Ocular Axial Length and Diabetic Retinopathy: The Kailuan Eye Study

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Purpose. To examine the role of ocular axial length as an ocular parameter for the prevalence and severity of diabetic retinopathy (DR).

Methods. The cross-sectional Kailuan Diabetic Retinopathy Study included patients with diabetes who participated in the community-based longitudinal Kailuan Study and who had undergone ocular fundus photography. The fundus photographs were graded using the Early Treatment of Diabetic Retinopathy Study criteria.

Results. The study included 1096 patients with diabetes (mean age: 60.8 ± 9.4 years; axial length: 23.37 ± 0.92 mm). In binary regression analysis, a higher DR prevalence was associated with shorter axial length ($P = 0.007$; odds ratio [OR]: 0.81; 95% confidence interval [CI]: 0.70, 0.95) after adjusting for longer known duration of diabetes ($P = 0.02$; OR: 1.13; 95%CI: 1.02, 1.24) and higher fasting blood glucose concentration ($P < 0.001$; OR: 1.38; 95%CI: 1.26, 1.52). A more severe DR stage was associated (regression coefficient r: 0.46) with shorter ocular axial length ($P = 0.047$; standardized regression coefficient β: −0.06) after adjusting for higher fasting blood glucose ($P < 0.001$; β: 0.41) and longer known duration of diabetes ($P = 0.045$; β: 0.07). Longer axial length was associated with a lower DR prevalence ($P = 0.003$; β: −0.10) after adjusting for younger age ($P < 0.001$), male sex ($P < 0.001$), higher body mass index ($P = 0.016$), and lower fasting blood glucose concentration ($P = 0.036$).

Conclusions. After adjusting for systemic risk factors, DR prevalence decreased by 19% (95%CI: 5, 30) for each millimeter increase in axial length. With longer axial length being a surrogate for axial myopia, the marked increase in myopia prevalence worldwide may lead to a relative decrease in the prevalence and incidence of DR in future.

Keywords: diabetic retinopathy, diabetes mellitus, hyperopia, axial length, myopia, Kailuan study

Diabetic retinopathy (DR) has become one of the most common causes of visual impairment and blindness worldwide.[1,2] Previous studies have described systemic risk factors influencing the prevalence and incidence of DR. These factors included elevated blood glucose concentrations and higher glycosylated hemoglobin values, high arterial blood pressure, longer known duration of diabetes, and type I versus type II diabetes.[1,3–6] In addition, hyperlipidemia, obesity, and decreased kidney function were found to be risk factors for DR in some study populations.[1,3] Only a few studies addressed the question whether ocular factors in addition to the systemic parameters play a role in the development and stage of DR.[7–14] These studies were mostly cross-sectional investigations, included only relatively small study populations, and due to their cross-sectional design, measured the systemic risk factors for DR only once. We therefore conducted this study to assess in a relatively large study sample a potential association between the prevalence and stage of DR and the axial length of the eye as a potential major ocular parameter for DR. In addition, we measured the systemic risk factors for DR repeatedly at 2-year intervals before conducting this study, so that the risk of a bias due to a single random sample measurement was reduced.

Methods

The Kailuan Diabetic Retinopathy Study is a cross-sectional study that included participants of the longitudinal Kailuan Study. The research followed the tenets of the Declaration of

Helsinki. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol, and informed consent was obtained from the individuals after explanation of the nature and possible consequences of the study. The community of Kailuan is located in the city of Tangshan with approximately 7.2 million inhabitants. Tangshan is situated approximately 150 km southeast of Beijing and is a center of the coal mining industry. The study population included employees and retirees of a coal mining company (Kailuan Group Company). At baseline, the study population consisted of 101,510 individuals with an age ranging between 18 and 98 years. The study participants were repeatedly and prospectively examined at 2-year intervals.[15–17] The cohort of the present study consisted of patients with diabetes type II who had undergone an ophthalmologic examination including ocular fundus photography.

For all study participants, an interview was performed with standardized questions about the level of education, known major systemic diseases, and lifestyle parameters (such as smoking status, alcohol consumption and physical activity). Body height and weight and the circumference of the waist and hip were measured and the body mass index was calculated. The blood pressure and heart rate were assessed with the participants sitting for at least 5 minutes. Under fasting conditions, blood samples were collected to determine the concentrations of blood glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol, total protein, albumin, uric acid, hypersensitive C-reactive protein, glutamate pyruvate transaminase, total bilirubin, direct bilirubin, urea, urine pH, the red blood count, white blood count, neutrophil count and blood platelet count, and the hemoglobin concentration. Five repeated follow-up examinations at 2-year intervals were conducted from 2006 to 2014.

The diagnostic criterion for diabetes was any measurement of the fasting blood glucose concentration of $\geq$7.0 mM during the 10-year follow-up period, or a self-reported history of diabetes, or a history of medication with hypoglycemic agents.

The ophthalmologic examinations included measurement of visual acuity, tonometry, slit-lamp assisted biomicroscopy of the anterior segment of the eye, ocular biometry applying optical low-coherence reflectometry (Lenstar 900 Optical Biometer; Haag-Streit, Koeniz, Switzerland) for the determination of the central corneal thickness, anterior chamber depth, lens thickness and axial length, and optical coherence tomography (OCT) (AngioPlex; Carl Zeiss Meditec, Dublin, CA, USA). Using a nonmydriatic fundus camera (CR6-45NM; Canon, Inc., Ōsta, Tokyo, Japan), we obtained two 45° fundus photographs centered on the optic nerve head and on the macula. If the pupil diameter did not allow taking fundus photographs with sufficient photographic quality, we dilated the pupil medically by applying eye drops containing 0.5% tropicamide and 0.5% phenylephrine hydrochloride. Using the enhanced depth imaging mode of the OCT and the in-built software (Cirrus 5000 AngioPlex Metrix Version 10.0), we measured the subfoveal choroidal thickness.

Using the fundus photographs, DR was assessed in a masked manner without knowledge of other ocular or systemic parameters of the study participants. Both eyes were evaluated. The level of retinopathy was based on the eye with the more severe stage of DR, and the eye with more severe stage was included in the study. The grading was performed according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria.[18] The minimum criterion for diagnosis of DR was the presence of at least one microaneurysm. The severity of DR was graded into mild nonproliferative DR (20 $\leq$ ETDRS level $<$ 43 with at least one microaneurysm), moderate nonproliferative DR (43 $\leq$ ETDRS level $<$ 53), severe nonproliferative DR (53 $\leq$ ETDRS level $<$ 61), and proliferative DR (ETDRS level $\geq$ 61). Eyes that had previously undergone panretinal laser photocoagulation were classified as proliferative DR. The photographs were assessed by an experienced and trained ophthalmologist (Q.W.). In case of doubt, the photographs were reassessed by a panel including several ophthalmologists (Q.W., M.C.Y., Y.X.W., J.B.J., W.B.W.). Based on the information obtained in the interview about the history of diabetes and the medication taken, we estimated the known duration of diabetes for each patient.

The statistical analysis was performed using a commercially available statistical software program (SPSS for Mac, version 25.0; IBM/SPSS, Chicago, IL, USA). The results were expressed as mean $\pm$ standard deviation or as mean and the 95% confidential interval (CI). Baseline characteristics of the study participants with and without DR were compared using the χ^2 test for proportions or Student's *t*-test for the comparison of means. Logistic regression models were used to estimate the odds ratios (ORs) and their 95% CIs of each risk factor for DR. Linear regression models were used to analyze potential associations between the ocular/systematic parameters and the level of DR. A *P* value of $<$0.05 was considered statistically significant.

Results

The diagnostic examinations were performed for 1154 patients with diabetes (946 [82.0%] men) with a mean age of 60.98 $\pm$ 9.55 years (median, 62.0 years; range, 26.0–83.0 years), and data on axial length were available in 980 individuals, with a mean of 23.36 $\pm$ 0.93 mm (median, 23.30 mm; range, 20.80–27.85 mm). The fundus photographs of 58 (5.02%) patients could not be analyzed due to poor photographic quality, so that eventually 1096 patients (902 [82.3%] men) were included in the study, and axial length was available in 947 participants. The group of study participants with a mean age of 60.8 $\pm$ 9.4 years (median, 62.0 years; range, 26.0–83.0 years) and a mean axial length of 23.37 $\pm$ 0.92 mm (median, 23.30 mm; range, 20.80–27.05 mm) was significantly younger ($P = 0.008$) than the group of patients without assessable fundus photographs, while the two groups did not vary significantly in axial length ($P = 0.63$).

The prevalence of DR was 546/1096 or 49.8% (95%CI: 46.7%, 52.8%). Out of the 546 patients, 350 (64.1%) individuals had mild DR, 154 (28.2%) individuals had moderate DR, 15 (2.7%) had severe nonproliferative DR, and 27 (4.9%) had proliferative DR.

In univariate analysis, the group with DR as compared to the group without DR had a significantly longer known duration of diabetes ($P < 0.001$), a higher fasting blood glucose concentration ($P < 0.001$), a lower uric acid concentration ($P < 0.001$), a lower hypersensitive C-reactive protein concentration ($P = 0.038$), thicker lens thickness ($P = 0.007$), shorter axial length ($P < 0.001$), and thicker subfoveal choroidal thickness ($P = 0.03$) (Table 1). The two groups did not differ significantly in sex ($P = 0.29$), age ($P = 0.98$), systolic ($P = 0.56$) and diastolic ($P = 0.39$) blood pressure, body mass index ($P = 0.84$), and blood lipid concentrations (all $P > 0.15$) (Table 1).

The multivariable binary analysis included the presence of DR as dependent parameter and those variables as independent parameters that were associated with the presence of DR in the univariate analysis with a *P* value of $\leq$0.10 (Table 1). We first dropped the parameters of lens thickness and subfoveal choroidal thickness out of the list of independent variables due to their collinearity with axial length. Due to a lack of statistical significance, we then dropped step-by-step the parameters of serum urea concentration ($P = 0.56$), uric acid concentration ($P = 0.34$), and creatinine concentration ($P = 0.18$). In the resulting model, a higher prevalence of DR was associated with longer known duration of diabetes ($P = 0.02$), higher fasting

Table 1. Differences Between the Group of Diabetic Participants With Diabetic Retinopathy Compared With the Group of Diabetic Participants Without Diabetic Retinopathy in the Kailuan Diabetic Retinopathy Study

Parameters	Diabetic Retinopathy	No Diabetic Retinopathy	*P* Value
n (%)	546 (49.8)	550 (50.2)	
Age, y	60.8 ± 8.7	60.8 ± 10.1	0.98
Sex, men, *n* (%)	456 (83.5)	446 (81.1)	0.29
Known duration of diabetes, y	7.56	5.68	<0.001
<2 y (%)	79 (14.5)	91 (16.5)	
2–4 y (%)	107 (19.6)	185 (33.6)	
4–6 y (%)	76 (13.9)	84 (15.3)	
6–8 y (%)	48 (8.8)	49 (8.9)	
8–10 y (%)	88 (16.1)	67 (12.2)	
>10 y (%)	148 (27.1)	74 (13.5)	
Mean systolic blood pressure, mm Hg	138.3 ± 16.3	137.7 ± 15.5	0.56
Mean diastolic blood pressure, mm Hg	85.8 ± 8.8	85.4 ± 8.1	0.39
Mean fasting blood glucose, mM	8.7 ± 2.3	7.4 ± 1.5	<0.001
Mean heart rate, beats/min	75.9 ± 9.4	75.3 ± 10.1	0.31
Mean waist/hip ratio	0.90 ± 0.09	0.90 ± 0.10	0.51
Mean body mass index, kg/m^2	26.5 ± 3.3	26.5 ± 3.3	0.84
Mean high-density lipoprotein cholesterol concentration, mM	1.4 ± 0.3	1.4 ± 0.3	0.88
Mean low-density lipoprotein cholesterol concentration, mM	2.8 ± 0.7	2.8 ± 0.7	0.63
Mean triglyceride, mM	2.2 ± 1.9	2.1 ± 1.5	0.16
Mean total cholesterol concentration, mM	5.4 ± 1.0	5.4 ± 0.9	0.28
Mean uric acid concentration, μM	305 ± 76	323 ± 75	<0.001
Mean hypersensitive C-reactive protein concentration, mg/L	2.7 ± 2.9	3.4 ± 6.0	0.038
Mean total protein concentration, g/L	75.5 ± 4.0	75.7 ± 4.5	0.64
Mean albumin, g/L	46.1 ± 2.2	46.3 ± 2.1	0.15
Mean glutamate pyruvate transaminase, U/L	25.0 ± 13.1	26.2 ± 15.1	0.21
Mean total bilirubin, μM	15.5 ± 5.7	15.2 ± 4.3	0.42
Mean direct bilirubin, μM	4.8 ± 2.2	4.6 ± 1.3	0.17
Mean urea, mM	6.0 ± 1.4	5.9 ± 1.1	0.086
Mean urine pH	5.6 ± 0.4	5.6 ± 0.4	0.85
Mean red blood cell count, $10^{12}/L$	5.0 ± 0.4	5.1 ± 4.1	0.36
Mean white blood cell count, $10^9/L$	6.8 ± 1.5	6.7 ± 1.3	0.28
Mean blood platelet count, $10^9/L$	225 ± 51	224 ± 51	0.93
Mean hemoglobin, g/L	151 ± 12	152 ± 18	0.21
Mean neutrophil cell count, $10^9/L$	4.2 ± 1.8	4.1 ± 2.1	0.66
Central cornea thickness, μm	538 ± 31	538 ± 31	0.85
Anterior chamber depth, mm	2.6 ± 0.5	2.6 ± 0.4	0.78
Lens thickness, mm	4.6 ± 0.4	4.5 ± 0.4	0.007
Axial length, mm	23.3 ± 0.9	23.5 ± 0.9	<0.001
Subfoveal choroidal thickness, μm	368 ± 122	351 ± 122	0.03

blood glucose concentration ($P < 0.001$), and shorter axial length ($P = 0.007$) (Table 2). Adding the parameters of sex ($P = 0.13$), systolic blood pressure ($P = 0.73$), diastolic blood pressure ($P = 0.21$), alcohol consumption ($P = 0.96$), smoking ($P = 0.63$), and blood concentrations of triglycerides ($P = 0.70$), high-density lipoproteins ($P = 0.53$), low-density lipoproteins ($P = 0.60$), and cholesterol ($P = 0.70$), body mass index ($P = 0.34$), and level of education ($P = 0.66$) did not show significant associations with the prevalence of DR. The model revealed that for each millimeter increase in axial length, the prevalence of DR decreased by 19% (95%CI: 5, 30) (Table 2).

In univariate analysis, a more severe stage of DR was associated with longer diabetic duration ($P < 0.001$), higher fasting blood glucose ($P < 0.001$), higher heart rate ($P = 0.02$), lower serum uric acid concentration ($P = 0.001$), thicker lens ($P = 0.02$), and shorter axial length ($P = 0.002$) (Table 3). The multivariable regression analysis included the stage of DR as the dependent parameter and as independent parameters all those variables that were associated with the stage of DR in the univariate analysis with a *P* value of ≤0.10 (Table 3). We first dropped the parameter of lens thickness due to its collinearity with axial length. Due to a lack of statistical significance, we then dropped the parameters of serum uric acid concentration ($P = 0.97$), heart rate ($P = 0.75$), and serum albumin concentration ($P = 0.11$). In the final model, a more severe stage of DR was associated (regression coefficient *r*: 0.46) with

Table 2. Associations (Multivariable Logistic Regression Analysis) Between the Prevalence of Diabetic Retinopathy and Ocular and Systemic Parameters in the Kailuan Diabetic Retinopathy Study

Parameters	Odds Ratio	95% Confidence Interval for OR	*P* Value
Known duration of diabetes, y	1.13	1.02, 1.24	0.017
Mean fasting blood glucose, mM	1.38	1.26, 1.52	<0.001
Axial length, mm	0.81	0.70, 0.95	0.007

Table 3. Associations (Univariate Analysis) Between the Severity of Diabetic Retinopathy and Ocular and Systemic Parameters in the Kailuan Diabetic Retinopathy Study

Parameters	*P* Value	Standardized Regression Coefficient β	Nonstandardized Regression Coefficient B	95% Confidence Interval of B
Age, y	0.35	0.03	0.003	−0.003, 0.009
Sex, men	0.58	0.02	0.04	−0.10, −0.18
Known duration of diabetes, y	<0.001	0.20	0.10	0.07, 0.13
Mean systolic blood pressure, mm Hg	0.20	0.04	0.002	−0.001, 0.006
Mean diastolic blood pressure, mm Hg	0.88	−0.01	−0.001	−0.007, 0.006
Mean fasting blood glucose, mM	<0.001	0.45	0.20	0.17, 0.22
Mean heart rate, beats/min	0.02	0.08	0.007	0.001, 0.013
Mean waist/hip ratio	0.85	0.006	0.06	−0.53, 0.64
Mean body mass index, kg/m^2	0.97	−0.001	0.000	−0.018, 0.017
Mean high-density lipoprotein cholesterol concentration, mM	0.17	0.04	0.13	−0.05, 0.30
Mean low-density lipoprotein cholesterol concentration, mM	0.29	−0.03	−0.04	−0.12, 0.04
Mean triglyceride, mM	0.62	0.02	0.01	−0.02, 0.04
Mean total cholesterol concentration, mM	0.46	0.02	0.02	−0.04, 0.08
Mean uric acid concentration, μM	0.001	−0.11	−0.001	−0.002, −0.001
Mean hypersensitive C-reactive protein concentration, mg/L	0.13	−0.05	−0.009	−0.021, 0.003
Mean total protein concentration, g/L	0.62	−0.02	−0.01	−0.02, 0.01
Mean albumin, g/L	0.07	−0.08	−0.04	−0.07, 0.002
Mean glutamate pyruvate transaminase, U/L	0.33	−0.03	−0.002	−0.006, 0.002
Mean total bilirubin, μM	0.35	0.03	0.01	−0.01, 0.02
Mean direct bilirubin, μM	0.50	0.03	0.02	−0.03, 0.06
Mean urea, mM	0.15	0.05	0.03	−0.01, 0.08
Mean urine pH	0.23	−0.04	−0.09	−0.23, 0.06
Mean red blood cell count, $10^{12}/L$	0.46	−0.02	−0.01	−0.03, 0.01
Mean white blood cell count, $10^9/L$	0.50	0.02	0.01	−0.03, 0.06
Mean blood platelet count, $10^9/L$	0.82	0.01	0.000	−0.001, 0.001
Mean hemoglobin, g/L	0.27	−0.04	−0.002	−0.006, 0.002
Mean neutrophil cell count, $10^9/L$	0.70	0.01	0.01	−0.02, 0.04
Central cornea thickness, μm	0.71	−0.01	0.000	−0.002, 0.002
Anterior chamber depth, mm	0.18	0.04	0.09	−0.04, 0.22
Lens thickness, mm	0.02	0.08	0.19	0.03, 0.34
Axial length, mm	0.002	−0.10	−0.10	−0.16, −0.04
Subfoveal choroidal thickness, μm	0.74	0.01	0.00008	0.000, 0.001

higher fasting blood glucose ($P < 0.001$), shorter axial length ($P = 0.047$), and longer known duration of diabetes ($P = 0.045$) (Table 4). Adding the parameters of sex ($P = 0.69$), systolic blood pressure ($P = 0.99$), diastolic blood pressure ($P = 0.95$), alcohol consumption ($P = 0.18$), smoking ($P = 0.38$), and blood concentrations of triglycerides ($P = 0.50$), low-density lipoproteins ($P = 0.28$), and cholesterol ($P = 0.85$), body mass index ($P = 0.320$), and level of education ($P = 0.37$) did not show significant associations with the stage of DR.

In univariate analysis, study participants with longer axial length as compared to study participants with shorter axial length had a significantly lower incidence of DR ($P = 0.001$), lower rate of progression of DR ($P = 0.03$), younger age ($P = 0.001$), higher preponderance of male sex ($P = 0.001$), lower serum concentration of high-density lipoprotein cholesterol ($P = 0.011$), higher serum concentration of uric acid ($P < 0.001$) and hemoglobin ($P = 0.009$), and a thinner subfoveal choroidal thickness ($P < 0.001$) (Table 5).

In multivariable linear regression analysis, longer axial length was associated with a lower prevalence of DR after adjusting for younger age ($P < 0.001$), male sex ($P < 0.001$), higher body mass index ($P = 0.016$), and lower fasting blood glucose concentration ($P = 0.036$) (Table 6). The association between axial length and prevalence of DR remained significant ($P < 0.001$; β: −0.12; B: −0.22; 95%CI: −0.34, −0.11) when the parameter of fasting blood glucose concentration was dropped from the model or when the parameter of known duration of diabetes ($P = 0.52$) was added to the model. Applying the model showed that for each millimeter increase in axial length, the prevalence of DR decreased by 19% (95%CI: 5, 30).

There were no marked differences in the results of the regression analyses if, instead of the mean values of the last five examinations, the last measurement values of the parameters were taken for the statistical analysis.

Discussion

In our study on patients with diabetes type II, a higher prevalence of DR was associated with shorter ocular axial length ($P = 0.007$) after adjusting for the systemic parameters of longer known duration of diabetes and higher fasting blood glucose concentration. For each millimeter increase in axial length, the prevalence of DR decreased by 19% (95%CI: 5, 30). Correspondingly, a more severe stage of DR was associated with shorter ocular axial length after adjusting for higher fasting blood glucose and longer known duration of diabetes. As a corollary, longer axial length was associated with a lower prevalence of DR ($P = 0.003$; β: −0.10) after adjusting for younger age, male sex, higher body mass index, and lower fasting blood glucose concentration.

An association between ocular axial length and prevalence of DR has long been debated. Since the 1960s, myopia has been put forward as a potential protective factor against DR.[7]

Table 4. Associations (Multivariable Regression) Between the Severity of Diabetic Retinopathy and Ocular and Systemic Parameters in the Kailuan Diabetic Retinopathy Study

Parameters	*P* Value	Standardized Regression Coefficient β	Nonstandardized Regression Coefficient B	95% Confidence Interval of B	Variance Inflation Factor
Axial length, mm	0.047	−0.06	−0.06	−0.11, −0.001	1.01
Duration of diabetes, y	0.045	0.07	0.04	0.001, 0.07	1.38
Fasting blood glucose concentration, mM	<0.001	0.41	0.18	0.15, 0.21	1.38

Table 5. Differences Between the Subgroup of Hyperopic Eyes, Emmetropic Eyes, and Myopic Eyes in the Kailuan Diabetic Retinopathy Study

Parameters	Hyperopic Eyes, Axial Length ≤ 22 mm	Emmetropic Eyes, 22 mm < Axial Length < 24 mm	Myopic Eyes, Axial Length ≥ 24 mm	*P* Value
n (%)	44 (4.6)	706 (74.6)	197 (20.8)	
Age, y	60.3 ± 6.3	61.5 ± 8.8	58.3 ± 11.2	<0.001
Sex, men, *n* (%)	26 (59.1)	583 (82.6)	174 (88.3)	<0.001
Known duration of diabetes, *n* (%)				
<2 y	4 (9.1)	36 (5.1)	16 (8.1)	0.55
2–4 y	7 (15.9)	215 (30.5)	57 (28.9)	
4–6 y	8 (18.2)	112 (15.9)	32 (16.2)	
6–8 y	5 (11.4)	66 (9.3)	23 (11.7)	
8–10 y	7 (15.9)	114 (16.1)	28 (14.2)	
>10 y	13 (29.5)	163 (23.1)	41 (20.8)	
Diabetic retinopathy, *n* (%)	28 (63.6)	351 (49.7)	84 (42.6)	0.029
Diabetic retinopathy severity, *n* (%)				
Level 1	14 (31.8)	237 (33.6)	52 (26.4)	0.021
Level 2	13 (29.5)	84 (11.9)	27 (13.7)	
Level 3	0	11 (1.6)	1 (0.5)	
Level 4	1 (2.3)	19 (2.7)	4 (2.0)	
Mean systolic blood pressure, mm Hg	138.0 ± 15.1	138.3 ± 16.0	137.3 ± 16.1	0.76
Mean diastolic blood pressure, mm Hg	84.8 ± 7.0	85.5 ± 8.6	86.2 ± 8.1	0.49
Mean fasting blood glucose, mM	8.6 ± 2.3	8.1 ± 2.0	7.9 ± 1.9	0.14
Mean heart rate, beats/min	74.3 ± 8.8	75.8 ± 9.9	75.2 ± 9.6	0.51
Mean waist/hip ratio	0.90 ± 0.04	0.90 ± 0.07	0.90 ± 0.10	0.85
Mean body mass index, kg/m^2	25.8 ± 2.8	26.5 ± 3.4	26.8 ± 3.1	0.18
Mean high-density lipoprotein cholesterol concentration, mM	1.5 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	0.037
Mean low-density lipoprotein cholesterol concentration, mM	2.8 ± 0.9	2.8 ± 0.7	2.8 ± 0.8	0.96
Mean triglyceride, mM	1.8 ± 1.0	2.1 ± 1.6	2.1 ± 1.5	0.31
Mean total cholesterol concentration, mM	5.3 ± 1.1	5.4 ± 0.9	5.4 ± 1.0	0.63
Mean uric acid concentration, μM	283 ± 68	313 ± 74	328 ± 78	0.001
Mean hypersensitive C-reactive protein concentration, mg/L	2.4 ± 2.7	3.0 ± 5.1	3.3 ± 3.5	0.45
Mean total protein concentration, g/L	75.2 ± 4.3	75.7 ± 4.2	75.5 ± 3.9	0.80
Mean albumin, g/L	46.0 ± 1.6	46.1 ± 2.1	46.4 ± 2.1	0.55
Mean glutamate pyruvate transaminase, U/L	26.0 ± 11.9	25.1 ± 14.2	26.9 ± 13.7	0.26
Mean total bilirubin, μM	14.7 ± 5.0	15.4 ± 4.9	15.3 ± 5.1	0.61
Mean direct bilirubin, μM	3.9 ± 0.8	4.8 ± 1.8	4.6 ± 1.6	0.08
Mean urea, mM	5.8 ± 1.0	5.9 ± 1.2	5.9 ± 1.4	0.79
Mean urine pH	5.5 ± 0.3	5.6 ± 0.4	5.6 ± 0.4	0.95
Mean red blood cell count, $10^{12}/L$	4.8 ± 0.4	5.1 ± 3.4	5.0 ± 0.4	0.88
Mean white blood cell count, $10^9/L$	6.6 ± 1.3	6.7 ± 1.4	6.8 ± 1.3	0.28
Mean blood platelet count, $10^9/L$	230 ± 51	224 ± 51	226 ± 51	0.66
Mean hemoglobin, g/L	148 ± 11	151 ± 16	154 ± 12	0.03
Mean neutrophil cell count, $10^9/L$	4.2 ± 1.7	4.1 ± 1.4	4.4 ± 2.6	0.08
Central cornea thickness, μm	538 ± 35	537 ± 30	542 ± 31	0.13
Anterior chamber depth, mm	2.2 ± 0.5	2.6 ± 0.4	2.9 ± 0.4	<0.001
Lens thickness, mm	4.8 ± 0.4	4.6 ± 0.4	4.4 ± 0.4	<0.001
Axial length, mm	21.7 ± 0.3	23.1 ± 0.5	24.7 ± 0.7	<0.001
Subfoveal choroidal thickness, μm	394 ± 119	370 ± 125	317 ± 115	<0.001

Table 6. Associations (Multivariable Linear Regression) Between Ocular Axial Length, Prevalence of Diabetic Retinopathy and Other Systemic Parameters in the Kailuan Diabetic Retinopathy Study

Parameters	*P* Value	Standardized Regression Coefficient β	Nonstandardized Regression Coefficient B	95% Confidence Interval of B	Variance Inflation Factor
Prevalence of diabetic retinopathy	0.003	−0.10	−0.18	−0.30, −0.06	1.12
Fasting blood glucose concentration, mM	0.036	−0.07	−0.03	−0.06, −0.002	1.13
Age, y	<0.001	−0.17	−0.02	−0.02, −0.01	1.01
Sex, men/women	<0.001	−0.17	−0.42	−0.57, −0.27	1.01
Body mass index, kg/m^2	0.016	0.08	0.02	0.004, 0.04	1.02

The association between myopia and a decreased risk of DR has, however, been inconsistent in those studies, and the sample sizes of the diabetic study populations were usually relatively small.[8–14] In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, myopia was not associated with the incidence or progression of DR in univariate analyses, but showed a protective effect against progression to proliferative DR in persons with younger-onset diabetes in multivariable models.[10] In contrast, in the Singapore Malay Eye Study, Lim and colleagues[12] found that eyes with myopia were less likely to have any DR. Our study is so far the investigation with the largest diabetic study population with axial length measurements available, and in which shorter axial length was a main factor associated with a higher prevalence of DR.

The association between shorter axial length and higher prevalence of DR is paralleled by findings obtained in recent population-based studies in which shorter axial length was a major risk factor for the development and prevalence of age-related macular degeneration.[19–23] The etiology of both diseases, DR and age-related macular degeneration, includes vascular endothelial growth factor (VEGF) as the major growth factor involved the pathogenesis.

The mechanism underlying the protective effect of a longer axial length or of axial myopia against DR has remained elusive so far. Interestingly, studies on eyes without macular or retinal diseases revealed that the intraocular concentration of VEGF decreased significantly with increasing axial length, and as a corollary, with increasing myopic refractive error.[24–26] Since axial length is related to ocular volume and assuming that hyperopic eyes and myopic eyes do not differ markedly in the physiological production rate of VEGF, one may infer that the lower intraocular concentrations of VEGF in the axially elongated myopic eyes were due to a more marked dilution of VEGF in the myopic eyes. Since VEGF plays an important role in the pathogenesis of intraocular neovascular and edematous diseases such as exudative age-related macular degeneration and DR, one may assume that the physiologically lower intraocular concentration of VEGF in myopic eyes versus hyperopic eyes may be one of the reasons for the lower prevalence of DR (and of age-related macular degeneration) in myopic eyes.[27] Other reasons, besides a larger intraocular volume leading to dilution, for the lower VEGF concentration in axially long eyes may be differences in the consistency of the vitreous body, which is less viscous in axially elongated eyes. A higher fluidity of the vitreous may be associated with a faster turnover of VEGF out of the eye. An additional factor may be the posterior vitreous detachment (PVD), whose prevalence is associated with longer axial length[28,29] and which might be a protective factor for DR. Previous studies demonstrated that in patients with DR an attached vitreous portends a worse prognosis than PVD, probably related to mechanical effects as well as higher intraocular VEGF levels in eyes without PVD,[30,31] and that the risk of proliferative DR is less in eyes with PVD than in eyes with an attached posterior vitreous.[32]

Other findings obtained in our study are in agreement with observations made in previous investigations. As in previous investigations, a higher prevalence and stage of DR in our study population were associated with a longer known duration of diabetes and higher fasting blood glucose concentration.[1,2–6] Interestingly, there was not a major difference in our study if the mean of the previous five examinations of blood glucose measurements obtained in the last 10 years, or the value measured at the last examination, was taken for the statistical analysis. The subfoveal choroidal thickness was not related with the prevalence and stage of DR in our study population, confirming a finding obtained in the population-based Beijing Eye Study.[33]

The association between a lower prevalence and stage of DR and longer axial length or more marked axial myopia is of public health importance, since the prevalence of myopia has markedly increased in the young generations in last two decades worldwide and in particular in East Asia, and it is forecast to increase further.[34] Taking into account the aging of the young myopic generations of today within the next three decades to an age at which DR develops, a relative decrease in the prevalence and severity of DR in the future may be indicated if other risk factors for DR remain stable.

Potential limitations of our study should be discussed. First, the recruitment of the study participants was not population–based, so that a selection artifact might have occurred. It is, however, unlikely that such a selection artifact might have influenced the relationship between axial length and DR within the group of patients with diabetes. Second, this was a cross-sectional investigation, which does not allow conclusions on the associations of risk factors. Third, we used two-field photographs instead of seven-field fundus photographs to identify DR lesions, so that some microaneurysms and peripheral neovascularizations might have remained undetected. This potential limitation, however, may be valid for the hyperopic group with short ocular axial length as for the myopic group with longer axial length.

In conclusion, the prevalence and severity of DR were associated with the ocular factor of shorter axial length after adjusting for systemic risk factors such as known duration of diabetes and fasting glucose blood concentration. For each millimeter increase in axial length, the prevalence of DR decreased by 19% (95%CI: 5, 30). Longer ocular axial lens or axial myopia was protective against presence and severity of DR in patients with diabetes. The marked increase in prevalence and incidence of myopia worldwide may relatively decrease the prevalence and incidence of DR.

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