DIABETES ALTERS THE MAGNITUDE OF VITREOMACULAR ADHESION

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Purpose: To quantify the changes in vitreomacular interactions that occur with aging in diabetic eyes in comparison with age-matched control eyes.

Methods: Spectral-domain optical coherence tomography (Spectralis; Heidelberg Engineering) foveal scans of diabetic patients, without evidence of cystoid macular edema, were included. Twenty-five raster foveal scans were performed on every subject. Area of vitreomacular adhesion was delineated using the Spectralis drawing tool and calculated in square millimeter. Data collected included gender, race, best-corrected visual acuity, and posterior vitreous detachment status. Subjects were divided into age groups according to decade of life.

Results: Spectral-domain optical coherence tomography scans from 141 diabetic patients were analyzed. Area of vitreomacular adhesion (mm^2) showed a hyperbolic decline in diabetic patients (35.5 ± 0, 35.0 ± 3, 34.0 ± 3, 33.9 ± 5, 33.7 ± 6, 29.0 ± 11, 23 ± 15, 13 ± 15). With aging, incidence of posterior vitreous detachment increased and incidence of complete attachment decreased.

Conclusion: Diabetes affects the magnitude of attachment of the vitreous gel to the macula that results in stronger and longer lasting attachment of the gel throughout life. Gender differences were not noticed in diabetic patients, suggesting that vitreomacular adhesion remains robust in both genders in diabetes despite aging.

RETINA 37:749–752, 2017

Vitreomacular adhesion (VMA) is an optical coherence tomography (OCT) finding in which there is separation of the perifoveal vitreous with persistent vitreomacular attachment without any change in retinal contour.[1] The International Vitreomacular Traction Study group proposed the above definition of VMA, and also defined vitreomacular traction in various stages, using an OCT-based anatomical classification.[1] This interest in classifying the vitreomacular interface through the use of advancing OCT technology has led to the study of VMA and its role in various vitreoretinal diseases, as well as the overall evolution of posterior vitreous detachment (PVD).[2,3]

In our previous study, we quantified the area of VMA, as seen on spectral-domain OCT (SD-OCT), in healthy subjects throughout nine decades of life. With aging, the percentage of patients with PVD increased, whereas percentage of patients with complete VMA decreased. As to gender, men were found to have significantly larger area of VMA compared with women in several decades of life. These findings demonstrate that vitreomacular interface interactions throughout life are age and gender dependent in healthy subjects.

The purpose of the current study was to quantify the area of VMA in diabetic subjects. In diabetic patients, diabetic macular edema (DME) is a leading cause of severe visual impairment worldwide in the working-age population, with DME affecting up to 7% to 8% of patients with diabetes.[4–6] Although it is known the pathogenesis of DME involves breakdown of the blood–retinal barrier resulting in fluid accumulation in the retinal layers,[7] the complete process is multifactorial and not yet fully understood. One contributing

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Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc, New York, NY. The funding organization had no role in the design or conduct of this research.

None of the authors have any conflicting interests to disclose.

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factor to the development and persistence of DME in diabetic patients, which has been studied throughout the years, is the vitreous and its adhesions to the retina.[8,9]

Using the same method in our previous study, the current study quantifies area of VMA, using SD-OCT, in diabetic patients throughout life.

Methods

This study was reviewed and approved by the Institutional Review Board at the University of Louisville. Twenty-five raster SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) foveal scans were obtained from 141 diabetic patients between the ages of 20 to 80 years and were compared with 250 age-matched and gender-matched healthy controls. Patients with proliferative diabetic retinopathy or with DME were excluded from the study. Patients suffering from any underlying systemic disease other than systemic hypertension that was well controlled medically were excluded from the present study. Subjects with foveal scans not of sufficient quality to view the vitreoretinal interface were also excluded. All subjects underwent a complete ophthalmic examination including dilated fundoscopy. Data collected included gender, race, best-corrected visual acuity, and PVD status.

Image Analysis

Two independent, masked trained readers analyzed each scan to determine the status of the vitreoretinal interface: complete vitreous adhesion, partial PVD with persistent VMA, or complete PVD. A scan was categorized as having complete PVD if detached vitreous was seen in all 25 raster scans or if there was total absence of the posterior hyaloid on SD-OCT and the presence of PVD was confirmed clinically with the identification of a detached posterior vitreous cortex with a Weiss ring. For those scans categorized as having partial PVD with persistent VMA, the two points at which the vitreous intersected the inner retinal surface were marked on each raster scan. This was done using the existing Spectralis software. The points were then connected using the draw region tool on the corresponding fundus image, with the resulting area automatically calculated by the Spectralis software based on the standardized SD-OCT measurement scale. The area of attachment was expressed in square millimeter.

Statistical Analysis

Statistical analysis was performed using SPSS software (Version 17.0; SPSS Inc, Chicago, IL). Area outliers of more than 2 standard deviations from the mean were excluded for the purpose of gender, race, and lens status comparisons and analysis. Multivariate analysis was performed using the two-way analysis of variance. A *P*-value was considered significant if less than 0.05.

Results

A total of 141 diabetic patients were included in the study, of which 68 were men, and 39 were African-American (others were white). Patients of the control group included 250 patients who were age and gender matched. In the control group, 56 patients were African-American and the rest were whites.

Subjects with complete vitreous attachment on SD-OCT imaging were assigned a value of 35.0 mm^2, which corresponds to the total scanned area on SD-OCT imaging. Figure 1 demonstrates that the area of VMA (mm^2) decreased through each decade of life in a hyperbolic manner (35.5 ± 0, 35.0 ± 3, 34.0 ± 3, 33.9 ± 5, 33.7 ± 6, 29.0 ± 11, 23 ± 15, 13 ± 15). The VMA area in normal group followed a sigmoidal decline. There was a significant difference ($P < 0.05$) in the VMA area between diabetic patients and controls in the sixth, seventh, and eighth decade of life, where persistent attachment was noted in diabetic patients (Figure 1). The mean age at which 50% of the posterior hyaloid, by area, had detached from the imaged macular surface was 72 years (56 years in the normal group, $P < 0.05$). Figure 2 demonstrates that while in the normal group of patients (left panel) persistent

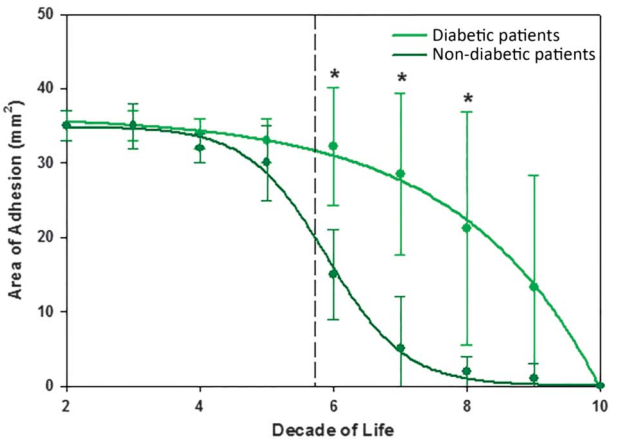

Fig. 1. Area of vitreomacular adhesion (mm^2) for each decade of life in diabetic patients and healthy subjects.

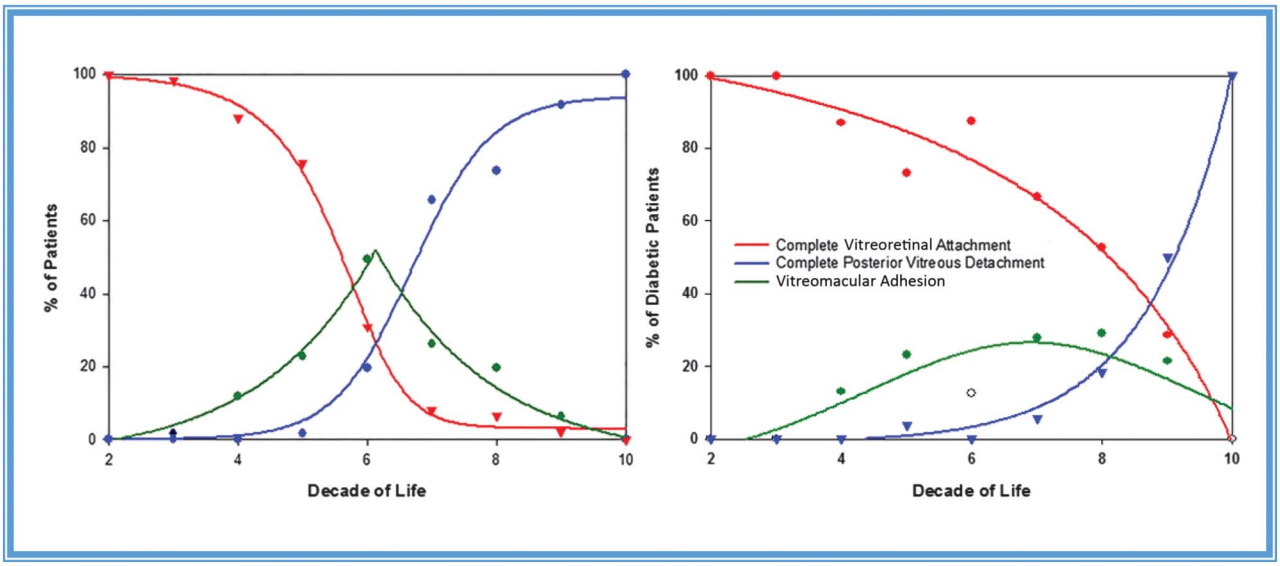

Fig. 2. Percentage of patients with complete VMA, complete PVD, and PVD with persistent VMA in healthy patients (left) and diabetic patients (right) for each decade of life.

VMA peaked at the sixth decade of life, in diabetic patients VMA remained greater in magnitude through the sixth, seventh, and eighth decade of life. With aging, the prevalence of PVD increased, whereas the prevalence of complete vitreous adhesion decreased (Figure 2, right panel). In this diabetic cohort of patients, men and women were not found to have any significant difference in the area of VMA throughout the decades of life.

Discussion

The role of the vitreous in the development and clinical course of DME is not completely understood; however, the firmer adhesion of the vitreous to the retina in diabetic patients is a factor in the clinical course of DME. Nasrallah et al[10] found that in older patients, diabetic patients without macular edema have significantly higher rates of PVD than those with macular edema, whereas in younger diabetic patients, those with macular edema have significantly higher rates of PVD than those without macular edema.[11] The authors postulated that in older patients, the PVD was secondary to vitreous gel syneresis and was in fact protective of the macula from traction.[11] In contrast, in younger diabetic patients, PVD is secondary to diabetes-related vitreous contraction that caused traction on the macula and thus DME.[11] Hikichi et al[12] suggested that separation of the vitreous from the macula may assist the spontaneous resolution of DME.

This role of the adherent vitreous in DME is important in terms of management of diabetic patients. Vitrectomy has been proposed for the treatment of DME, in cases with a taut and thickened posterior hyaloid as well as with PVD.[13–19] The status of VMA in patients receiving treatment with anti–vascular endothelial growth factor agents for DME is also important, as it has been shown that those patients with focal VMA who subsequently demonstrate PVD may have a greater potential for improvement in visual outcomes with anti–VEGF therapy.[20]

This study is the first to investigate the area of VMA in diabetic patients by measuring the area of VMA using SD-OCT imaging. In both healthy subjects, as seen in our previous study, and in diabetic patients, the area of VMA decreased significantly with each decade of life; sigmoidally in healthy subjects and in a hyperbolic manner in diabetic patients. In both groups, incidence of PVD increased and incidence of complete attachment decreased with aging, but patterns differed significantly between healthy and diabetic patients. Significant differences between the genders were noted in the area of VMA in healthy subjects (women were found to have smaller areas of attachment and early PVD in comparison with men). This difference in VMA progression that was noticed in healthy patients was not statistically significant in diabetic patients.

These differences between the healthy and diabetic groups suggest that diabetes affects the magnitude of attachment of the vitreous gel to the macula, resulting in strong and longer lasting attachment of the gel throughout life. This difference may be explained by the difference in composition of the vitreous found in diabetic patients. The vitreous in diabetic patients has

been found to contain an increase in nonenzymatic glycation products.[21–23] This increase in advanced glycation end products may result in stronger "glue-like" vitreoretinal adhesions.

In conclusion, this study quantifies the area of VMA in diabetic patients. Our results further the understanding of this normal aging process in diabetic patients and can be a valuable tool in the management of DME.

Key words: vitreomacular adhesion, diabetes.

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