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LETTER TO THE EDITOR

Relationship between age and subfoveal choroidal thickness and its clinical implications

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Abstract

The retrospective study by Lei *et al* is an investigation of the relationship between age and subfoveal choroidal thickness (SFCT) in Chinese patients with proliferative diabetic retinopathy. Elements of the study design prevent the generalizability of the study findings, limiting their clinical implications. We recommend consideration of stricter eligibility criteria, other variables like duration of diabetes, interpretation of gender-differences in SFCT, longitudinal follow-up, use of newer choroidal flow indices, comparison of values with normal controls, subgroup analysis to determine the effect of prior treatment, as well as consideration of various real-world scenarios in future studies.

Key Words: Diabetic retinopathy; Optical coherence tomography; Phenotypic sex; Research design; Visual acuity

Core Tip: The retrospective study by Lei *et al* is an investigation of the relationship between age and subfoveal choroidal thickness (SFCT) in Chinese patients with proliferative diabetic retinopathy. Elements of the study design prevent the generalizability of the study findings, limiting their clinical implications. We recommend consideration of stricter eligibility criteria, other variables like duration of diabetes, interpretation of gender-differences in SFCT, longitudinal follow-up, use of newer choroidal flow indices, comparison of values with normal controls, subgroup analysis to determine the effect of prior treatment, as well as consideration of various real-world scenarios in future studies.

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TO THE EDITOR

We read with interest the retrospective study on the non-linear relationship between age and subfoveal choroidal thickness (SFCT) in Chinese patients with proliferative diabetic retinopathy (PDR) by Lei *et al*[1] recently published in the *World Journal of Diabetes*. We commend the authors on their attempt to elucidate the changes in blood dynamics of the choroidal circulation occurring in the clinical setting of PDR[1].

This cross-sectional retrospective study has been conducted in the Chinese population among hospitalized individuals with type 2 diabetes who underwent vitrectomy for PDR-and the contralateral eyes of these individuals were included for the study[1]. We commend the authors for applying appropriate statistical tests such as measures of descriptive data, multivariate linear regression model with spline smoothing for the non-linear relationship thus discovered, and the recursive algorithm to calculate the inflection point. The authors developed a multivariate linear regression model to describe the relationship, which is a technically correct approach to minimize residual confounders. The authors have also indicated that the trend is consistent in all strata except in patients of anemia, proving robustness of their model.

Previously, Xu *et al*[2] have investigated the SFCT in diabetic patients with and without diabetic retinopathy (DR) in the population-based Beijing Eye Study in 2011, including nearly 3500 individuals aged 50-93 years. They concluded that patients with diabetes mellitus (DM) had statistically significantly more SFCT, whereas the presence and stage of DR were not associated additionally with abnormal SFCT[2]. As the present study was undertaken including a comparatively younger patient cohort, its contrasting findings were expected to have important implications for the Chinese population by serving to add on to the findings of the Beijing eye study. However, we believe that there are elements of the study design which prevent the generalizability of the study findings and make them exclusive to the present study, limiting their clinical implications. We would like to highlight these factors which should be taken into account while interpreting the study and utilizing it in clinical practice.

In the present study, the sample included patients who underwent unilateral vitrectomy, and the SFCT was measured in contralateral eyes using extended depth imaging (EDI) on optical coherence tomography (OCT). Considering that the severity of DR is generally symmetrical between the two eyes of the patient, and given that vitrectomy is primarily recommended for severe PDR or its complications like high-risk PDR, non-resolving vitreous haemorrhage or vitreomacular interface (VMI) abnormalities, it is reasonable to argue if the findings of the study align with such advanced PDR cases only[3]. The decrease of SFCT has been found to be significant after the onset of severe DR, and is proportionate to the severity of DR[4]. The authors have not commented if any high-risk characteristics or VMI abnormalities were observed in any subset of the eyes included, and if so, what were the changes in SFCT in these eyes.

It is commendable that the authors took into account and tried to eliminate the possibility of diurnal variation influencing choroidal thickness by obtaining images in the afternoon. It would have been interesting to know the reason for the same, given that the peaks for SFCT and various related indices of choroidal circulation occur between 2:00 and 6:00[5]. Also, it is not known whether these indices remain well-correlated with SFCT in eyes with DR. In line with the authors' recommendations for future studies, OCT angiography could be used to simultaneously measure these choroidal indices to reveal the true changes in choroidal dynamics in PDR in this population[6].

In all the three adjusted models, gender is a common parameter. This has to be viewed in the light of the correlation of SFCT with gender elucidated in available literature, that SFCT is thicker in men than women[7]. The authors found significant difference in the results of stratified analysis between age and SFCT in males but not in females. This finding has not been discussed by the authors and thus, the clinical implications of this finding are presently unclear.

In the present study, yearly reduction in SFCT in PDR patients was found to be 1.68 microns, based on the measurements of SFCT in patients of varying age. It is well-known that SFCT decreases with increasing duration of diabetes. However, the inference that the rate is similar to the average rate of loss of 1.40 to 4.80 microns/year in healthy participants, appears erroneous. Choroidal thickness has been found to decrease in diabetic patients even without evidence of DR[4]. One then wonders why the rate of loss is the same as that in healthy subjects instead of being significantly greater? There is need to longitudinally follow-up individual participants and perform serial EDI-OCT measurements of SFCT to derive the actual rate of SFCT reduction in the subjects. It should also take into account the duration of diabetes in these subjects. This approach is supported by the arguments provided by the authors, on the mechanisms of how hyperglycaemia causes choroidopathy and hence influences choroidal thickness.

The authors concluded that age is a significant determinant in the SFCT, which is in concurrence with previous studies showing significant decrease in SFCT after the age of 60 years[8]. However, caution should be exercised in interpreting the finding that there occurs an inflection point at 54 years regarding trends in SFCT with age. The authors remark that identifying the turning point of age 54 and SFCT in PDR increased statistical power and clinical significance of the study but fail to elaborate as to how they reached this conclusion. It would have been pertinent to perform subgroup analysis amongst treatment naïve patients to elucidate the relationship in question more accurately[9]. It would also be pertinent to compare age related changes in choroidal indices, notably choroidal vascularity index (CVI) and SFCT amongst normal individuals of the same area and ethnicity with those having DM without PDR, treated PDR with and without treated diabetic macular edema (DME), and treatment naïve PDR[10].

Finally, considering that contradictory results observed in studies for SFCT in PDR patients the world over, it is difficult to understand the clinical implications of the findings of the present study. Presently, the evidence does not adequately support the assumption that thinner SFCT-for example in myopia-is associated with any visual acuity changes in otherwise normal patients[11]. However, as *per* recent research, reduced SFCT is associated with poorer gain in visual acuity after vitreoretinal intervention, such as that for epiretinal membrane, and this may be attributable to changes in ocular blood flow[12]. Whether the reduced SFCT results in similarly poor visual acuity gains after intervention for PDR is not fully understood. Dourandeesh *et al*[13] recently concluded an evaluation of changes in SFCT in cases of tractional DME after pars plana vitrectomy, wherein they observed that SFCT decreased and visual acuity increased significantly following the intervention[13]. However, there was no subgroup analysis comparing subjects operated early and those who presented late in their disease course. In addition, there is paucity of evidence regarding the longitudinal change of SFCT after vitreoretinal surgery for PDR[14]. Thus, whether progressive reduction of SFCT is altered by early vitreoretinal surgery for PDR is another future avenue to be explored. Recently, chorioretinal vascularity is being increasingly accepted as a biomarker of predictiveness in vitreomacular surgery as well as anti-vascular endothelial growth factor (VEGF) treatment[15,16]. Whether the newer anti-VEGF agents have some beneficial effects in preventing or reversing alterations of choroidal circulation in PDR in the same way as they do in neovascular age-related macular degeneration, are some of the real-world questions which require further studies.

In conclusion, the present study adds to current literature by providing information on the SFCT in advanced PDR subjects. The results have limited generalizability and unclear clinical implications. Future studies are recommended, involving newer diagnostic tools like OCT angiography, newer indices like CVI, longitudinal comparative study designs, subgroup analyses and comparisons between normal, treated and treatment naïve eyes, as well as SFCT measurements in real-world scenarios.

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FOOTNOTES

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