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RESEARCH ARTICLE

STUDIES ON CONJUNCTIVAL VESSEL MORPHOLOGY IN DIABETIC PATIENTS

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ABSTRACT

Diabetes mellitus is a disease associated with both micro and macro-vascular angiopathy. The classical example is the manifestation seen in the retinal vessels. Diabetes is also associated with loss of capillaries and macro-vessel dilatation in the conjunctiva, similar to well-known vessel changes in the retina. The studies conducted on the conjunctival vessel in diabetic patients clearly demonstrate macrovesseldilation associated with diabetes may result in vessel engorgement and straightening, especially among those with longer duration of disease. Increased tortuosity associated with diabetes among conjunctival capillaries mirrors established vessel changes observed in the retina. Evaluation of conjunctivalangiopathy associated with diabetes may help in detecting changes in the retina more easily, maybe earlier even by para-clinical workers

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INTRODUCTION

Diabetes mellitus is a disease associated with both micro and macro-vascular angiopathy. The classical example is the manifestation seen in the retinal vessels. Paralleling the manifestation in the retina are the manifestations in the renal, cardiac, and cerebral circulations. The visual deficits which arise out of the manifestation in the retina and the life threatening complications which arise out of the manifestations in the kidney, heart and CNS have been responsible for the extensive studies done on the same which have been extensively studied documented and treated. Though the retinal vessels differ in the histology from that elsewhere in the body due the presence of pericytes, the conjunctival vessels have a similarity that they can be easily visualized and documented. Diabetes is also associated with loss of capillaries and macro-vessel dilation in the conjunctiva, similar to well-known vessel changes in the retina. Involvement of the conjunctiva in patients with diabetes has been an area of study since long (Ditzel *et al*., 1954). It was earlier hypothesized that that the vessels of the fundus of the eye were closely connected to the circulation of the cerebral flow whereas the changes of the conjunctival vascular bed might possibly correlate in a better way with the peripheral vessels and that majority of the patients with a high index at the bulbar conjunctiva suffer from peripheral occlusive disease (Dexel *et al*., 1977). However, Vasiutkova, (1978) employed Biomicroscopy to study the state of microcirculation of the bulbar conjunctiva in 166 patients with diabetes mellitus at different stages of the ophthalmoscopic assessment of the fundus of the eye. The author found altered conjunctival micro hemodynamics in 89.7% of the patients, in the presence of retinopathy in all the cases and in 69.3 % in cases of normal picture of the fundus of the eye. The author found that the qualitative and quantitative changes in microcirculation of the conjunctiva depended on the stage and form of diabetic retinopathies. Values of changes of the total conjunctival index and its constituents were on an increase with aggravation of a pathological process in the fundus of the eye. Vascular changes prevailed in the diabetic-sclerotic and diabetic-hypertensive forms of retinopathies, intravascular changes and perivascular edema prevailed diabetic-renal form. Marked derangement of the end blood flow was expressed in the appearance of perivascular, vascular, and intravascular lesions, increasing with the progress of diabetes mellitus. Adequate therapy gave positive results with the disappearance or reduction of perivascular lesions in the microcirculation, and also improvement of the rheological

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properties of the blood. Danilova, (Danilova, 1980) in a study comparing the results of a study of the conjunctival and retinal vessels found conjunctival microcirculation to be disturbed in 68% of patients with the normal ophthalmological picture of the optic fundus and in all patients with diabetic retinopathies. This study recommended that microphotography of the conjuctival vessels in patients with diabetes mellitus for early diagnosis of micro hemodynamic disturbances. Utiamyshev RI *et al*. (Utiamyshev *et al*., 1985) studied basal blood flow and responses of the microcirculatory channel to physiological and pharmacological loads in health and diabetes mellitus using the method of photon-correlation spectroscopy in the light fiber variant. The rate of the basal blood flow in patients with diabetes mellitus (irrespective of the diabetes type) as compared to that in health was significantly lower in the fingertip and tended towards reduction in the inner side of the forearm, lobule of the auricle and in the conjunctiva. The presence of retinopathies in patients with diabetes mellitus resulted in a significant decrease in the rate of the blood flow in the conjunctiva as compared to those in good health and diabetes mellitus without retinopathy.

The response of the blood flow to physiological (orthostatic and ischemic) and pharmacological (nitroglycerin and pentoxifyllin) tests in patients with diabetes mellitus was also low; the presence of angiopathies caused a more acute reduction of the reactive power of the microcirculatory channel to the orthostatic test. The nature of the nitroglycerin effect in good health and diabetes mellitus was different: in the first case noticeable vascular reactions were observed; in the second case a persistent vasodilative effect was observed. The pentoxifyllin effect was characterized by an elevated rate of the blood flow in health and diabetes mellitus. Several teams have emphasized the value of conjunctivalangioscopy (CA) and peri-ungualcapillaroscopy (PUC), describing suggestive anomalies: microectatic venous dilatation (V/A greater than 4.5), sludge on CA, "fish shoal" capillaries (Lagrue *et al*., 1988). Cheung, (2001) *et al* studied conjunctivalmicrovascular abnormalities in the bulbar conjunctiva of 14 patients with T2DM and in age-matched healthy control subjects without diabetes. They videotaped and objectively studied by using computer-assisted intravital microscopy (CAIM), a novel and quantitative real-time technology. Patients with T2DM (N = 14) had significantly (P<0.01) wider conjunctival vessel diameters (71.9 +/- 5.2 mm) than healthy nondiabetic control subjects (54.0 +/- 4.4 mm). In the study patients, microvascular distribution was significantly (P<0.01) abnormal (36.7 +/- 18.2 versus 45.3 +/- 9.6 cm per unit area, patients versus control subjects), and vessel distribution was uneven on the surface of the bulbar conjunctiva. The arteriole: venule (A:V) ratio in patients with T2DM was extremely variable and differed significantly (P<0.01) from that in the nondiabetic control subjects (A:V approximately 1:2). In addition, a unique sinusoidal (hypertensive) vascular pattern frequently existed in some of the large veins of all study patients with T2DM but in none of the nondiabetic control subjects. They identified the presence of microvascular changes (abnormalities) in the conjunctival microcirculation of patients with T2DM. Although all these abnormalities did not appear in the same patient at the same time, the sum total of their presence in each patient correlated significantly with disease severity, as noted in the medical records. The severity of microvascular abnormalities, however, did not correlate with the duration of the disease since diagnosis.

VanZijderveld *et al*. (2003) used Orthogonal Polarization Spectral (OPS) imaging to compare the conjunctival microvasculature in diabetic and age-matched non-diabetic persons in order to establish a diagnostic index of micro vascular changes in diabetes mellitus. For this purpose, the eyes of15 diabetic patients and 15 nondiabetic controls were investigated. The experiments were performed on the inferior and nasal part of the bulbar conjunctiva of each eye. The images were computer analyzed and several parameters were measured. In addition, a qualitative characterization of the conjunctival microvasculature was performed. In diabetic patients, a lower percentage of conjunctival microvessels were measured than in controls. Furthermore, a significant increase in diffusion distance was revealed in the diabetic population.

Microvascular abnormalities, such as capillary elongation, sludging, vessel distension and vessel tortuosity were more frequently present in the diabetic group, as compared to the controls. Other frequently seen abnormalities in diabetic patients were beaded vessels, box car blood flow phenomenon, hemosiderin deposits and blocked vessels. OPS imaging was found to be a reliable technique to visualize the conjunctival microcirculation and to measure systemic microvascular parameters. Microcirculation of diabetic patients exhibited significant differences in relation to the controls, in particular decreased vascularity. OPS imaging is an easy to handle diagnostic device with interesting opportunities in diagnosis of microvascular conjunctival and systemic disorders.

Owen *et al*. (2008) emphasized that though diabetes is associated with loss of capillaries and macrovessel dilatation in the conjunctiva, similar to well-known vessel changes in the retina, little is known about the effect of diabetes on the tortuosity of vessels of the conjunctiva. The authors examined the tortuosity of conjunctival vessels in participants with and without diabetes. They conducted a case-control study on fifty-three patients with diabetes (17 with type 1 diabetes, 36 with type 2 diabetes) and 60 controls (all aged 20-94 years). Digital red-free images of conjunctivae were analyzed using an automated computer algorithm to identify vessel axes and to quantify vessel tortuosity. Differences in vessel tortuosity were adjusted for age, gender, blood pressure, and smoking status. Tortuosity was expressed in units of curve energy (the square of the radian angular change between subsequent locations identified by the algorithm, standardized by vessel length). A longer duration of diabetes was associated with a reduction in overall vessel tortuosity (-2.8%; 95% confidence interval [CI], -4.3% to -1.3% per decade). This inverse association was driven by changes in larger vessels (40 microm in width or more), whereas increased tortuosity was observed in capillary sized vessels (<25 microm, 4.0%; 95% CI, -0.2% to 8.2% per decade). Compared with controls, those with type 1 diabetes (median duration of disease, 26 years) showed a 17.9% increase (95% CI, 4.7% to -31.0%) in capillary tortuosity. Conversely, those with type 1 diabetes showed a 7% decrease (95% CI, -11.8% to -2.3%) in tortuosity among vessels 40 to 80 microm or less in size and a 26.8% decrease (95% CI, -66.2% to 12.7%) in the fewer number of vessels more than 80 microm in size compared with controls. Similar, but smaller differences were seen in those with type 2 diabetes with shorter duration of diabetes (median, 7 years). They found that macrovessel dilation associated with diabetes may result in vessel engorgement and straightening, especially among those with longer durations of disease.

Increased tortuosity associated with diabetes among conjunctival capillaries mirrors established vessel changes observed in the retina. This study group concluded that conjunctivalangiopathy associated with diabetes may contribute to susceptibility to anterior eye disease among patients with diabetes.

Worthen *et al*. (1981) analyzed the photographs of the bulbar conjunctiva of 56 diabetic and 59 nondiabetic control patients by newly developed morphometric techniques. When compared to controls diabetic patients showed: (1) decreased vascularity in the capillary bed but an increased vascularity of the venules with a volume shift in the distribution of blood into the venules; (2) an increased capillary pressure but comparable flow and therefore increased capillary resistance; (3) an increase in the range of background density suggesting either focal thickening of the interstitial tissue or variable amounts of fluid within the tissue; (4) a decrease in the percentage of the area occupied by microvessels; and (5) an increase in diffusion distance to all vessels.

To *et al*. (2011) hypothesized that T2DM vasculopathy can be revealed and quantified in the bulbar conjunctiva prior to its pathologic presentation in the retina [Owen *et al*., 2008]. Using computer-assisted intravital microscopy (CAIM), an objective, non-invasive approach can provide a viable complement to retinal fundus photography to possibly screen patients for early signs of real-time, in vivo T2DM vasculopathy. Fundus photography was utilized to determine the retinopathy level (RL) in T2DM patients with non-proliferative diabetic retinopathy (NPDR) and control subjects. CAIM was used to quantify microangiopathy in the bulbar conjunctiva in the same patients, and reported on a severity index (SI). The average RL for the T2DM patients in this study is 19.68 ± 9.91, which differs from control subjects (RL = 10 ± 0.0; $p < 0.05$). A significant difference in vasculopathy was observed in the conjunctival microcirculation in the same patients (SI = 5.81 ± 1.30) when compared with control subjects (SI = 1.33 ± 1.58; $p < 0.05$).

The results provide evidence that significant vasculopathy had developed in the microcirculation in the bulbar conjunctiva, though diabetic retinopathy had not developed significantly in the same patients - indicative of the presence of a time window for early intervention of T2DM before non-proliferative retinopathy develops, and the real-time availability of the conjunctival microvasculature as an in vivo platform to monitor disease progression.

Conclusion

The studies conducted on the conjunctival vessel in diabetic patientsclearly demonstrate macrovessel dilation associated with diabetes may result in vessel engorgement and straightening, especially among those with longer durations of disease. Increased tortuosity associated with diabetes among conjunctival capillaries mirrors established vessel changes observed in the retina. Thus evaluation of conjunctivalangiopathy associated with diabetes may help in detecting changes in the retina more easily, maybe earlier even by para-clinical workers.

Conflicts of interest: All the authors have none to declare

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