Journal of Eye Disorders and Therapy

Review Article Open Access

Oxidative Stress in Vitreous Fluid Associated with Rhegmatogenous Retinal Detachment

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Received: Sep 01 2024, **Accepted:** Oct 10 2024; **Published:** Oct 16, 2024, DOI: 10.59462/jedt.1.2.108

Citation: Suzuki Y, Adachi K, Takahashi S, Maeno A, Nakazawa M, et al. (2017) Oxidative Stress in Vitreous Fluid Associated with Rhegmatogenous Retinal Detachment. Journal of Eye Disorders and Therapy ,1(2):108

Abstract

Purpose: To characterize the biological antioxidant potential (BAP) in the vitreous fluid in patients with rhegmatogenous retinal detachment (RRD).

Design: Laboratory investigation.

Materials and methods: Undiluted vitreous fluid was obtained at the time of vitrectomy from patients with RRD (45 eyes), proliferative diabetic retinopathy (PDR, 93 eyes), retinal vein occlusion (14 eyes), epiretinal membrane (ERM, 18 eyes) and macular hole (MH, 24 eyes). The BAP values were determined by measuring the reducing potential shown by the conversion of Fe^{3+} to Fe^{2+}. Clinical features including the extent of the detachment, duration of symptoms, presence of proliferative vitreoretinopathy or vitreous hemorrhaging, and macular status (on or off), as well as the patient age were analyzed.

Results: RRD patients exhibited a significantly lower BAP than MH patients, and PDR patients had a significantly lower BAP than ERM and MH patients. Regarding the clinical features, although the BAP in RRD patients was significantly correlated with the extent of the detached area ($\beta=-0.384$, $p=0.008$), there was no significant correlation between the BAP and the other features in a multivariate regression analysis.

Discussion: The present results suggest that significantly increased oxidative stress was present in RRD patients compared to MH Patients. Controlling oxygen stress may be an effective treatment for photoreceptor protection in cases of RRD.

Keywords: Biological antioxidant potential; Macular hole; Oxidative stress; Proliferative diabetic retinopathy; Retinal detachment; Retinal vein occlusion; Vitreous fluid

Introduction

Oxidative stress is one of the main factors inducing cell damage and triggering cell death mechanisms. In many vitreoretinal disorders, oxidative stress has been implicated as a factor inducing the development of retinal cellular damage [1]. Uese disorders include proliferative diabetic retinopathy (PDR), [2-5] retinitis pigmentosa, [6-9] age-related macular degeneration, [10-13] and rhegmatogenous retinal detachment (RRD) [14,15]. Furthermore, previous experimental studies have revealed that photoreceptor cells themselves have the potential to produce reactive oxygen species (ROS) by NAPDH oxidase when they are stressed by the deprivation of serum in culture conditions [16]. In RRD, the separation of the photoreceptors from the retinal pigment epithelium (RPE) causes the photoreceptors to be deprived of oxygen and nutrients, thereby causing severe stress that can lead to the overproduction of ROS in the photoreceptors. Uerefore, preoperative antioxidant treatment using ROS scavengers might be a beneficial therapy for RRD in the future.

Oxidative cell damages are generally accelerated by an imbalance between ROS production and antioxidant scavengers in the tissues. In humans, these scavengers include both endogenous materials such as albumin, transferrin, ceruloplasmin, bilirubin, urea, glutathione reductase, superoxide dismutase and catalase, and exogenous substances such as α-tocopherol, ascorbic acid, anthocyanin, β-carotene, catechins and curcumin [17]. Ue combined total activity of these individual scavengers determines the antioxidant capacity of the tissues. Uerefore, a decreased tissue antioxidant capacity may indirectly indicate increased oxidative stress: by evaluating the tissue antioxidant capacity, we can estimate the level of oxidative stress. Ue biological antioxidant potential (BAP) is a marker of the antioxidant potential that is determined by quantitating the reducing capacity of various antioxidants from ferric (Fe^{3+}) ions to ferrous (Fe^{2+}) ions [18,19]. Although the BAP was initially used to evaluate the antioxidant potential in blood samples, it can also be measured using the vitreous fluid as well [20].

Clinically, it is important to know the di9erences in the oxidative stress levels that occur in RRD, PDR, retinal vein occlusion (RVO), epiretinal membrane (ERM) and macular hole (MH), in order to understand the pathogenesis of the eventual photoreceptor cell death in these various disorders. In addition, this information can be used to design further protocols for antioxidant therapy. Furthermore, understanding the background clinical features of RRD may also help determine their influence on the level of oxidative stress, thereby making it possible to estimate the oxidative stress in RRD. We

previously reported the BAP values and levels of inflammatory cytokines in the vitreous fluid from patients with RRD [15,21]. In those studies, we found that the BAP was significantly decreased while the levels of macrophage chemotactic factor-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), interferon-inducible 10-kDa protein (IP-10), interleukin-6 (IL-6), and IL-8 were significantly increased in the vitreous fluid in RRD patients, indicating significantly increased oxidative stress and inflammatory reaction on the retinal cells [15,21].

In the present report, we present the results of additional analyses and discuss the significance of controlling oxidative stress and inflammatory reactions with the goal of photoreceptor protection as an adjunctive treatment against RRD.

Subjects and Methods

Ue present study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of Hirosaki University Graduate School of Medicine (2014-353). AIer receiving an explanation of the nature and possible consequences of taking part in the study, each patient provided their informed consent.

Patients

Using a previously described method, [22] we collected undiluted vitreous fluid from patients with RRD (45 eyes), PDR (93 eyes), RVO (14 eyes), ERM (18 eyes) or MH (24 eyes) at the time of their virectomy at Hirosaki University Hospital. In brief, vitreous fluid (approximately 0.5 ml) was obtained from each eye prior to starting the fluid irrigation at the initial stage of the vitrectomy procedure. Vitreous samples were immediately cooled on ice in a dark container for approximately 1 to 2 h and then kept frozen at −80°C until the analysis.

Background clinical data for the preoperative conditions were obtained from each patient's medical records. For RRD, in addition to the patient age and gender, we also collected information on the extent of detachment (quadrant), duration of subjective symptoms (weeks), vitreous status including the presence of proliferative vitreoretinopathy (PVR) or vitreous hemorrhaging (VH), and the macular status (on or o9). All participants enrolled in this study were undergoing vitrectomy for the first time, and if a patient required reoperation, they were excluded from the analyses. All participants exhibited primary RRD. Patients with RRD secondary to trauma or other disorders, and those with RRD associated with diabetes mellitus were excluded. All PDR patients were diagnosed with type 2 diabetes mellitus based on the criteria recommended by the World Health Organization. All RVO patients demonstrated VH that had not been absorbed for three months or longer. Ue background data for RRD patients and other disorders are summarized in Tables 1 and 2, respectively.

Quantitative analyses of BAP

Ue BAP was determined by quantitating the ability of vitreous samples to reduce ferric (Fe^{3+}) ions to ferrous (Fe^{2+}) ions using the F.R.E.E. systemTM (Wismerll, Tokyo, Japan) in line with the manufacturer's instructions as previously reported [15]. In brief, the solution is initially colorized when Fe^{3+} ions are dissolved in the thiocyanate derivative solution (colored solution), and aIer addition of the vitreous samples, the Fe^{3+} ions are reduced to Fe^{2+}, which causes decolorization of the solution. Ue level of the reducing ability was quantified colorimetrically by measuring the absorbance at 505 nm [23,24]. Ue reaction was performed by initially mixing 10 µl of the vitreous sample with the colored solution. AIer incubation at 37°C for 5 min, the intensity of the chromatic change was then measured by reading the optical density at 505 nm. Ue reducing ability was expressed as µM.

Statistical analyses

Statistical analyses were performed using the SPSS version 22 soIware program (IBM, Armonk, NY, USA), with $p<0.05$ considered significant. All data are presented as the mean ± standard deviation. Ue Shapiro-Wilk test was employed to examine the normality of distribution. Regression analyses (Pearson) were used for comparisons between the BAP and the patients' age. An analysis of variance (ANOVA) was employed to examine whether there was any statistical di9erence among members in the same group, or not. In addition to the results previously reported, [15] we performed multivariate regression analysis conducted using a stepwise method, and incorporated the extent of the detachment, duration of symptoms, vitreous status, macular status and patient age as the independent variables for the analysis of the BAP.

Results

Vitreous BAP in the examined disorders

Because the average age of the patients with the five disorders was statistically di9erent (Table 1), the Pearson's regression coefficient was calculated for each disease group. We detected no significant correlation between the BAP and the patients' age in any of the five groups (Table 2), suggesting that the patient age does not likely influence the BAP values in the five disorders studied. Uese findings demonstrated that di9erences in age were not a concern and would not cause problems in any of our further analyses. Ue BAP values in the examined disorders were previously reported [15] and are summarized in Table 2. In brief, the results showed that the BAP values were statistically distinguishable among the five groups by ANOVA. For RRD in particular, the post hoc analysis demonstrated that there was a statistically significant di9erence in the average BAP between the RRD and MH patients ($p= 0.012$), but there was not between the RRD and PDR patients as reported previously [15]. Although PDR is not a main focus of this study, Table 2 shows that the BAP value in PDR was significantly decreased comparing to those in ERM ($p=0.019$) and MH ($p<0.001$), as reported previously [15].

	RRD	PDR	RVO	ERM	MH
No. of eyes	45	93	14	18	24
Age* (years)	62.5 ± 10.5	57.3 ± 13.3	68.8 ± 10.0	67.1 ± 9.1	66.6 ± 13.8
Male/Female	23/22	44/49	6/8	6/12	11/13

Table 1: Patient background data (Age*: ANOVA, $p<0.001$ Age*: Dunnet's T3, PDR : RVO, $p=0.022$; PDR : ERM, $p=0.007$; PDR : MH, $p=0.049$).

	RRD	PDR	RVO	ERM	MH
BAP*	1860.50 ± 470.59	1647.76 ± 460.53	1863.14 ± 413.76	2169.23 ± 594.01	2258.83 ± 450.79
R** between BAP & age	0.019 (p=0.903)	-0.006 (p=0.954)	-0.189 (p=0.556)	-0.107 (p=0.682)	-0.021 (p=0.923)

Table 2: BAP in the vitreous fluid of patients with vitreoretinal disorders (BAP*: ANOVA, p<0.001 BAP*: Dunnet's T3, RRD : MH, p=0.012; PDR : ERM, p=0.019; PDR : MH, p<0.001 R**: Spearman's correlaton coefficeint between the BAP and patient age).

BAP in RRD and clinical features

Tables 3 summarizes the relationships between the intravitreal BAP in RRD patients and the clinical features. Regarding the extent of the detached area, the averages BAP values were not considered to be statistically the same among the four ranges of the extent of the detachment (ANOVA, p<0.001), with the BAP values for the detached areas confined within 2 quadrants significantly greater than those extended over 3 quadrants (Student's t, p=0.002), as reported previously [15]. Regarding the other factors, which included duration of symptoms, vitreous status, and macular status, there were no statistically significant relationships with the BAP values. Ue stepwise multivariate regression analysis presented in Table 4 showed that only the extent of the detached area was statistically significantly associated with the BAP (ß=−0.384, p=0.008) when the other factors, including duration, vitreous status, macular status, and patient age, were excluded.

Clinical Features	No. of eyes	BAP	p value
Extent of detachment			
quadrant			
1	12	1986.58 ± 396.69	<0.001
2	18	1996.22 ± 418.06	ANOVA
3	6	1519.01 ± 650.27	
4	9	1601.21 ± 356.68	
1-2	30	2006.59 ± 401.17	0.002
3-4	15	1568.33 ± 474.82	t-test
Duration			
number of weeks			
1	15	1812.73 ± 391,87	0.392
2	13	1821.7 ± 504.99	ANOVA
3	6	1766.96 ± 567.62	
4	6	1985.98 ± 454.07	
8	2	2516.95 ± 65.83	
10 <	3	1681.78 ± 576.2	
Vitreous status			
PVR(-) VH(-)	31	1935.32 ± 462.37	0.206
PVR	9	1675.72 ± 441.5	ANOVA
VH	5	1654.17 ± 486.95	
Macular status			
on	13	2015.15 ± 420.31	0.097
off	32	1771.14 ± 472.83	t-test

Table 3: E9ets of preoperative clinical features on BAP

Discussion

Ue present and previous studies [15] measured the BAP in the vitreous fluid collected from patients with RRD, PDR, RVO, ERM or MH. Ue BAP was originally developed and used to quantitate the total activity of antioxidant scavengers present in blood samples [18,19, 23,24]. Hashimoto et al. [20] reported that the BAP could also be measured using human vitreous samples, with a positive correlation in the BAP values detected between the serum and vitreous fluid in diabetic patients. Other parameters besides the BAP that can be used to evaluate the total antioxidant power in the vitreous fluid have also been developed [2-4]. We used the BAP in this study simply because it is a reproducible method that only requires 10 µl of samples.

Clinical Features	β	p value
Extent of detachment	−0.389	0.008
<factors ruled out>		
Duration	0.207	0.156
Vitreous status	−0.101	0.511
Macular status	−0.014	0.939
Patient age	−0.007	0.959

Table 4: Relationships between the BAP and clinical features Multivariate regression analysis (stepwise) (β: standardized partial regression coefficient).

Recently, oxidative stress has garnered increasing attention with regard to its role in the pathogenesis of many diseases. An imbalance between the ROS production and the antioxidant ability increases the chances of peroxidation of many substances like proteins, lipid, polysaccharides, and DNA, which can eventually lead to the damage of various cell functions and structures, and ultimately cell death. In the human body, the coordinated activity between many kinds of scavengers is able to reduce ROS, eliminate oxidative stress and maintain the redox homeostasis. Since the BAP reflects the total activity of many of these antioxidant scavengers, increased oxidative stress causes a reduction in the BAP value; reduced BAP values are therefore, indicative of increased oxidative stress in the tissue.

Our previous study demonstrated that the BAP was significantly decreased in the vitreous fluid of patients with RRD and PDR compared with MH, although the di9erences in the BAP between patients with RRD and those with PDR, RVO, or ERM were not statistically significant [15]. Increased oxidative stress has been reported in the vitreous fluid in PDR patients, and oxidative stress has been speculated to be related to retinal cell damage in such patients [2-5]. In addition, the BAP values were decreased in the vitreous fluid from patients with RVO [20]. Our results suggest that oxidative stress is also elevated in RRD, suggesting that increased oxidative stress may be a factor that modifies the photoreceptor cell death in RRD. Uese results not only confirm the findings from the previous study by Cederlund et al. [14] but also demonstrate that oxidative stress is elevated in the vitreous fluid in RRD patients at levels that are not significantly di9erent from those observed in PDR patients.

Of the possible clinical features that might influence the BAP in RRD, only the extent of the detachment was significantly correlated with the BAP, with no significant relationship found for the duration, presence of PVR or VH, macular status, or patient age. Although free hemoglobin can be a source for generating ROS, the presence of VH in our patients with RRD did not result in any marked di9erence in the BAP. Uese results suggest that the presence of a detached retina itself has a much greater influence on the intravitreal BAP than the presence of free hemoglobin. In addition, these results also provide a clue as to the mechanism underlying the generation of ROS and the impact of the oxidative stress on the photoreceptor cell damage in RRD. Ue separation of the photoreceptor outer segment from the RPE severely interferes with the oxygen and nutrient supply to the photoreceptors, which eventually results in hypoxic stress and deprivation of neurotrophic factors in the photoreceptors. Photoreceptors are also extremely susceptible to oxidative stress, due to their high oxygen consumption, [25] high polyunsaturated fatty acid content, [26,27] and light exposure even under physiologic conditions. Although the precise details of these molecular mechanisms remain unclear, the hypoxic condition induces dysfunction in both the mitochondria in the inner segment and the recently recognized enzymes in the extra-mitochondrial aerobic ATP synthesis in the outer segment, [28] thereby leading to the overproduction of ROS, which accelerates the photoreceptor cell death [1,29]. Uese molecular events are supported by experimental retinal detachment studies that have shown successful photoreceptor protection by means of treatment with antioxidant scavengers like docosahexaenoic acid, [30] edaravone [31] and tauroursodeoxycholic acid [31]. Ue present study results are also in line with the previous experimental retinal detachment findings proposing that mechanisms of ROS overproduction can be applied to the clinical field [31-34].

Inflammation is another factor that induces oxidative stress. In the previous study, we demonstrated that MCP-1, MIP-1β, IP-10, IL-6, and IL-8 were up-regulated in the vitreous fluid of patients with RRD [21]. Namely, the level of IL-8 was significantly correlated with the levels of MCP-1, MIP-1β, and IP-10. Furthermore, the level of IL-8 was significantly correlated with the extent of RRD, a trend that was similar to that of oxidative stress. Uese results suggest that IL-8 may trigger other inflammatory cytokines, IL-8 may have a close relationship to oxidative stress, and anti-inflammatory therapy may be considered to reduce oxidative stress to the retinal cells in RRD.

Several limitations associated with the present study warrant mention. First, while our measurements of the BAP in this study demonstrated the antioxidant potential, this finding cannot be used to determine the direct amount of oxidative stress itself. However, BAP values are still useful, as this is a simple method of evaluation that can be easily utilized with clinical samples. Second, because the BAP indicates the total antioxidant potential and is a summation of the scavengers' reducing activities in total, we were unable to predict the role of the individual scavengers based on only the BAP. Uese limitations will need to be addressed in the future. Uird, because we did not measure the BAP value in the normal vitreous fluid, we do not know the normal range of the BAP in the vitreous fluid. As there is no retinal detachment and obvious glial proliferation in the vitreous in patients with MH, we considered that the vitreous condition in MH is closer to normal than those in other disorders. Uerefore, we used vitreous samples from MH patients as controls in this study like other reports [14,15, 21,22].

Ue results of our previous and present studies suggest that future photoreceptor protection in RRD patients can potentially be achieved through the usage of antioxidants and/or anti-inflammatory agents either locally or systemically at the proper time point in combination with detachment surgery, as discussed above [15,21]. Additional studies that examine the e9ectiveness of using these scavengers or anti-inflammatory agents in the clinical field will need to be performed in the future.

Acknowledgments

Ue present study was supported, in part, by the Grants-in Aid for Scientific Research (15K20246, 16K11313, 17K16955) from the Japan Society for the Promotion of Science. Ue authors thank Mr. Brian Quinn for his English editing.

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