Assessment of Conjunctival Microangiopathy in a Patient with Diabetes Mellitus Using the Retinal Function Imager

Nicolle Stuebiger1,2, William Smiddy1, Jianhua Wang1, Hong Jiang1 and Delia Cabrera DeBuc1*
1Bascom Palmer Eye Institute, University of Miami, 900 NW 17th Street, Miami, Florida, 32136, USA
2Charite, Universitaetsmedizin Berlin, Campus Benjamin Franklin, University Eye Hospital, Hindenburgdamm 30, 12200 Berlin, Germany

Abstract

Diabetes mellitus (DM) is notorious for causing retinal microangiopathy, but bulbar conjunctival microangiopathy (CM) mirroring the established retinal vessel changes, has also been observed. Recent studies suggest that CM occurs in all DM patients in various degrees depending on disease severity and occur even before non-proliferative retinopathy develops. Thus, CM might provide a means of early detection or even form a basis for early intervention of disease progression in DM patients. Herein we present - to our knowledge for the first time-the feasibility and applicability in diagnostic imaging of CM in a diabetic patient using a commercially available Retinal Function Imager (RFI, Optical Imaging Ltd, Rehovot, Israel).

Keywords: Diabetes mellitus; Conjunctival microangiopathy; Retinal function imager; Retinal microangiopathy; Optical imaging

Introduction

Patients with Diabetes mellitus (DM) mostly develop changes in the blood flow [1-3], leading to well-known vessel changes in the conjunctiva and in the retina, such as loss of capillaries, microaneurysms, vessel dilation and vascular tortuosity [1,4-8]. Retinal vascular function and morphology measures, such as the blood flow (BF) velocity and capillary perfusion, have been assessed without contrast using the Retinal Function Imager (RFI). The RFI is a fundus camera-based device with an attachment of a specific camera (a 60-Hz, 1024 × 1024-pixel digital camera) that captures reflectance changes as a function of time under stroboscopic illumination (wavelengths between 530 and 590 nm). This device was originally designed to measure the BF velocity directly and noninvasively (without using any contrast agent) in secondary and tertiary retinal arteries and veins and to generate non-invasive capillary perfusion maps (nCPMs) of the retinal microvasculature while using the hemoglobin in the red blood cells as an intrinsic motion-contrast agent [9-11]. The study was approved by the Institutional Review Board of the University of Miami, Miami, FL, USA. The research adhered to the tenets set forth in the declaration of Helsinki and written informed consent was obtained from the subject.

Case Report

The conjunctival and retinal vasculature was imaged in a 38-year-old black female DM patient without DR with a commercially available RFI device. This patient was a non-smoking female with a history of Type-2 DM (T2DM) since 2009. She was being treated with Metformin 2 x 500 mg per day. Hemoglobin A1C was 5.3% (34 mmol/mol) and glucose was 87 mg/dL. Diastolic blood pressure was slightly elevated (120/90 mmHg). Ocular history included a nasally located pterygium removal in both eyes in 2010 and occasional seasonal allergic eye disease. The eye examination disclosed CM in the temporal area of the DM patient’s left eye (Figure 1A).

All the other findings were within normal limits in both eyes; specifically, there were no clinical signs of acute allergic eye disease or diabetic retinopathy (DR) and the visual acuity was 20/20. The temporal conjunctiva and the retina of the patient’s left eye (Figure 1A-1D) were imaged under normal conditions with the RFI by the same operator. The overall conjunctival and retinal BF velocities and nCPMs were calculated using the proprietary software of the RFI device as an average of selected arteriole and venule segments (Figure 1C and 1D). In addition to the conjunctival BF calculation we analyzed a region of interest (ROI) incorporating the microangiopathy of the conjunctival vessels, (Figure 1A), and compared it to regions without morphometric abnormalities.

When imaging the temporal conjunctival microvasculature with the RFI we could illustrate microaneurysms, vessel dilation, abnormal vessel distribution and vascular tortuosity (Figure 1A) in the patient’s left eye. The nCPMs were successfully acquired and revealed the intricate capillary network structure on the temporal bulbar conjunctiva (Figure 1B). The microvasculature anatomy appeared...
unevenly distributed, and lower numbers of blood vessels along with lower degree of complexity of their branching patterns were evident when compared with a normal healthy eye (Figure 1A-1B vs. 1E-1F).

The overall BF velocity (Figure 1C) in the temporal conjunctival vessels of the diabetic patient was $0.68 \pm 0.31$ mm/s compared to $0.86 \pm 0.08$ mm/s in healthy controls [12] ($p=0.61$). Compared to regions without morphometric abnormalities ($0.62 \pm 0.25$ mm/s), the BF velocity was increased to $1.01 \pm 0.37$ mm/s ($p=0.007$) in the ROI incorporating the conjunctival vessel dilatation, microaneurysms, and more packing of tortuous vessels (Figure 1A). Retinal BF velocity in the same eye (Figure 1D) disclosed increased arterial BF velocity of $5.16 \pm 1.66$ mm/s compared to $4.19 \pm 0.99$ mm/s in healthy controls [13] ($p=0.03$), whereas the venous BF calculation revealed values similar to healthy controls [13] ($2.99 \pm 0.85$ mm/s versus $3.03 \pm 0.59$ mm/s; $p=0.3$).

The microvasculature visualization enhancement showing the microvasculature anatomy in detail, otherwise invisible even in the sharpest red-free image (Figure 1A). The microvasculature anatomy appeared unevenly distributed.

The overall BF velocity (Figure 1C) in the temporal conjunctival vessels of the diabetic patient was $0.68 \pm 0.31$ mm/s compared to $0.86 \pm 0.08$ mm/s in healthy controls [12] ($p=0.61$). Compared to regions without morphometric abnormalities ($0.62 \pm 0.25$ mm/s), the BF velocity was increased to $1.01 \pm 0.37$ mm/s ($p=0.007$) in the ROI incorporating the conjunctival vessel dilatation, microaneurysms, and more packing of tortuous vessels (Figure 1A). Retinal BF velocity in the same eye (Figure 1D) disclosed increased arterial BF velocity of $5.16 \pm 1.66$ mm/s compared to $4.19 \pm 0.99$ mm/s in healthy controls [13] ($p=0.03$), whereas the venous BF calculation revealed values similar to healthy controls [13] ($2.99 \pm 0.85$ mm/s versus $3.03 \pm 0.59$ mm/s; $p=0.3$).
Discussion

This case report is the first to demonstrate the feasibility of optical imaging using the RFI for obtaining high-resolution nCPMs and providing the BF velocity of the bulbar conjunctiva vessels in a diabetic patient. The DM patient in this study had CM with overall conjunctival BF velocity comparable to that previously reported in healthy controls except for a significant increase of the BF velocity in the altered conjunctival area due to marked vessel dilatation (Figure 1A). These conjunctival vessel alterations were clinically visible and clearly imagined despite the absence of clinically discernable retinal microangiopathic findings (Figure 1D). The retinal BF velocity calculated with the RFI’s custom-built software RFI in the same eye detected increased BF velocity in the retinal arteries, while the venous velocity revealed no significant alteration compared to healthy controls. Increased BF velocity in the retinal arteries has been described in patients with pre-retinopathy [13]. The most plausible physiologic explanation for this scenario is that retinal arteries widen in response to impaired capillary perfusion, while retinal venous diameters remain relatively constant [13].

The conjunctival vessel alterations observed in this DM patient may have been influenced by the allergic eye disease or the slightly elevated diastolic blood pressure because both could lead to conjunctival vessel alterations [5,14]. While allergic eye disease induce vessel dilatation [14], it was unlikely in our patient since allergic symptoms were not present while doing the RFI examination. Elevated blood pressure could also be responsible for CM [5,8], in particular conjunctival tortuous vessels have been linked with hypertension [5]. But an influence in our patient is more than improbably - on the one hand only the diastolic blood pressure was slightly elevated to 90 mmHg and on the other hand recent studies demonstrated that diabetic CM predominates in those patients with both diabetes and elevated blood pressure [5].

In the United States more than 23 million people suffer from diabetes mellitus, an increasingly prevalent disorder. Extensive research has been conducted to determine effective methods of detection and treatment of diabetes mellitus and its attendant ocular complications. Studying methods to detect these complications in their earliest stages may inspire development of early treatment strategies before clinical signs are apparent, mitigating irreversible damage to the microvasculature. This is essential in diabetic patients because early treatment, e.g. intensive glycemic control or pancreas transplantation, of diabetic vessel alterations has been shown to retard both their development and progression in adults; in childhood, if detected early, the vessel changes could even be reversed [7,15].

In conclusion because recent studies suggest that conjunctival vessels seem to mirror the established vessel changes observed in the diabetic retina, and may even be evident before diabetic retinopathy develops [4-7], CM might merit more attention. This study demonstrates a possible role for the RFI as an in vivo platform to monitor these conjunctival vessel alterations. A pilot study with a larger amount of patients should be initiated to figure out if there might be an indication for the presence of a time window for early intervention in DM patients with conjunctival microangiopathy before non-proliferative DR develops. It may also allow new insights on the pathogenesis of vascular changes in the diabetic eye.

Acknowledgments

This study was supported in part by the research grants NIH R01EY020607, NIH R01EY020607S, NIH Center Grant P30 EY014801 and a grant from Research to Prevent Blindness (RPB). No potential conflicts of interest relevant to this article were reported. All authors edited the manuscript and contributed to the discussion. The first author, N.S., would like to thank Dr. Janet Davis of the Bascom Palmer Eye Institute of the University of Florida for facilitating her research scholarship at the Bascom Palmer Eye Institute and Dr. Wen-Tsiang Lee of the Bascom Palmer Eye Institute of the University of Florida for introducing her to the Advanced Imaging for Diabetic Retinopathy Study (AIDRS) group.
References