Alterations in Retinal Vascular and Oxygen Metrics in Treated and Untreated Proliferative Diabetic Retinopathy: A Case Report

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Abstract
Proliferative diabetic retinopathy (PDR) is a vision-threatening complication of diabetes. Panretinal photocoagulation (PRP) and anti-vascular endothelial growth factor (anti-VEGF) are approved treatment modalities aimed at regressing neovascularization. Data are lacking about abnormalities in retinal vascular and oxygen metrics before and after combination treatments. A 32-year-old Caucasian male diagnosed with PDR in the right eye was treated by a combination of PRP and multiple anti-VEGF treatments over a 12-month period. The subject underwent optical coherence tomography (OCT) angiography, Doppler OCT, and retinal oximetry before treatment and at 12 months, which was 6 months following the last treatment. Measurements of vascular metrics (vessel density [VD] and mean arterial and venous diameters [DA, DV]) and oxygen metrics (total retinal blood flow [TRBF], inner retinal oxygen delivery [DO2], metabolism [MO2], and extraction fraction [OEF]) were obtained. Both before and after treatments, VD, TRBF, MO2, and DO2 were below the normal lower confidence limits. Additionally, DV and OEF were decreased after treatments. Alterations in retinal vascular and oxygen metrics were reported for the first time in untreated and treated PDR. Future studies are warranted to evaluate the clinical value of these metrics in PDR.

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Introduction

Diabetic retinopathy (DR) is the leading cause of vision loss in the working-age population in the industrialized world. DR may progress to the advanced stage proliferative diabetic retinopathy (PDR). It is characterized by the growth of abnormal newly formed vessels on the retina, optic disc, iris, or angle. Progression to PDR increases the risk of vision loss [1].

The National Eye Institute’s Diabetic Retinopathy Study (DRS) provided the first conclusive evidence to confirm the safety and efficacy of panretinal photocoagulation (PRP) as a treatment modality for PDR [2]. Furthermore, among different cytokines and growth factors upregulated in DR, vascular endothelial growth factor (VEGF) has been identified to play a critical role in neovascularization. Accordingly, anti-VEGF compounds have been used as an adjunct to PRP and as a primary treatment in PDR.

Several investigations have reported improvement in visual function [3], alterations in retinal blood flow [4, 5], vascular oxygen saturation [6], and reduced vessel density [7] following either PRP or anti-VEGF treatment for PDR. However, alterations in inner retinal oxygen metabolism (MO$_2$) and delivery (DO$_2$) have not been previously reported. This case report demonstrates changes in retinal vascular and oxygen metrics in a PDR subject before and after treatment.

Case Presentation

Subject

A 32-year-old Caucasian, non-obese male with type 1 diabetes for 18 years presented with progressive blurry vision in his right eye over 8 weeks. His HbA1c value was 6.9 mmol/mol. The subject had no hypertension or hyperlipidemia, and his family history was unremarkable. He denied alcohol consumption but had a history of daily marijuana use and had discontinued tobacco smoking more than 5 years ago. The best-corrected visual acuity was 20/25 in both eyes. A slit-lamp examination of the anterior segments of both eyes was unremarkable. Detailed clinical retinal examination and fluorescein angiography (FA) demonstrated high-risk PDR in the right eye and low-risk PDR in the left eye. Central subfield thickness was 308 μm on optical coherence tomography (OCT). Based on the treatment plan, he received two sessions of PRP and seven anti-VEGF intravitreal injections (1 Bevacizumab and 6 Aflibercept) in the right eye over a 6-month period. At the 12-month follow-up evaluation, which was 6 months after the last treatment, neovascularization had regressed, and no new vitreous or pre-retinal hemorrhage was detected. The subject was imaged before treatment (baseline) and at 12-month follow-up.

Imaging

Optical coherence tomography angiography (OCTA) images were acquired by a high-density scan protocol encompassing a 6 × 6 mm region centered on the fovea. Vessel density (VD) in the superficial vascular complex was determined using our previously published method [8]. VD values range from 0 to 1, corresponding to the fraction of the imaged area occupied by vessels. En face Doppler OCT imaging was performed in a 2 × 2 mm region centered on the optic nerve head to measure total blood flow (TRBF) as previously described [8].

Retinal oximetry was performed in a 5 × 5-mm region centered on the optic nerve head using our previously published method [9]. Mean arterial (D$_{A}$) and venous (D$_{V}$) diameters and retinal oxygen saturation in arteries (SO$_{2A}$) and veins (SO$_{2V}$) were measured and converted to retinal arterial (O$_{2A}$) and venous (O$_{2V}$) oxygen contents. Retinal arteriovenous oxygen content difference (O$_{2AV}$) was calculated as O$_{2A}$ − O$_{2V}$. According to our previous publication [10],
MO$_2$ and DO$_2$ were calculated as TRBF × O$_{2AV}$ and TRBF × O$_{2A}$, respectively. Oxygen extraction fraction (OEF) was calculated as MO$_2$/DO$_2$. Abnormalities were determined based on previously published normal 95% confidence interval (CI) in VD and TRBF [8], $D_A$, $D_V$, and OEF [11], MO$_2$ and DO$_2$ [10].

**Results**

Figure 1 shows FA and OCTA images acquired at baseline. The FA image revealed multiple areas of leaking neovascularization on the vascular arcades. The OCTA showed the presence of capillary anomalies, a foveal avascular zone, and regions of capillary non-perfusion.

Measurements of retinal vascular and oxygen metrics at baseline and 12-month follow-up are presented in Table 1. VD was lower than normal at baseline and follow-up, and $D_A$ was within the normal CI, whereas $D_V$ was lower than normal at follow-up. At both baseline and 12-month follow-up, TRBF, MO$_2$, and DO$_2$ were lower than normal. OEF was lower than normal only at the 12-month follow-up.

**Discussion**

VD was lower than normal at baseline, which is in agreement with a previous study in untreated DR [7]. Additionally, the current study showed no considerable change in decreased VD after combined PRP and multiple anti-VEGF treatments over a 12-month period. This finding is consistent with recent studies that did not show changes in VD after PRP [12] or anti-VEGF treatment [13]. Previously reported changes in $D_A$ and $D_V$ after PRP treatment were variable [4, 5, 11, 14–16]. The results of the current study showed $D_A$ was normal while $D_V$ was lower than normal at the 12-month follow-up. It is unclear whether the observed reduction in $D_V$ is the result of treatment only or the combined effects of disease progression and treatment. TRBF was lower than normal at baseline and after combination treatments, consistent with reports in untreated PDR [17, 18] and after PRP [4, 5].
Previously, lower retinal oxygen extraction has been reported in diabetic subjects with no or mild DR [19]. Our finding of impairments in DO$_2$ and MO$_2$ in untreated PDR is indicative of reductions in both oxygen supply and demand. However, OEF was maintained at baseline, suggesting adequacy of oxygen supply to meet the reduced metabolic demand. Nevertheless, considering OEF measurements were global, there were likely retinal areas that were not adequately supplied with oxygen due to vascular pathologies. There is no information in the literature regarding changes in DO$_2$ and MO$_2$ after PDR treatment. Consistent with our finding of lack of improvement in DO$_2$ and MO$_2$, a previous study has shown increased arterial and venous oxygen saturation after PDR treatment [15]. At the 12-month follow-up, OEF was reduced, consistent with a previous study in PDR subjects treated with PRP [11]. The finding of a reduction in OEF suggests a disproportionately greater reduction in oxygen demand as compared to the reduction in supply, likely attributed to the effects of both treatment and PDR progression. Another factor that likely contributed to the finding of reduced DO$_2$ was increased oxygen diffusion from choroid to the retina after PRP, as previously established [20].

Although the causative relationship between vascular and oxygen metrics is not known, the following speculation may be considered based on this case report: vascular endothelium changes due to diabetes cause retinal capillary non-perfusion (reduced VD) that leads to tissue hypoxia. Prolonged inadequate oxygenation can cause cellular dysfunction or death and a consequent decrease in oxygen demand (reduced MO$_2$), which can result in an autoregulatory reduction in oxygen supply (reduced TRBF and DO$_2$). Some cells may have suffered irreversible damage due to disease progression despite treatment, resulting in a change of reductions of MO$_2$ relative to DO$_2$ as reflected in a decrease in OEF.
Conclusion

In conclusion, the current report showed alterations in retinal vascular and oxygen metrics due to PDR. Future studies in a larger cohort are warranted to elucidate the differential effects of treatment and disease progression and evaluate the clinical value of these metrics in management of PDR.

Statement of Ethics

The study was approved by the Institutional Review Board of the University of Southern California (approval reference number HS-19-00575, April 3, 2018) and was conducted in accordance with the Tenets of Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

None of the authors have any proprietary or conflicts of interest related to this submission.

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Author Contributions

All the authors attest that they meet the current ICMJE criteria for authorship. Mansour Rahimi collected, analyzed, and interpreted the data and drafted and revised the manuscript. Amir H. Kashani provided clinical evaluation of the subject and reviewed the manuscript. Norman P. Blair provided critical revisions to the manuscript. Mahnaz Shahidi conceptualized the study and made critical revisions to the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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