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Impact of Diabetes Mellitus on Retinal Microvasculature in Patients without Clinical Retinopathy Using Optical Coherence Tomography Angiography

Study Protocol Submitted for Partial Fulfillment
of Master Degree in ophthalmology

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2024

Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM) and is the leading cause of preventable blindness in working aged people [1].

Fluorescein angiography (FA) is the gold standard investigation for evaluation of Diabetic Retinopathy, yet it is time-consuming and requires invasive intravenous dye administration that may cause various reactions such as vomiting and urticaria [2].

The advent of Optical Coherence Tomography Angiography (OCTA) overcame these disadvantages and added value of imaging rapid and high-resolution images of the retinal microvasculature without intravenous dye administration [3, 4].

OCTA identifies features of preclinical retinopathy that are not detectable by clinical examination and evaluates early ischemic changes as enlarged foveal avascular zones (FAZ) [5-8] , reduced vessel density [8, 9] that are reported to present without clinical retinopathy and also microaneurysm formation which is the most common early clinically visible manifestation of DR [10].

Duration of diabetes has been reported to be a strong predictor for the progression of DR as persistent elevated blood glucose level gradually leads to weakening of the walls of small retinal blood vessels leading to tiny bulges and even leakage [11, 12].

Aim of the work

To assess the impact of duration of DM on OCTA parameters in diabetic patients without clinical Diabetic retinopathy.

Patients and Methods

Study design: Observational, Cross-sectional study.

Study setting: Sohag University Hospital, department of Ophthalmology.

Study population: patients will be recruited from diabetics who will present for retinopathy screening examination at outpatient clinic of Sohag University Hospital.

Sample size determination: every group would include from 60 to 80 eyes calculated by Yamane's formula: n = N/ (1+N (e) 2, where n = the sample size, N = the population of the study and e = the margin error in the calculation.

The study will be conducted after acquiring the approval of the Medical Research Ethics Committee in the Faculty of Medicine, Sohag University considering that all study participants will be carefully cognized with the nature, presentation and potential consequences of the disease, investigation options and importance of regular follow up and tight control by an informed consent.

Inclusion criteria:

1) Age : Above 40 years old
2) Type of DM: Type 2.
3) Fundus examination: no macular edema or other signs of clinical retinopathy.

Exclusion criteria:

1) Age : below 40 years old
2) Ocular history : any history of significant ocular injury or disease that could affect the retinal microvasculature such as retinal vascular occlusion, glaucoma, or vitreo-macular disease, as such conditions have also been noted to show sub-clinical OCTA changes [13, 14].
3) Fundus examination: macular edema or any other signs of clinical retinopathy.

Procedure: patients recruited for the study will be subjected to the following:

- Personal history: including name, age, sex, occupation and residency.
- Medical history: including duration of DM, type of DM, use of DM medications, most recent hemoglobin A1C and presence of comorbid diseases.
- Ocular examination: including extra-ocular examination, anterior segment examination, visual acuity assessment, IOP measurement and posterior segment examination.

Signs of diabetic retinopathy to be detected include; Micro-aneurysm, Dot and Blot hemorrhages, Flame-shaped splinter hemorrhages, Retinal edema and hard exudates, Cotton-wool spots, venous loops and venous and Intra-retinal microvascular abnormalities (IRMA).

Patients who meet the inclusion criteria will be divided into three groups depending on the duration of diabetes: 0–5 years (short), 6–10 years (medium), and more than 10 years (long). Fourth control group of patients who meet the criteria and don't have DM will be included.

OCTA images will be obtained for the patients by a comprehensive wide-field OCT device (Optovue RTVue XR 100 Avanti, Germany) with 6 × 6 mm field of view centered at the fovea.

One eye will be selected for inclusion from each patient. If both eyes from an individual patient are similar the right eye will be included in the study. The effect of eye motion-related artifacts is minimized using VTRAC eye tracking software [19].

Images to be included in the study will be required to have a signal strength greater than 7, minimal motion artifacts, decentralization from the foveal center of less than 20 μm, and minimal evidence of obscuration by media opacities [20].

Image analysis will be automatically performed by the AngioVue Comprehensive software, which will provide automated segmentation and calculation of retinal microvascular metrics such as FAZ-related and SVD. The analysis will include the inner retina between the inner limiting membrane and an anterior offset from the retinal pigment epithelium of 110 μm. The superficial capillary plexus (SCP) as the superficial 70% of the inner retina, and the deep capillary plexus (DCP) is the remaining 30% [21].

OCTA parameters derived from the SCP and DCP will be classified into two categories:

(1) FAZ related metrics: FAZ area, FAZ perimeter and FAZ flow density (FD)

(2) Vessel density-related metrics: superficial vessel density (SVD) and deep vessel density (DVD) in the 6 mm patch (6 mm diameter around the foveal center), 1 mm patch (1 mm diameter around the foveal center), and inner ring (1 mm patch excluding the FAZ) [9, 20].

Statistical Analysis

Statistical analysis will be performed using SPSS software 23 (SPSS, Inc., Chicago, IL, USA). The Shapiro–Wilk test will be used. Comparisons between groups will be made using the Kruskal–Wallis H test or one-way ANOVA test. Differences between two groups will be estimated with a Mann– Whitney U test or t-test. Multivariate linear regression models will be used to analyze potential associations between each OCTA parameter and systemic risk factors. All p values will be based on two-tailed testing and considered to be statistically significant if $p < 0.05$. A Bonferroni correction will be applied when appropriate.

References

1) Cheung, N.; Mitchell, P.; Wong, T.Y. Diabetic Retinopathy. Lancet 2010, 376, 124–136.
2) Early Treatment Diabetic Retinopathy Study Research Group. Classification of Diabetic Retinopathy from Fluorescein Angiograms: ETDRS Report Number 11. Ophthalmology 1991, 98, 807–822.
3) Khadamy, J.; Aghdam, K.; Falavarjani, K. An Update on Optical Coherence Tomography Angiography in Diabetic Retinopathy. J. Ophthalmic Vis. Res. 2018, 13, 487.
4) Hwang, T.S.; Gao, S.S.; Liu, L.; Lauer, A.K.; Bailey, S.T.; Flaxel, C.J.; Wilson, D.J.; Huang, D.; Jia, Y. Automated Quantification of Capillary Nonperfusion Using Optical Coherence Tomography Angiography in Diabetic Retinopathy. JAMA Ophthalmol. 2016, 134, 367–373.
5) de Carlo, T.E.; Chin, A.T.; Bonini Filho, M.A.; Adhi, M.; Branchini, L.; Salz, D.A.; Baumal, C.R.; Crawford, C.; Reichel, E.; Witkin, A.J., Jay S. Duker, Nadia K. Waheed. Detection of Microvascular Changes in Eyes of Patients with Diabetes but not Clinical Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Retina 2015, 35, 2364–2370.
6) Takase, N.; Nozaki, M.; Kato, A.; Ozeki, H. Enlargement of Foveal Avascular Zone in Diabetic Eyes Evaluated by En Face Optical Coherence Tomography Angiography. Retina 2015, 35, 2377–2383.
7) Yasin Alibhai, A.; Moult, E.M.; Shahzad, R.; Rebhun, C.B.; Moreira-Neto, C.; McGowan, M.; Lee, D.; Lee, B.; Baumal, C.R.; Witkin, A.J., Elias Reichel , Jay S Duker , James G Fujimoto , Nadia K Waheed . Quantifying Microvascular Changes Using OCT Angiography in Diabetic Eyes without Clinical Evidence of Retinopathy. Ophthalmol. Retina 2018, 2, 418–427.
8) Dimitrova, G.; Chihara, E.; Takahashi, H.; Amano, H.; Okazaki, K. Quantitative Retinal Optical Coherence Tomography Angiography in Patients With Diabetes Without Diabetic Retinopathy. Investig. Ophthalmol. Vis. Sci. 2017, 58, 190–196.
9) Cao, D.; Yang, D.; Huang, Z.; Zeng, Y.; Wang, J.; Hu, Y.; Zhang, L. Optical Coherence Tomography Angiography Discerns Preclinical Diabetic Retinopathy in Eyes of Patients with Type 2 Diabetes without Clinical Diabetic Retinopathy. Acta Diabetol. 2018, 55, 469–477.
10) Wiley, H.E.; Ferris, F.L. Retina, 5th ed.; Elsevier Health Sciences: Amsterdam, the Netherlands, 2012; pp. 940–968. ISBN 1-4557-0737-6.
11) Klein, R.; Klein, B.E.; Moss, S.E.; Davis, M.D.; DeMets, D.L. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and Risk of Diabetic Retinopathy When Age at Diagnosis Is Less than 30 Years. Arch. Ophthalmol. 1984, 102, 520–526.
12) Klein, R.; Klein, B.E.; Moss, S.E.; Davis, M.D.; DeMets, D.L. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and Risk of Diabetic Retinopathy When Age at Diagnosis Is 30 or More Years. Arch. Ophthalmol. 1984, 102, 527–532.
13) Sun, J.K.; Keenan, H.A.; Cavallerano, J.D.; Asztalos, B.F.; Schaefer, E.J.; Sell, D.R.; Strauch, C.M.; Monnier, V.M.; Doria, A.; Aiello, L.P.; et al. Protection from Retinopathy and Other Complications in Patients with Type 1 Diabetes of Extreme Duration: The Joslin 50-Year Medalist Study. Diabetes Care 2011, 34, 968–974.
14) Tsai, G.; Banaee, T.; Conti, F.F.; Singh, R.P. Optical Coherence Tomography Angiography in Eyes with Retinal Vein Occlusion. J. Ophthalmic Vis. Res. 2018, 13, 315–332.
15) Rao, H.L.; Pradhan, Z.S.; Suh, M.H.; Moghimi, S.; Mansouri, K.; Weinreb, R.N. Optical Coherence Tomography Angiography in Glaucoma. J. Glaucoma 2020, 29, 312–321.
16) Katulanda, P.; Ranasinghe, P.; Jayawardena, R. Prevalence of Retinopathy among Adults with Self-Reported Diabetes Mellitus: The Sri Lanka Diabetes and Cardiovascular Study. BMC Ophthalmol. 2014, 14, 100.

17) Seferovic, J.P.; Bentley-Lewis, R.; Claggett, B.; Diaz, R.; Gerstein, H.C.; Køber, L.V.; Lawson, F.C.; Lewis, E.F.; Maggioni, A.P.; McMurray, J.J.V. Jeffrey L Probstfield, Matthew C Riddle, Scott D Solomon, Jean-Claude Tardif, Marc A Pfeffer; . Retinopathy, Neuropathy, and Subsequent Cardiovascular Events in Patients with Type 2 Diabetes and Acute Coronary Syndrome in the ELIXA: The Importance of Disease Duration. J. Diabetes Res. 2018, 2018, 1631263.
18) Schneider, A.L.C.; Pankow, J.S.; Heiss, G.; Selvin, E. Validity and Reliability of Self-Reported Diabetes in the Atherosclerosis Risk in Communities Study. Am. J. Epidemiol. 2012, 176, 738–743.
19) Rosenfeld, P.J.; Durbin, M.K.; Roisman, L.; Zheng, F.; Miller, A.; Robbins, G.; Schaal, K.B.; Gregori, G. ZEISS Angioplex TM Spectral Domain Optical Coherence Tomography Angiography: Technical Aspects. OCT Angiogr. Retin. Macular Dis. 2016, 56, 18–29.
20) Laotaweerungsawat, S.; Psaras, C.; Liu, X.; Stewart, J.M. OCT Angiography Assessment of Retinal Microvascular Changes in Diabetic Eyes in an Urban Safety-Net Hospital. Ophthalmol. Retina 2020, 4, 425–432.
21) Durbin, M.K.; An, L.; Shemonski, N.D.; Soares, M.; Santos, T.; Lopes, M.; Neves, C.; Cunha-Vaz, J. Quantification of Retinal Microvascular Density in OCTA Images in Diabetic Retinopathy. JAMA Ophthalmol. 2017, 135, 370–376.