1968 as the major transporter of vitamin A from the liver to peripheral tissues [22]. RBP4 is a cardiovascular risk factor and is closely related to insulin resistance [23-25]. Studies have shown that RBP4 might be associated with early vascular dysfunction [26,27].

Norseen et al. [28] found that RBP4 induces the expression of proinflammatory cytokines in mice and human macrophages by activating the c-Jun N-terminal protein kinase and Toll-like receptor 4 (TLR4) pathway. Another study [29] demonstrated that RBP4 is able to stimulate the expression of proinflammatory molecules involved in leukocyte recruitment and endothelial adhesion—vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), E-selectin, monocyte chemoattractant protein 1 (MCP-1), and interleukin-6 (IL-6)—in primary human retinal capillary endothelial cells (HRCECs) and human umbilical vein endothelial cells (HUVECs). These studies suggest that an increased RBP4 level might lead to induction of endothelial cell inflammation, which, in turn, impairs retinal microvessels and increases retinal vascular permeability. In another study, Du et al. [30] reported that transgenic mice that overexpress RBP4 develop progressive retinal degeneration. The simultaneous overexpression of pre-IL-18 mRNA and IL-18 and activation of early-onset microglia indicated that the retinal degeneration is driven by a proinflammatory mechanism. Studies have also shown that increased serum levels of RBP4 may be a risk factor for retinal damage and loss of vision.

In addition, studies [11,12] investigating the ability of RBP4 antagonists to reduce plasma RBP4 concentrations in mice found a decrease in retinal lipofuscin and cytotoxic retinol in the RPE. This suggests that RBP4 may promote retinal dysfunction, retinal degeneration, and neurodegeneration.

In the present study, similarly to APOA1, RBP4 was found in the highest concentrations in the RRDCD group, followed by the RRD group, with the lowest concentrations found in the IEM group. Also, similarly to APOA1, the concentrations of RBP4 in the RRDCD and RRD groups increased concurrently with an increase in the number of affected retinal quadrants. The correlations were found to be statistically significant. With these results, we can conclude that RBP4 is a significant biomarker of RRDCD and may be useful in predicting disease severity. As a proinflammatory fat factor that is capable of inducing cytokine production in macrophages, RBP4 may be involved in the RRDCD inflammatory process. This includes RBP4's possible role in enhancing vascular permeability of the retina which may aggravate disease progression. We believe that RBP4 might be involved in the retinal dysfunction process after retinal detachment. Therefore, RBP4 has the potential for use as an RRDCD-specific biomarker. As statistically significant positive correlations were found in APOA1 and RBP4 to RRDCD, clinical tests done using both biomarkers to assess whether RRDCD may result in enhanced predictive power.

There are several limitations in this study. First, serum protein levels might affect the level of the proteins in the vitreous humor. However, the small sample size was the main limitation. Smaller sample sizes have a tendency to increase the chances of a statistically significant finding. Future studies will be aimed at increasing the sample size, as well as the incorporation of more accurate methods of measuring clinical parameters.

In conclusion, the results demonstrate that the vitreous humor concentrations of APOA1 and RBP4 were statistically significantly higher in patients with RRDCD. APOA1 is positively correlated with RBP4 statistically significantly in the RRDCD and RRD groups. These results indicate that APOA1 and RBP4 may be useful as specific biomarkers of RRDCD. The findings of this study may contribute to an increased understanding regarding the role of APOA1 and RBP4 in RRDCD.

ACKNOWLEDGMENTS

Supported by Wuxi Health and Family Planning Commission (LCZX003) and Science and Technology Department of Wuxi (BE2017627). None of the authors have any conflicting interests to disclose.

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Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 26 March 2018. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.