

Optical Density of Subretinal Fluid in Retinal Detachment

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PURPOSE. To investigate the changes over time in optical density (OD) characteristics of subretinal fluid (SRF) in rhegmatogenous retinal detachment (RRD) and their clinical relevance.

METHODS. The study included patients with first-onset RRD and no history of intraocular illness who underwent optical coherence tomography (OCT) and whose OCT scans showed sufficient SRF for sampling (08/2013–09/2014). The highest quality B-scan (as graded by the OCT image acquisition software) containing SRF was analyzed. Optical density measurements were obtained using ImageJ. Optical density ratios (ODRs) were calculated as SRF OD divided by vitreous OD. Time from onset of RRD was determined by first signs of visual loss as described in the patient's anamnesis. Patients were divided into three groups by RRD duration: acute (≤ 1 week), subacute (between 1 week and 1 month), and chronic (> 1 month).

RESULTS. Thirty-five eyes (34 patients) met the inclusion criteria. The ODR measurement was significantly associated with RRD duration. The ODR had a significant ($P < 0.0001$) association with the 3-month postoperative visual acuity (VA). Vitreous OD did not differ significantly between the three groups.

CONCLUSIONS. The increase over time in the ODR of the SRF in RRD might reflect a change in SRF composition and state of the retina. This, together with a significant association between preoperative ODR values and postoperative VA suggest its potential as a biological prognostic marker.

Keywords: retinal detachment, subretinal fluid, OCT, optical density

Rhegmatogenous retinal detachment (RRD) is the most common type of retinal detachment. It occurs when a tear or a hole in the retina leads to accumulation of subretinal fluid (SRF), resulting in a separation of the neurosensory retina (NSR) from the underlying RPE. Although the manner in which the SRF accumulates is known, the nature and composition of its content are less clear.¹ It has been shown that the physical characteristics of the SRF change with time. For example, Edmund² showed that the presence of an increase in osmotic pressure depends upon the duration and extent of the RRD.

Optical coherence tomography (OCT), which is widely used to evaluate the anatomical and semihistologic cross-sections of the retina, can precisely detect even small amounts of intra- and subretinal fluid.^{3,4} Unlike subjective anatomical evaluations, it enables quantitative analysis of light reflectivity profiles from the resultant image.⁵

One of the important parameters measured by OCT is substance reflectivity values usually termed optical density (OD). Optical density parameters inside the retina and in accumulations of SRF have been correlated with the type of pathology causing the fluid accumulation. Our group⁶ used OD parameters of the SRF and the overlying vitreous located at exactly the same lateral site above the SRF to calculate the mean reflectivity of the SRF, expressed as optical density ratios (ODRs). We demonstrated that the ODR enables the differentiation between pathologies, and that it can be used in difficult diagnostic cases. Several studies have described changes in the ODR over time.^{1,7–9} We sought here to implement the technique we used in our previous study to measure the ODR in primary RRD cases and

determine if the duration of detachment affects the measurement. We also investigated whether these measurements correlate with postsurgical correction outcome. We speculated that analysis of the ODR and its variations would correlate with the duration of detachment and provide information on the pathophysiology of the condition, possibly enabling better prediction of surgical outcome.

METHODS

Patient Selection and Data Collection

Patients diagnosed between August 2013 and September 2014 with retinal detachment who underwent OCT scan prior to undergoing any intervention were selected. Their medical records were extracted and reviewed by senior ophthalmologists (AB, MN) for confirmation of the diagnosis of first-onset RRD. Exclusion criteria were coexisting ophthalmic pathology, ophthalmic treatments, eye surgery apart from cataract extraction, intravitreal injections before the earliest available OCT scan, and any medical condition that might affect ODR results. Demographic data (e.g., sex, age) and detailed anamnesis of symptoms and their time of onset were also taken from the patients' medical files.

Duration of RRD

Time of RRD onset was defined as the appearance of the sudden loss or deterioration of vision in the affected eye as

reported by the patient. The patients were divided into three groups based on the duration of symptoms: acute (≤ 1 week), subacute (between 1 week and 1 month), and chronic (> 1 month). Retinal detachment characteristics and digital drawings of the RRD were obtained from the patients' charts. The location, type and number of breaks, presence of proliferative vitreoretinopathy (PVR), extent of retinal detachment, foveal involvement, and vitreous state were recorded. Each patient's best corrected visual acuity (BCVA) was measured by Snellen charts both at admission and during the postoperative follow-up visit to the department's retina clinic.

OCT Scans

The patient's earliest OCT exam (SPECTRALIS, spectral-domain OCT [SD-OCT]; Heidelberg Engineering, Heidelberg, Germany) exhibiting SRF was chosen for analysis. The OCT image acquisition software scores the quality of each image based on the signal-to-noise ratio,¹⁰ enabling the selection of the highest quality B-scan containing SRF. This feature provided an objective and reproducible selection process for the B-scan, and minimized the amount of noise in our calculations. The single B-scan that had the highest image quality score and contained the largest volume of SRF for sampling without including edges was chosen, regardless of its location or proximity to the macula. Cases in which OCT scan had a maximum image quality score of less than 15 were excluded. The OCT scans were exported from the OCT acquisition software as grayscale, compression-free, quality-preserving BMP format images. Image quality and acquisition mode high resolution/high speed [HR/HS] were recorded.

The study was approved by the institutional ethics committee, and its protocol complied with the standards of the Declaration of Helsinki. All OCT examinations were performed at the Department of Ophthalmology, Tel Aviv-Sourasky Medical Center, Israel. Informed consent to use their data was obtained from the subjects.

ODR Measurements

Optical density ratios measurements were obtained using ImageJ¹¹ software (<http://imagej.nih.gov/ij/>; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA), an open-code Java-based image processing software. We used the technique of "regions of interest (ROI) selection method" described in our previous study.⁶ Briefly, two ROIs of identical shape and size were chosen, one for the SRF compartment and the other for the vitreous space (Fig. 1). Regions of interest were chosen on the same vertical line to avoid errors associated with refraction nonhomogeneities of the various intraocular structures (e.g., corneal opacifications, cataract, vitreous floaters, or other causes of nonhomogeneous signal intensity at the retinal level). We excluded OCT images in which no vertical line could be found for the measurement or if the vitreous could not be identified with a relative certainty. Retinal reflectivity was not measured due to its negligible effect on the OCT beam and expected insignificant effect on ODR. A detailed explanation of the physics appear in the Supplementary Material. Vertical coordinates of the two ROIs took into account the attenuation of light intensity due to passage through the tissue. Quadrangular-shaped ROIs were chosen in a manner that avoids tissue-fluid interfaces as well as any debris, vitreous hemorrhage, or other artifacts that might influence the measurement. Selection of ROIs of the SRF compartment and vitreous space was initially done by one of the authors and later approved by two different observers all blinded to detachment duration.

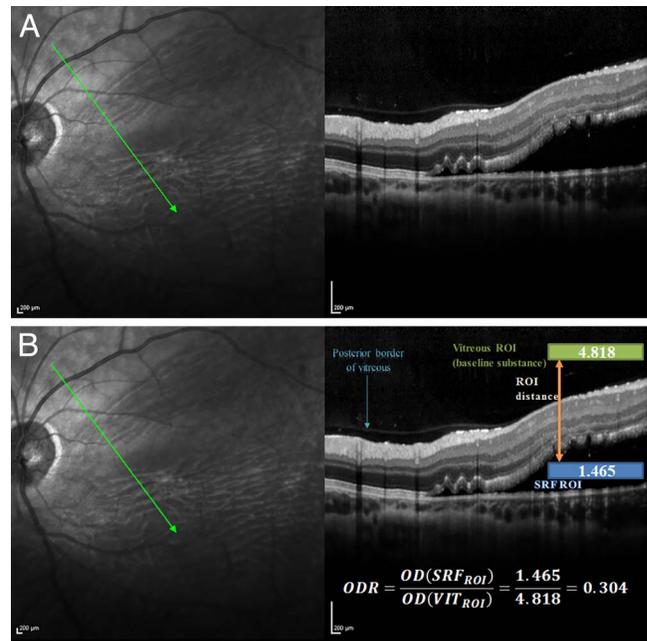


FIGURE 1. Representative ODR measurement. (A) Original OCT image. (B) Regions of interest selection, OD, and ODR calculations.

A clear advantage of using the vitreous space as a baseline medium for comparing reflectivity profiles is its distinct borders, which enable accurate identification of its contours by different observers. Although the OCT acquisition device applies a noise suppression algorithm to provide a "cleaner" image, which might have cut down the lower reflectivity values, our previous study had shown that this algorithm does not significantly affect the end result of the ODR measurement.⁶

Optical densities were extracted from the measured gray level intensity of the corresponding ROI selection in the SRF compartment and vitreous space on a scale of 0 (pure black) to 255 (pure white). Optical density ratios were the measured ODs of the SRF and vitreous calculated according to the formula

$$\text{ODR} = \text{OD}(\text{SRF}_{\text{ROI}}) / \text{OD}(\text{Vitreous}_{\text{ROI}}). \quad (1)$$

The ratio of the two measurements gives a cleaner value in the attempt to neutralize the properties of the image itself (such as picture angle or quality).

All the data and measurements were collected in a Microsoft ACCESS 2013 (ACCESS 2013; Microsoft, Redmond, WA, USA) database designed by one of the authors (LA) specifically for the purpose of this study.

Statistical Analysis

Data were analyzed by statistical analysis software (SPSS for Windows, version 21; SPSS, Inc., Chicago, IL, USA). Significance was defined as a type α error probability less than 0.05. We used nonparametric testing because of the relatively small sample size of each group. The Kruskal-Wallis test was applied to test for overall variations between the groups. The Mann-Whitney U test was used for two independent samples to compare between any two groups and to exclude significant differences in the baseline medium (vitreous) ODs and patient or retinal detachment characteristics, which might account for the observed differences in ODR values between the duration groups. A multiple linear regression was applied to rule out the

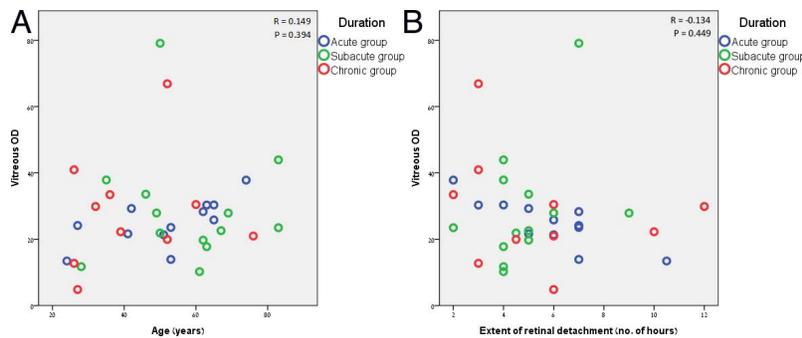


FIGURE 2. (A) Scatterplots of the vitreous OD versus age and (B) size of detached retina.

effect of certain confounders that correlated linearly with ODR values (i.e., image quality and vertical distance between the SRF ROI and the vitreous ROI), and might have influenced ODR measurements. Finally, we examined whether the admission data might be useful in determining prognosis. The Snellen acuity was converted to logMAR equivalent for statistical purposes. The logMAR values were calculated by using the logarithm of the reciprocal of the visual acuity

$$\log\text{MAR} = \log\left(\frac{1}{\text{Snellen equivalent}}\right). \quad (2)$$

Based on Lange,¹² counting fingers and hand motion were estimated to be logMAR values of 1.98 and 2.28, respectively. Multiple linear regression analysis was used to identify factors influencing BCVA on follow-up 3 months after surgery. The BCVA at 3 months after silicon oil removal was used in patients who were treated with silicon oil injection (SOI). Logistic regression was used to identify predictors of recurrence within 6 months of treatment.

RESULTS

The study population included 35 eyes with RRD (34 patients), of which 29 were phakic and six were pseudophakic at the time of diagnosis. The mean age of the 23 males and 11 females was 51.2 ± 16.94 years. Based on patient description of symptom onset, 12 cases were assigned to the acute duration group (time from onset ≤ 1 week), 13 to the subacute duration group (1 week to 1 month), and nine to the chronic duration group (>1 month). One patient reported deterioration of vision 14 days before admission, but examination and parsplana vitrectomy (PPV) surgery disclosed several signs of a longstanding detachment (including PVR, thickened detached retina, clear demarcation line between detached and attached areas), and this patient was assigned to the chronic duration group. As expected, the percentage of cases with foveal involvement was significantly higher in the combined acute and subacute duration groups compared with the chronic duration group (84% vs. 50%, respectively, $P = 0.038$). Twenty-six eyes underwent PPV, of which 14 were tamponade at the end of surgery using C3F8 16% gas, and 12 were tamponade using SOI, one of them after failure of scleral buckle. Four of the patients were treated by scleral buckle and four by pneumatic retinopexy using SF6 100% gas. One patient had bilateral retinal detachment and was not treated surgically in the left eye. Seven patients experienced recurrence of detachment and needed further treatment.

Figure 2 shows a scatterplot for the OD of the baseline media used in the analysis versus the age of the study population (Fig. 2A) and extent of retinal detachment (Fig. 2B). The Pearson correlation coefficients analysis showed that

the OD of the baseline medium (vitreous) was not influenced by the patients' age or extent of retinal detachment. The vitreous reflectivity did not differ significantly between the three duration groups.

A significant variation in ODR was observed between the three duration groups ($P = 0.022$). The mean ODRs were significantly lower in the acute and subacute groups (0.44 ± 0.16 and 0.39 ± 0.14 , respectively) compared with the chronic group (0.61 ± 0.21 , $P < 0.05$). There was no significant difference in mean ODR between the acute and subacute duration groups ($P = 0.242$). After obtaining these results, we divided the entire study population into two groups by combining the acute and subacute duration groups (combined acute group). The mean ODR was significantly lower in the combined acute duration group compared with the chronic duration group (0.42 ± 0.15 vs. 0.61 ± 0.21 , $P = 0.010$; Figs. 3A, 3B, respectively). Foveal status had no significant effect on ODR. There were no significant group differences for any of the other analyzed variables (Table 1).

We compared vitreous reflectivity values between the two duration groups to make certain that the aforementioned differences in ODR values were not simply the result of differences in vitreous fluid reflectivity ($P = 0.913$). The presence of PVR or foveal involvement had no significant effect on the ODR, nor was there was a significant difference with regard to detachment location (superior/inferior) or scanning protocol (HS/HR).

The Pearson correlation test yielded a significant ($P < 0.005$) negative correlation between ODR measurements to both OCT image quality and the vertical distance between the ROIs (Table 2). We applied a multiple linear regression model to test for a possible confounding effect using the independent parameters image quality and vertical distance between the ROIs. The significant difference between the two groups persisted after correcting for the influences of those variables on ODR ($P = 0.023$).

Lastly, we examined the data for prognostic capabilities. Best-corrected visual acuity measurements at 3 months following surgery were available in 20 subjects, 5 in the chronic duration group and 15 in the combined acute group. Of these 20 patients, seven developed cataract after the surgery, and two of those seven underwent treatment for cataract (for details see Supplementary Table S1). Data on the 3-month BCVA was missing in 15 cases due to lack of follow-up ($n = 5$), recurrence of detachment ($n = 7$), or other complications ($n = 3$). The combined acute duration group had a better BCVA compared with the chronic duration group at 3 months (median 20/50 vs. 20/155). There was a significant association between ODR and the BCVA at 3 months (adjusted $R^2 = 0.572$, $P < 0.0001$), which remained significant ($P = 0.014$) after correction of admission BCVA. Using Matlab (version R2014A, The Mathworks, Inc., Natick, MA, USA) we

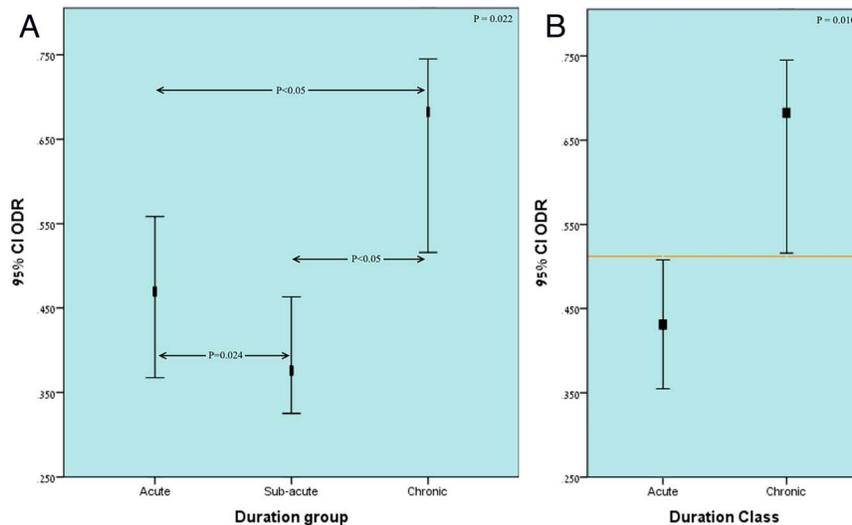


FIGURE 3. (A) Differences in ODR measurements by duration of retinal detachment, for the three duration groups and (B) after merging the acute and subacute duration groups and comparing it with the chronic duration group.

created a three-dimensional presentation of the association between ODR, logMAR on admission, and logMAR at 3 months after treatment for RRD (Fig. 4). Subgroup analysis according to foveal involvement status (for details see Supplementary Table S3) revealed a significant association between ODR and postoperative BCVA in fovea-off cases ($P = 0.047$) and a near significant association in fovea-on cases ($P = 0.062$). A multiple linear regression was applied to test for a possible confounding effect including the independent parameters detachment duration (days), posterior vitreous face status, preoperative foveal involvement, preoperative lens status, and surgical approach. In summary, only preoperative BCVA and ODR had significant predictive coefficients for 3 month postoperative BCVA (for details on the linear regression see Supplementary Material). No variable, including ODR, was associated with risk of detachment recurrence within 6 months, regardless of treatment type.

DISCUSSION

The use of OCT in RRD has expanded to include both preoperative and postoperative evaluations. Several studies

have employed OCT to detect microstructural retinal changes that might influence visual outcome in both macula-off and -on RRD.¹³⁻¹⁸ Hagimura et al.¹⁹ showed an inverse relationship between the height of retinal detachment and postoperative visual outcome. Leclaire-Collet et al.¹⁷ reported that the distance from the central fovea to the nearest undetached retina combined with the structure of the detached retina correlated highly with the final visual result ($r = 0.82$ $P < 0.00001$). Other studies observed changes in the retinal layers. Nakanishi et al.¹⁴ identified dropouts of the photoreceptor inner and outer segment junction (IS/OS) selectively at the fovea that correlated with both preoperative and postoperative visual acuities. Cho et al.²⁰ used SD-OCT to detect outer retinal corrugation in macula involved RRD that could predict a poor visual acuity outcome in nontraumatic RRD. Lai et al.²¹ reported a correlation between the presence of one or more abnormalities among the external limiting membrane, the IS/OS junction or the Verhoeff membrane and poor postoperative BCVA. All of these studies focused on retinal changes in RRD, as did most studies on the routine use of OCT in clinical practice. Very few studies dealt with the characteristics of fluid-containing cavities as demonstrated in OCT images.

TABLE 1. Comparison of the Three Detachment Duration Groups by the Different Parameters Studied

Duration Group	Statistics	Age, y	Extent of Retinal Detachment, hr	ROI Size, Pixels	Vertical Distance Between ROIs, Pixels	Image Quality	logMAR on Admission	IOP on Admission, mm Hg
Acute (≤ 1 wk)	N	12	12	12	12	12	11	11
	Mean	51.67	5.79	5086.42	157.50	26.75	1.18	12.82
	SD	15.59	2.23	5871.36	32.16	4.05	0.84	2.401
Subacute (between 1 wk and 1 mo)	N	13	13	13	13	13	13	12
	Mean	57.38	4.88	6531.54	181.85	25.85	0.84	14.42
	SD	16.53	1.71	5841.53	39.55	4.18	0.84	2.193
Chronic (> 1 mo)	N	10	10	10	10	10	10	10
	Mean	42.60	5.55	4544.90	140.50	24.30	0.77	14.90
	SD	16.86	3.25	3401.98	65.13	6.40	0.99	7.68
Total	N	35	35	35	35	35	34	33
	Mean	51.20	5.39	5468.46	161.69	25.71	0.93	14.03
	SD	16.94	2.37	5195.64	47.99	4.82	0.88	4.57
P value		0.135	0.453	0.755	0.133	0.344	0.302	0.238

TABLE 2. Pearson Correlation Between the Studied Parameters and ODR

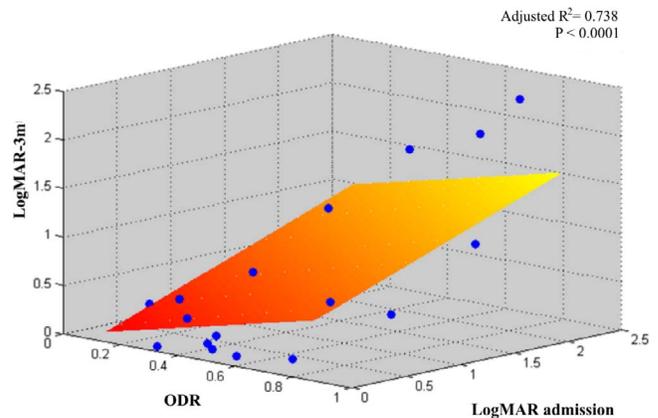
Parameter	Correlation	P
Age	0.056	0.751
Extent of retinal detachment	0.044	0.804
ROI size	-0.264	0.125
Vertical distance between ROIs	-0.480	0.004
OCT image quality	-0.551	0.001
OCT ART	-0.288	0.094
logMAR on admission	-0.038	0.832
IOP on admission	0.218	0.223

Values in bold are statistically significant ($P < 0.05$).

The use of OD reflectivity for identification of possible etiologies and outcome has been explored in the past. Barthelmes et al.²² were the first to show that it is possible to differentiate degenerative from exudative macular disease by comparing the reflectivity of hyporeflective spaces in the neuroretina to vitreous reflectivity. Ahlers et al.²³ later demonstrated a correlation between SRF OD changes and BCVA changes under intravitreal ranibizumab therapy for AMD.

In a previous study by our group,⁶ spectral-domain OCT was used to evaluate OD of subretinal spaces in neovascular AMD, diabetic retinopathy, RRD, central serous retinopathy, retinoschisis, and pseudophakic cystoids macular edema. We demonstrated that reflectivity ratios can be used as diagnostic markers to differentiate between retinal pathologies. Kashani et al.²⁴ used the same method to investigate changes in the OD of the SRF after RRD repair. They found that ODR measurements increase significantly over time after surgery, and might reflect an increased concentration of photoreceptor OS fragments in the SRF as the serous component is absorbed. We implemented the same technique in the present study in patients with first-onset RRD and found that RRD duration causes a significant change in ODR measurements regardless of age, detachment size or location, or foveal involvement status. As in our previous study, ODR negatively correlated with image quality and vertical distance between ROIs, and both were found not to cause bias in predicting detachment duration. A detailed explanation on these findings appear in the Supplementary Material.

There have been several studies on the effect of detachment duration, most of them focused on the duration of macular detachment. Unlike other preoperative factors that have been found to correlate with RRD surgical correction outcome (e.g., preoperative visual acuity, detachment height, age, comorbidities), detachment duration is of special importance because it is the only one that might be influenced by timing of surgical intervention. The literature on the effect of detachment duration on visual prognosis is not uniform. The significant increase in ODR seen in our study only after 1 month corresponds to the reports of Salicone et al.²⁵ and Doyle et al.²⁶ of a significant difference in visual acuity only when surgery is done after more than 30 days from onset. Still, other studies showed no significant difference within the first 7 days of detachment duration,²⁷⁻²⁹ although BCVA was significantly better in cases treated within 7 days.²⁹ Van Bussel et al.³⁰ recently published a systematic review and meta-analysis on the influence of detachment duration and postoperative visual acuity and concluded that scleral buckling should be performed within 3 days of the event in order to optimize visual outcome. One of the major limitations in these studies is that the duration of detachment is based mainly on the patient's self-reporting. Our findings of a significant change in ODR

**FIGURE 4.** A three-dimensional model of the association between ODR, logMAR on admission, and logMAR at 3 months after treatment for RRD.

measurements over time in RRD, unrelated to age, detachment size, detachment location, or foveal involvement status, suggest that ODR might be a useful objective marker of duration.

The SRF in RRD is believed to originate from three sources: the vitreous,³¹ serum,³² and retina.³³ Several studies have shown that the composition of SRF includes proteins,³⁴ the photoreceptor OS,³⁵ lipids,³⁶ cells (primarily inflammatory cells),³⁷ glucose/carbohydrate compounds,¹ and inflammatory mediators.³⁸ Researchers have long been examining SRF composition changes in RRD over time to better understand its pathophysiology. Although earlier reports were conflicting, a more recent report by Berrod et al.⁷ showed that the total protein concentration and the size of the proteins present in the SRF appear to correlate with RRD duration. In an extensive review of the literature on the physiopathology and composition of the SRF in RRD, Quintyn and Brasseur¹ found evidence of several specific proteins that increase in concentration over time, including proteins involved in the healing process, such as apoprotein E and fibronectin, as well as other enzymes that might reflect a self-destruction process within the retina.

Lipids also constitute another major component of the SRF, as the external segments of photoreceptor cells are composed mainly of lipids. Therefore, it is not surprising that an increase in lipid degradation products, such as free fatty acids³⁹ and lecithin^{8,36} reflects the retinal condition. More recent studies found a positive correlation between RRD duration and other SRF components, among them syndecan-1,⁴⁰ matrix metalloproteinases,⁴¹ tissue factor,⁹ immunoreactive endothelin-1,⁴² and apoptotic factors.⁴³

Collection of SRF specimens for biochemical analysis is technically challenging, and there is no practical way to sample the fluid prior to surgery. Therefore, there is great need for noninvasive methods to determine fluid composition in vivo. Although OCT cannot detect the exact composition of the SRF, it can be assumed that a greater density of particles will cause higher reflectivity, expressed in an increased OD signal.^{44,45} In a recent study, Sonoda et al.⁴⁶ examined the effect of blood components on OCT reflectivity and concluded that OCT reflectivity is most strongly affected by the presence of triglycerides, and that molecules such as hemoglobin and fibrinogen significantly increase OCT reflectivity.

Ultimately the SRF in RRD is composed mostly of proteins and lipids, which have been shown to have a strong effect of OCT reflectivity. Total protein concentration and the size of the proteins present appear to correlate with RRD duration,⁷ which might explain the increase in the OD of the SRF, leading to increased ODR.

Another significant finding in our study is the connection between ODR and postoperative BCVA showing that ODR is superior to detachment duration in predicting final outcome. Ahlers et al.²³ also reported a correlation between baseline ODR and visual function in neovascular AMD patients under treatment. A recent study of the SRF after surgical repair of RRD did not find ODR to be a significant predictor of visual acuity.²⁴ To the best of our knowledge, and based on a careful search of PubMed.com (1988–2014, [in the public domain] <http://www.ncbi.nlm.nih.gov/pubmed>), this appears to be the first study to describe the relationship between preoperative measurement of ODR in RRD and visual outcome. As discussed above, OD is influenced by changes in fluid composition. Our finding suggests a significant association between SRF composition, RRD duration and the state of the neuro retina: the longer the retina is detached, the higher the ODR and the poorer the expected visual acuity.

Our study has several limitations. First, due to retrospective collection of data, we had no control over OCT acquisition protocol. Reliance on the patients' description of symptom onset to determine retinal detachment duration may have introduced a bias, especially in cases of peripheral detachments, and inferior detachments in which the patient may have noticed a change in vision only when there was foveal involvement. The relative small number of patients restricted our ability to evaluate the relationship between detachment duration and ODR measurements, and the analysis of subgroups according to foveal involvement or type of surgical treatment. It is also possible that a larger sample size would detect significant differences in ODR between the acute and subacute duration groups that were not found here. Another limitation is the difficulty in identifying the vitreous: We used the vitreous as baseline medium, but its posterior border is not always easily identifiable on OCT images.

We showed that RRD duration causes a significant change in ODR measurements over time unrelated to age, detachment size, detachment location, or foveal involvement status. These findings indicate that ODR can be a useful tool to assess the duration of RRD; indeed, future studies might prove its usefulness as a biological marker of duration. The increase in ODR over time might reflect retinal breakdown and help assess the general state of the retina. In addition, the significant association found between preoperative ODR values and the BCVA at 3 months following surgery suggest its potential as a biological marker for the prediction of postoperative visual results. Future studies are needed to better understand the pathophysiological processes in RRD and the reasons for failed recovery after treatment.

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