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축성근시에서 당뇨 및 당뇨망막병증의 억제효과

Axial Myopia and Low HbA1c Level are Correlated and Have a Suppressive Effect on Diabetes and Diabetic Retinopathy

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Purpose: The aim of this study was to investigate whether axial myopia has a suppressive effect on diabetes and diabetic retinopathy.
Methods: This retrospective, cross-sectional study used propensity-score matching to explore the correlations between axial myopia and diabetes and diabetic retinopathy. This study included patients who underwent ophthalmic surgery, including cataract surgery, between April 2009 and July 2016.
Results: With an increase of the axial length (AL < 24 mm; 24 mm ≤ AL < 26 mm; and AL ≥ 26 mm) in axial myopia, the prevalence of diabetes (35.9%, 27.9%, and 20.1%, respectively) and diabetic retinopathy (43.3%, 31.2%, and 24.1%, respectively) decreased ($p < 0.001$ and = 0.001, respectively). Similarly, glycosylated hemoglobin (HbA1c) level (7.00%, 6.67%, and 6.44%, respectively) decreased with an increase of AL in axial myopia ($p < 0.001$). Axial length and HbA1c level were significantly and negatively correlated, as determined by partial correlation analysis after adjusting for age and sex ($r = -0.127$; $p < 0.001$).
Conclusions: Axial myopia and low HbA1c level are correlated and have a suppressive effect on diabetes and diabetic retinopathy.

Keywords: Axial length; Diabetes mellitus; Diabetic retinopathy; Glycosylated hemoglobin; Myopia

Introduction

The worldwide prevalence of diabetes has been increasing steadily and is expected to increase more dramatically than previously estimated [1,2]. The prevalence of diabetes among Korean adults is approximately 10%, and it gradually increases with age until 60 years, at which point, the prevalence has been reported to range between 20% and 25% [3,4]. The prevalence of diabetic retinopathy (DR) increases with duration of diabetes and has been reported to be approximately 15% among Koreans with diabetes [5,6].

Several recent studies have suggested that myopia has a protective effect against DR [7-12]. Decreased blood flow in eyes with greater axial length (AL) has been suggested to be

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protective against the development of DR [9,13]. However, a subsequent experimental study reported that reduced retinal blood flow was not a major factor for progression of DR [14], and a population-based study failed to demonstrate any association between axial myopia and DR [15].

There are fewer studies on the correlation between myopia and diabetes than there are on the correlation between myopia and DR. Pierro et al. reported that, among patients with AL < 24 mm, those with diabetes exhibited a shorter AL than those without [16]. Herse conducted experiments in rabbits and reported that chronic hyperglycemia impedes axial development [17]. Li et al. reported that hyperglycemia induces lenticular swelling and causes myopic changes by increasing refractive power [18]. However, no study to date has clarified the exact relationship between axial myopia and diabetes. The present study aimed to evaluate the hypothesis that patients with axial myopia exhibit a relatively low prevalence of diabetes.

Materials and Methods

This study adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the institutional review board of Severance Hospital, Yonsei University, which waived the requirement for informed patient consent because of the retrospective study design.

Study population

This study retrospectively reviewed the data of 12,628 patients (18,449 eyes) who underwent extracapsular cataract extraction (ECCE) with intraocular lens (IOL) implantation at Severance Hospital, Seoul, South Korea, between April 1, 2009, and July 31, 2016. Data regarding patient age at the time of surgery, presence of hypertension, diabetes, DR, and intraoperative AL of both eyes were retrieved from medical records of physical and ophthalmologic examinations. For patients who underwent bilateral surgery, only data from the eye that was operated first were included. After excluding 465 patients under 40 years of age, 61 patients above 90 years of age, 57 patients with confirmed type I diabetes, and 100 patients with suspected secondary diabetes, the study finally included 11,945 patients. In addition, patients with data available for glycated hemoglobin (HbA1c) level, systolic blood pressure (SBP), diastolic blood pressure (DBP), height, and weight were grouped separately (n = 4,795; Fig. 1).

The subjects were divided into three groups based on mean AL (AL < 24 mm, 24 mm ≤ AL < 26 mm, and 26 mm ≤ AL). Differences among the three groups were determined based on age at the time of surgery, sex, and presence of hypertension, diabetes and DR. Propensity-score matching (PSM) analysis was performed in order to adjust for statistical bias (selection bias) and to confirm whether the same results would be obtained with other analytical methods. The model was used to obtain a 1:1 match using the nearest neighbor matching method. After matching the "24 mm ≤ AL < 26 mm" group with the "26 mm ≤ AL" group, the "AL < 24 mm" group was matched with the "24 mm ≤ AL" group.

Statistical analysis

Data for numeric variables are expressed as mean ± standard deviation. Biases due to differences in age, sex, and presence of hypertension were adjusted by PSM. Continuous

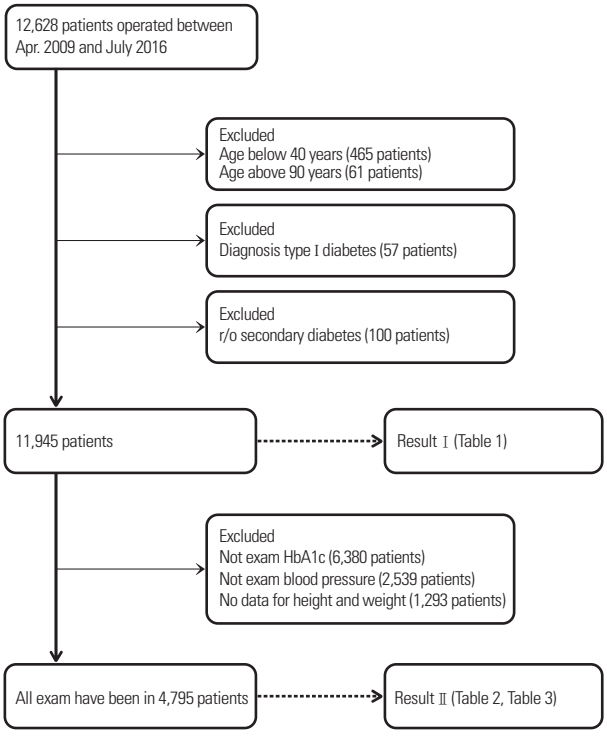

Figure 1. Study design. Out of 12,628 patients, 11,945 patients were included in the Result 1, and 4,795 patients were included in the Result 2. HbA1c = glycated hemoglobin or glycohemoglobin.

variables were compared by analysis of variance, followed by post-hoc analysis with Bonferroni correction. Categorical variables were compared by the chi-square test, followed by Bonferroni correction (Tables 1, 2). Partial correlation analysis was performed to investigate correlations among continuous variables (Table 3). In addition, the effect of an increase in AL on diabetes and DR was evaluated by multinomial logistic regression analysis (Table 4, 5). Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA), SPSS R-plugin PSMATCHING3, and R version 3.1.1 (R Foundation for Statistical Computing; http://www.r-project.org).

Results

The 11,945 patients included in this study were grouped based on AL as follows: AL < 24 mm, 7,684 patients; 24 mm ≤ AL < 26 mm, 2,965 patients; and 26 mm ≤ AL, 1,116 patients. After PSM, these three groups included 2,232, 1,116, and 1,116 patients, respectively. There was no significant difference in age, sex, or presence of hypertension among the three groups after PSM. However, the prevalence of diabetes (35.9%, 27.9%, and 20.1%, respectively) and DR (43.3%, 31.2%, and 24.1%, respectively) decreased significantly (both, $p < 0.001$; Table 1) with increasing AL (AL < 24 mm; 24 mm ≤ AL < 26 mm; and AL ≥ 26 mm).

The 4,795 patients with data available for HbA1c level, SBP, DBP, height, and weight were grouped based on AL as follows: AL < 24 mm, 3,325 patients; 24 mm ≤ AL < 26 mm, 1,120 patients; and 26 mm ≤ AL, 250 patients. After PSM, these three groups contained 500, 250, and 250 patients, respectively. There was no significant difference in age, sex, or presence of hypertension among the three groups after PSM. However, the prevalence of diabetes (78.8%, 70.0%, and 60.0%, respectively) and DR (49.5%, 38.9%, and 28.0%, respectively) decreased significantly (both, $p < 0.001$) with increasing AL (AL < 24 mm; 24 mm ≤ AL < 26 mm; and AL ≥ 26 mm). Similarly, the HbA1c level was found to decrease significantly with increasing AL ($p < 0.001$; Table 2).

The results of partial correlation analysis for associations between AL, HbA1c level, height, weight, SBP, and DBP revealed that AL and HbA1c were significantly negatively correlated ($p < 0.001$), while AL, height, and weight were significantly and positively correlated with each other (all, p

Table 1. Demographic characteristics of the study population

	AL < 24 mm	24 mm ≤ AL < 26 mm	26 mm ≤ AL	*p*-value*
Before matching	N = 7,864	N = 2,965	N = 1,116	
AL (mm)	23.03 ± 0.66[a]	24.67 ± 0.53[b]	28.25 ± 1.93[c]	<0.001
Age (years)	68.03 ± 9.08[a]	64.83 ± 10.43[b]	58.66 ± 10.42[c]	<0.001
Sex (male) (n, %)	2,514 (32.0)[a]	1,785 (60.2)[b]	485 (43.5)[c]	<0.001
Hypertension (n, %)	3,989 (50.7)[a]	1,377 (46.4)[b]	363 (32.5)[c]	<0.001
Diabetes (n, %)	3,264 (41.5)[a]	1,064 (35.9)[b]	224 (20.1)[c]	<0.001
Retinopathy in diabetes (n, %)	1,135 (34.8)[a]	333 (31.3)[a,b]	54 (24.1)[b]	0.001
After propensity-score matching	N = 2,232	N = 1,116	N = 1,116	
AL (mm)	23.07 ± 0.71[a]	24.72 ± 0.56[b]	28.25 ± 1.93[c]	<0.001
Age (years)	58.86 ± 10.36	58.94 ± 10.27	58.66 ± 10.42	0.803
Sex (male) (n, %)	975 (43.7)	465 (41.7)	485 (43.5)	0.522
Hypertension (n, %)	722 (32.3)	362 (32.4)	363 (32.5)	0.994
Diabetes (n, %)	802 (35.9)[a]	311 (27.9)[b]	224 (20.1)[c]	<0.001
Retinopathy in diabetes (n, %)	347 (43.3)[a]	97 (31.2)[b]	54 (24.1)[b]	<0.001

Data are presented as mean ± standard deviation or number (percentage).
AL = axial length.
*Analysis of variance and post-hoc analysis with Bonferroni correction for age; chi-square test and post-hoc analysis with Bonferroni correction for sex, diabetes, and hypertension; different letters in the same row indicate statistically significant differences among the groups.

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Table 2. Demographic characteristics of the study population

	AL < 24 mm	24 mm ≤ AL < 26 mm	26 mm ≤ AL	*p*-value*
Before matching	N = 3,325	N = 1,120	N = 250	
AL (mm)	23.05 ± 0.63[a]	24.63 ± 0.51[b]	27.81 ± 1.67[c]	<0.001
Age (years)	68.38 ± 8.94[a]	66.43 ± 10.08[b]	61.81 ± 9.54[c]	<0.001
Sex (male) (n, %)	2,514 (32.0)[a]	1,785 (60.2)[b]	485 (43.5)[c]	<0.001
Hypertension (n, %)	3,989 (50.7)[a]	1,377 (46.4)[b]	363 (32.5)[c]	<0.001
Diabetes (n, %)	2,496 (75.1)	834 (68.4)	150 (60.0)	<0.001
Retinopathy in diabetes (n, %)	958 (38.4)[a]	285 (34.2)[a,b]	42 (28.0)[b]	0.006
Height (cm)	157.80 ± 8.45[a]	163.56 ± 8.28[b]	164.01 ± 8.90[b]	<0.001
Weight (kg)	60.78 ± 10.08[a]	65.48 ± 11.09[b]	66.68 ± 12.47[b]	<0.001
BMI (kg/m^2)	24.39 ± 3.45	24.43 ± 3.44	24.67 ± 3.32	0.444
SBP (mmHg)	129.48 ± 16.29[a]	129.22 ± 16.25[b]	126.72 ± 13.91[b]	0.033
DBP (mmHg)	74.63 ± 10.41[a]	75.54 ± 9.92[a,b]	76.68 ± 9.72[b]	0.001
MAP (mmHg)	93.04 ± 10.88	93.03 ± 10.89	93.16 ± 10.67	0.941
HbA1c level (%)	6.83 ± 1.31[a]	6.65 ± 1.24[b]	6.44 ± 1.12[c]	<0.001
After propensity-score matching	N = 500	N = 250	N = 250	
AL (mm)	23.14 ± 0.58[a]	24.67 ± 0.49[b]	27.81 ± 1.67[c]	<0.001
Age (years)	61.98 ± 10.39	61.34 ± 10.08	61.81 ± 9.54	0.719
Sex (male) (n, %)	311 (62.2)	155 (62.0)	144 (57.6)	0.444
Hypertension (n, %)	217 (43.4)	107 (42.8)	114 (45.6)	0.793
Diabetes (n, %)	394 (78.8)[a]	175 (70.0)[b]	150 (60.0)[c]	<0.001
Retinopathy in diabetes (n, %)	195 (49.5)[a]	68 (38.9)[b]	42 (28.0)[c]	<0.001
Height (cm)	161.68 ± 8.44[a]	164.27 ± 8.66[b]	164.01 ± 8.490[b]	<0.001
Weight (kg)	63.60 ± 10.42[a]	66.73 ± 10.30[b]	66.68 ± 12.47[b]	<0.001
BMI (kg/m^2)	24.31 ± 3.45	24.70 ± 3.12	24.67 ± 3.32	0.199
SBP (mmHg)	129.60 ± 15.51[a]	127.84 ± 14.61[a,b]	126.72 ± 13.91[b]	0.034
DBP (mmHg)	76.84 ± 10.50	76.51 ± 9.49	76.68 ± 9.72	0.911
MAP (mmHg)	94.43 ± 10.63	93.62 ± 9.80	93.36 ± 9.92	0.337
HbA1c (%)	7.00 ± 1.42[a]	6.67 ± 1.21[b]	6.44 ± 1.12[c]	<0.001

Data are presented as mean ± standard deviation or number (percentage).
AL = axial length; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP, mean arterial pressure; HbA1c, glycated hemoglobin or glycohemoglobin.
*Analysis of variance and post-hoc analysis with Bonferroni correction for age, HbA1c level, BMI, and MAP; chi-square test and post-hoc analysis with Bonferroni correction for sex, diabetes, and hypertension; different letters in the same row indicate statistically significant differences among the groups.

< 0.001; Table 3). The results of multinomial logistic regression analysis for evaluating the effects of axial myopia on diabetes and DR revealed that the odds ratio (OR) of both diseases decreased with an increase in axial myopia (Table 4). However, the results of multinomial logistic regression analysis performed using all parameters, including HbA1c, revealed no significant effects of axial myopia on diabetes or DR (Table 5).

Discussion

Diabetes remains one of the leading causes of morbidity and mortality worldwide [19]. The prevalence of diabetes has been projected to reach 69% in developing countries and 20% in developed countries by the year 2030 [1,2]. Risk factors for diabetes include obesity, hypertension, lifestyle

Table 3. Partial correlation analysis among the study variables

Control	Variable		Axial length	HbA1c level	Height	Weight	SBP	DBP
Age, sex	Axial length	*r*	1	-0.127	0.184	0.114	-0.018	0.042
		p	-	<0.001	<0.001	<0.001	0.209	0.004
	HbA1c	*r*	-	1	-0.021	0.405	-0.032	-0.034
		p	-	-	0.145	<0.001	0.027	0.018
	Height	*r*	-	-	1	0.405	-0.032	-0.034
		p	-	-	-	<0.001	0.027	0.018
	Weight	*r*	-	-	-	1	0.026	0.071
		p	-	-	-	-	0.068	<0.001
	SBP	*r*	-	-	-	-	1	0.573
		p	-	-	-	-	-	<0.001
	DBP	*r*	-	-	-	-	-	1
		p	-	-	-	-	-	-

HbA1c = glycated hemoglobin or glycohemoglobin; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 4. Multinomial logistic regression analysis of diabetes severity according to age, sex, hypertension, and AL

	Diabetes		Diabetic retinopathy	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Before matching				
Age (years)	1.020 (1.015–1.025)	<0.001	0.967 (0.961–0.973)	<0.001
Sex				
Male	Reference		Reference	
Female	0.678 (0.618–0.744)	<0.001	0.581 (0.516–0.655)	<0.001
Hypertension				
No	Reference		Reference	
Yes	2.829 (2.584–3.097)	<0.001	3.478 (3.083–3.923)	<0.001
AL (mm)				
AL < 24	Reference		Reference	
24 ≤ AL < 26	0.810 (0.727–0.901)	<0.001	0.560 (0.846–0.646)	<0.001
26 ≤ AL	0.533 (0.444–0.639)	<0.001	0.196 (0.146–0.263)	<0.001
After propensity-score matching				
Age (years)	1.028 (1.020–1.037)	<0.001	0.982 (0.972–0.992)	<0.001
Sex				
Male	Reference		Reference	
Female	0.791 (0.673–0.931)	0.005	0.567 (0.464–0.693)	<0.001
Hypertension				
No	Reference		Reference	
Yes	3.290 (2.787–3.883)	<0.001	4.260 (3.464–5.239)	<0.001
AL (mm)				
AL < 24	Reference		Reference	
24 ≤ AL < 26	0.807 (0.666–0.978)	<0.001	0.479 (0.374–0.614)	<0.001
26 ≤ AL	0.554 (0.452–0.679)	0.029	0.226 (0.167–0.307)	<0.001

AL = axial length; OR = odds ratio; CI = confidence interval.

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Table 5. Multinomial logistic regression analysis of diabetes severity according to age, sex, hypertension, AL, height, weight, SBP, DBP, and HbA1c level

	Diabetes		Diabetic retinopathy	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Before matching				
Age (years)	1.003 (0.992–1.013)	0.627	1.003 (0.992–1.013)	<0.001
Sex				
Male	Reference		Reference	
Female	0.797 (0.615–1.033)	0.086	0.797 (0.615–1.033)	<0.001
Hypertension				
No	Reference		Reference	
Yes	1.793 (1.505–2.137)	<0.001	1.793 (1.505–2.137)	<0.001
AL (mm)				
< 24	Reference		Reference	
24–25.99	0.864 (0.706–1.056)	0.154	0.864 (0.706–1.056)	<0.001
≥ 26	0.729 (0.508–1.047)	0.087	0.729 (0.508–1.047)	<0.001
Height (cm)	0.995 (0.979–1.011)	0.542	0.995 (0.979–1.011)	0.723
Weight (kg)	1.013 (1.003–1.023)	0.014	1.013 (1.003–1.023)	0.743
SBP (mmHg)	1.013 (1.006–1.020)	<0.001	1.013 (1.006–1.020)	<0.001
DBP (mmHg)	0.979 (0.969–0.989)	<0.001	0.979 (0.969–0.989)	<0.001
HbA1c level	12.578 (10.465–15.118)	<0.001	12.578 (10.465–15.118)	<0.001
After propensity-score matching				
Age (years)	1.010 (0.988–1.032)	0.387	1.010 (0.988–1.032)	<0.001
Sex				
Male	Reference		Reference	
Female	0.905 (0.489–1.676)	0.751	0.905 (0.489–1.676)	0.013
Hypertension				
No	Reference		Reference	
Yes	1.678 (1.124–2.504)	0.011	1.678 (1.124–2.504)	0.001
AL (mm)				
< 24	Reference		Reference	
24–25.99	0.613 (0.379–0.992)	0.046	0.613 (0.379–0.992)	<0.001
≥ 26	0.837 (0.508–1.379)	0.485	0.837 (0.508–1.379)	0.076
Height (cm)	1.002 (1.002–1.037)	0.913	1.002 (1.002–1.037)	0.454
Weight (kg)	1.013 (0.989–1.037)	0.287	1.013 (0.989–1.037)	0.727
SBP (mmHg)	1.020 (1.002–1.037)	0.025	1.020 (1.002–1.037)	0.001
DBP (mmHg)	0.977 (0.953–1.002)	0.068	0.977 (0.953–1.002)	0.003
HbA1c level	21.387 (13.226–34.584)	<0.001	21.387 (13.226–34.584)	<0.001

AL = axial length; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA1c = glycated hemoglobin or glycohemoglobin; OR = odds ratio; CI = confidence interval.

changes, pancreatic dysfunction, and smoking [2,20].

Among patients with diabetes in the present study, the proportion of men and the frequency of hypertension were relatively high (data not shown). Several studies on the association between diabetes and sex have documented that men exhibit higher rates of diabetes than women, and that

male sex is a risk factor for diabetes [21-23]. In contrast, some studies have demonstrated a lack of association between these two factors [24]. With regard to this controversy, Nordström et al. [25] reported that the higher rates of diabetes among men was attributable to the higher proportion of visceral fat, and that being male was no longer a risk factor for diabetes after adjustment for visceral fat. Many studies on the association between hypertension and diabetes have found the former to be a risk factor for developing diabetes [20,26].

Myopia is known to induce nuclear and posterior sub-capsular cataract, causing patients with myopia to undergo early surgery [27,28]. In the present study, patients with a longer AL were younger than those with a shorter AL. In order to compensate for differences in age, sex, and hypertension due to AL, the AL groups in the present study were selected by PSM.

Previous studies have suggested that patients with relatively long AL exhibit decreased retinal perfusion, which is one of the factors contributing to the decreased incidence of DR. Therefore, some studies have described myopia as having a protective effect against DR [7-13]. However, in the present study, patients with axial myopia exhibited a relatively low prevalence of diabetes as well as DR. In addition, HbA1c levels were low among patients with axial myopia. The strength of the correlation between myopia and diabetes decreased after adjusting for HbA1c level. Based on the present findings, the authors suggest that axial myopia and low HbA1c level are correlated and have a suppressive effect on diabetes and DR (Fig. 2).

Further studies are warranted to investigate the mechanisms underlying the correlation between axial myopia and HbA1c level, as well as the suppressive effect of axial myopia on diabetes and DR. A follow-up study is being planned at our institute.

There are several limitations to the present study. First, the subjects in this study underwent ophthalmic surgery involving ECCE with IOL implantation at tertiary medical institutions. Second, the effects of socioeconomic status and education were not investigated. Consequently, the present findings on the prevalence of diabetes and hypertension might not be applicable in a population-based study. However, the aim of this study was not to evaluate the prevalence of diabetes or DR among patients with axial myopia, but rather to analyze differences based on the presence of axial myopia. This study was meaningful in that it included patients who underwent ECCE with IOL implantation over a period of more than seven years.

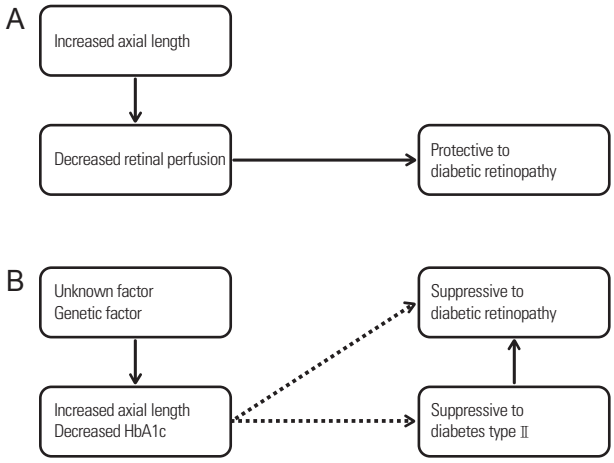

Figure 2. Study conclusions. Previous (A) and new (B) theories. HbA1c = glycated hemoglobin or glycohemoglobin.

In conclusion, even after adjusting for age, sex, and hypertension, patients with axial myopia exhibited a gradual decrease both in the prevalence of diabetes and DR and HbA1c level with increasing AL. Patients with axial myopia exhibited relatively low ORs of diabetes and DR; however, after adjusting for HbA1c level, the relationship between axial myopia and diabetes and DR was no longer significant. The authors believe that a decrease in HbA1c level with an increase in AL is the reason for the decreased prevalence of diabetes and DR among patients with axial myopia (Fig. 2). These findings demonstrate that axial myopia and low HbA1c level are correlated and have a suppressive effect on diabetes and DR.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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