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Optic disc morphology and peripapillary atrophic changes in diabetic children and adults without diabetic retinopathy or visual impairment

Qiurong Lin,[1,2,†] Yan Jia,[3,†] Tao Li,[1,2] Shanshan Wang,[1,2] Xian Xu,[1,2] Yi Xu,[2] Lina Lu,[2] Chenhao Yang[3] and Haidong Zou[1,2]

[1]Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, National Clinical Research Center for Eye Diseases, Shanghai Key laboratory of Ocular Fundus Diseases, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[2]Shanghai Eye Diseases Prevention & Treatment Center, Shanghai Eye Hospital, Shanghai, China
[3]Department of Ophthalmology, Children's Hospital of Fudan University, Shanghai, China

ABSTRACT.

Purpose: **To investigate the changes in optic disc morphology and peripapillary atrophy (PPA) in diabetic children and adults without diabetic retinopathy (DR) or visual impairment (VI).**

Methods: **This cross-sectional study included two groups of subjects. One group included 91 children with type 1 diabetes mellitus (T1DM) and 86 healthy children, and the other group included 444 adults with T2DM and 442 healthy controls. The optic disc parameters including major and minor axis lengths, optic disc ovality (ODO), optic disc tilt, optic disc area and β-PPA area were analysed in all subjects. Optic disc rotation and the Bergmeister papilla were analysed only in children. Patients with diabetes and healthy controls were compared in each group of the study population.**

Results: **In both groups, patients with diabetes and healthy controls were matched for age, sex and axial length (AL). Among the children, β-PPA area was significantly smaller in those with diabetes (0.29 ± 0.43 mm^2) than in the healthy controls (0.46 ± 0.58 mm^2, $p < 0.05$). Multiple linear regression analysis showed that diagnosis of DM was negatively associated with β-PPA area. Longer AL and higher body mass index (BMI) were positively associated with β-PPA area. Among adults, ODO was significantly larger in those with diabetes (1.14 ± 0.09) than in healthy controls (1.12 ± 0.06, $p < 0.05$). Multiple linear regression analysis showed that the BMI and DM were potential risk factors affecting ODO.**

Conclusion: **Hyperglycaemia had different effects on the optic disc in children and adults. Unlike in healthy controls, hyperglycaemia had an impact on the peripapillary tissue in children and on optic disc shape in adults before DR and VI development.**

Key words: adults – children – diabetes mellitus – optic disc – peripapillary atrophy

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Introduction

The number of patients with diabetes is increasing worldwide. The latest global estimate from the International Diabetes Federation (http://www.diabetesatlas.org. accessed August 20, 2019) shows that over 1.1 million children and adolescents below 20 years of age have type 1 diabetes mellitus (T1DM), 463 million adults aged 20–79 years (one in 11) have diabetes, and by 2045, there will be 629 million people with DM. Diabetes is a chronic disease that can cause complications in multiple organs, such as the heart, kidney, or nervous system, leading to individual dysfunction or even death. Ocular complications caused by diabetes can lead to different degrees of visual impairment (VI), and even blindness. Diabetic retinopathy (DR) is one of the major complications of diabetes. At present, DR is believed to be a kind of vascular neuropathy. In the early stage of DR, the retinal nerve fibre layer and retinal ganglion cells are damaged (Chhablani et al. 2015; Pekel et al. 2018; Vujosevic et al. 2018).

However, few studies have investigated the changes in the optic disc caused by early diabetes. A search of the PubMed database yielded only one population-based epidemiological study that analysed peripapillary atrophy (PPA) in adults with diabetes. In that epidemiological study conducted

in Beijing, Xu et al. (2009) found no statistical difference in optic disc area (ODA) and PPA between 381 patients with diabetes (mean age: 64.9 ± 9.4 years) and 2579 residents without diabetes (mean age: 59.7 ± 10.0 years). However, that study did not exclude patients with moderate or severe DR who might have serious accompanying optic nerve injury. In addition, data on axial length (AL) were not mentioned, and hence, the effect of stretching on the optic disc and peripapillary tissue could not be ruled out.

Human optic disc morphology (ODM) and peripapillary structure (PPS) parameters, such as optic disc tilt (ODT), optic disc rotation (ODR), ODA, PPA and the Bergmeister papilla (BP), could be used as reference indices to evaluate the growth of the eyeball and as morphological indicators to identify the occurrence and development of various fundus diseases. For instance, characteristic ODT and ODR could occur in high myopia (Tong et al. 2004; Park et al. 2013). The BP is a characteristic of incomplete regression of the hyaloid artery after birth, which can be absorbed and disappear gradually during childhood development (Bedell & Jokl 1954). Peripapillary atrophy (PPA) is closely associated with pathological myopia (Jonas et al. 2018). Eyes with high myopia and long ALs might show larger and more elongated optic discs than might emmetropic eyes, and this might be caused by stretching deformation of the eyeball (Hoffmann et al. 2007).

In order to understand whether hyperglycaemia caused changes in ODM and PPS, we conducted a series of studies on various ODM and PPS parameters in children and adults with diabetes who had not yet developed DR or VI. Meanwhile, healthy children or adults with similar ALs were selected as the control groups for comparative analysis to eliminate the mixed effects of AL on the optic disc.

Methods

This study was carried out in accordance with the tenets of Declaration of the Helsinki. It was a part of the Shanghai Children and Adolescent DM Eye study (SCADE) and the Shanghai Cohort Study of Diabetic Eye Disease study (SCODE). The included children with diabetes were from a cross-sectional population-based study based on the SCADE (clinicaltrials.gov identifier: NCT0366 6052). The study was approved by the Ethics Committee of Shanghai First People's Hospital (approval number: 2018KY209) and the Children's Hospital affiliated with Fudan University in Shanghai (approval number: 01[2018]). The children with diabetes were recruited from Shanghai Children's Hospital from January 2018 through January 2019, and the healthy children were simultaneously recruited from an ophthalmic clinic. A signed informed consent was obtained from the legal guardian of each child or both the legal guardian and the child over 6 years old at the examination site. The included adults with diabetes were from the SCODE (clinicaltrials.gov identifier: NCT03665090). The study was approved by the Ethics Committee of Shanghai First People's Hospital (approval number: 2013KY023). The adult control group included the elderly who participated in the eye disease screening conducted in Baoshan District of Shanghai in 2017. Each subject provided written informed consent.

The inclusion criteria for all subjects were as follows: (1) patients with diabetes already diagnosed with DM using the WHO diagnostic criteria (Wang et al. 2019) at the Department of Endocrinology; (2) best-corrected visual acuity (BCVA) ≥0.8, no matter myopia or hyperopia; and (3) intraocular pressure (IOP) in both eyes within 10–21 mmHg. The exclusion criteria were as follows: (1) presence of other eye diseases, such as glaucoma, DR, optic neuropathy, or hereditary eye diseases; (2) history of ophthalmic surgery, including lens surgery; (3) serious systemic diseases, such as diabetic nephropathy or diabetic cardiocerebrovascular disease; (4) inability to cooperate with the examination; and (5) poor eye fundus image quality unsuitable for further measurement. After the binocular parameters met the above criteria, random eye data were selected for analysis in this study.

The subjects' personal information was collected using a detailed questionnaire that included questions about age, sex, date of birth, general medical history, duration of DM, eye disease history and history of eye surgery. The subjects' height and weight were measured by the general practitioners. The haemoglobin A1c (HbA1c) levels were collected according to the medical records. The following ocular examinations were performed: (1) slit-lamp (SL130, Zeiss, Jena, Germany) examination of the orbit, conjunctiva, cornea, anterior chamber, iris, pupil and lens was conducted, and a +90 D non-contact lens (Volk, Mentor, OH, USA) examination of the vitreous, retina, and optic nerve was performed after pupil dilation; (2) BCVA and refractive power were measured using an automatic computerized optometry machine (ARK-1; NIDEK, Tokyo, Japan) and a Snellen chart after complete pupil dilation; (3) AL was measured using IOL master 700 (Carl Zeiss Meditec, Inc, Jena, Germany); (4) IOP was measured using a non-contact tonometer (NT510; NIDEK); and (5) swept-source OCT (ss-OCT; DRI OCT-1; Topcon, Tokyo, Japan) was performed using 12 radial meridian scans with a diameter of 6 mm focused on the optic disc, and the optic disc-centred fundus photograph was obtained using the fundus photography function of the ss-OCT machine (Fig. 1A).

The BP was observed using ss-OCT focused on the optic disc. The ODA, β-PPA area, and major axis (MA) and minor axis (MI) of the optic disc were measured using the built-in measuring tool in the fundus photography function of the ss-OCT machine. In addition, each full-size colour image of the fundus exported from the ss-OCT machine was imported to IMAGEJ (U.S. National Institutes of Health, Bethesda, MD, USA) for the analysis of ODR in the children. The above measurements were performed by two independent and experienced ophthalmologists and were repeated twice. The average value was taken as the final measurement value. Considering the size of the two-dimensional fundus photograph was affected by AL, Littmann's formula was used to correct the data of the MA, MI, ODA and β-PPA area (Bennett et al. 1994).

Optic disc morphology (ODM) was assessed using optic disc ovality (ODO), the ratio of the MA and MI. Optic disc deviation angle was defined as the deviation of the MA from the reference line, vertical to a horizontal line passing through the fovea and the centre of the optic disc (Fig. 1B). The optic disc was classified as tilted if ODO was >1.3. Optic disc rotation

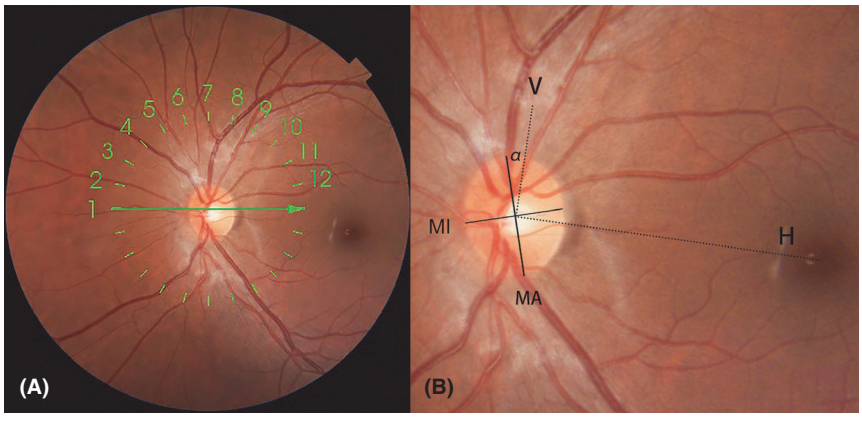

Fig. 1. Fundus photographs centred on the optic disc. (A) The fundus photograph was performed using 12 radial meridian scans with a diameter of 6 mm focused on the optic disc. (B) Solid lines are the major axis (MA) and minor axis (MI) of the optic disc. Optic disc ovality is defined as the ratio of MA to MI. H line refers to the line passing through the fovea and the centre of the optic disc. V line is vertical to H line. The angle between MA line and V line is defined as optic disc deviation angle.

(ODR) was defined as a >15° deviation in the MA from the reference line (Lee et al. 2017). β-peripapillary atrophy (β-PPA) was defined as the area in a fundus photograph characterized by a marked atrophy of the retinal photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris, along with the distinct visibility of large choroidal vessels in the sclera (Sun et al. 2018). β-peripapillary atrophy (β-PPA) area was measured from the RPE termination to the visual disc margin. The boundaries of the optic disc β-PPA were determined using OCT images of the optic disc by experienced ophthalmologists. The BP was the remnant of the hyaloid artery on the surface of the optic disc from the embryonic period, and it presented as a dense papillary/columnar protrusion with or without sparse connective tissue on the OCT scan, as shown in Fig. 2.

Statistical analysis

The body mass index (BMI) was calculated as the patients' weight (kg) divided by the square of their height (kg/m^2). Spherical equivalent refractive

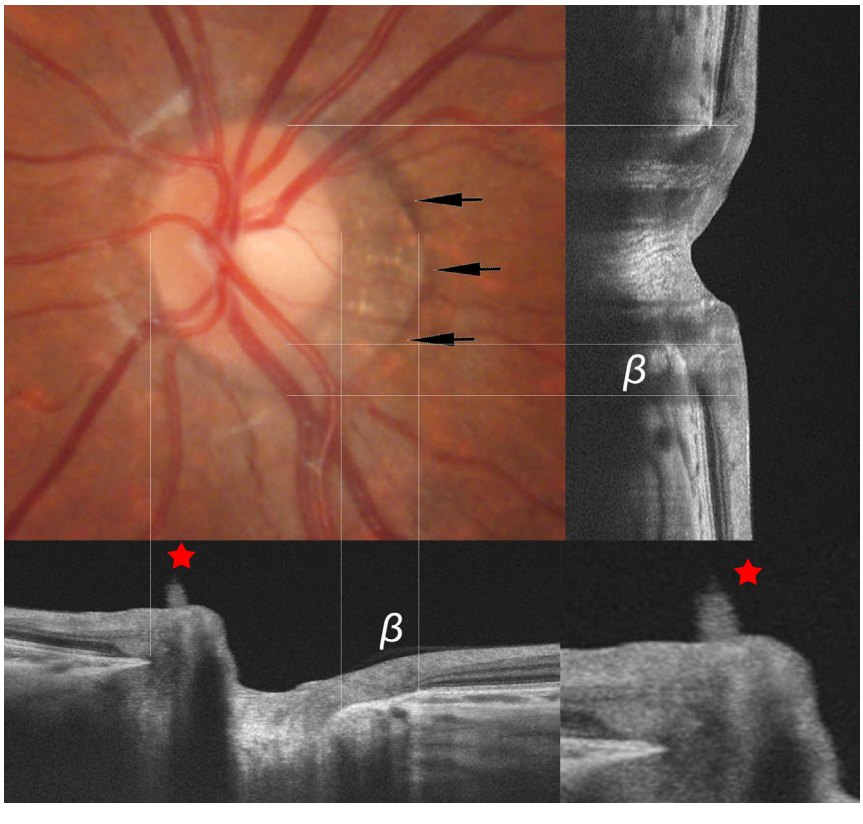

Fig. 2. A fundus photograph centred on the optic disc and its corresponding horizontal and vertical scanning swept-source OCT (ss-OCT) images. The arrows on the fundus photograph point to the boundary of the β-peripapillary atrophy (PPA). The ss-OCT region corresponding to β-PPA in the fundus photograph shows obvious retinal pigment epithelium defection. Red pentagon marks the location of Bergmeister papilla.

error (SE) was calculated as the spherical refractive error +1/2 cylindrical refractive error. Statistical analyses were conducted using IBM SPSS Statistics for Windows/Macintosh, Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean ± standard deviation, and categorical data were presented as frequency and percentage (%). For continuous data, Student's *t*-test was used for parametric data, while the Mann–Whitney *U* test was used for non-parametric data to compare groups. Categorical variables were analysed using the Chi-squared test. The optic disc indicators with significant differences between two groups found in the univariate analysis were used as dependent variables, and the stepwise linear regression analysis was used to analyse the independent risk factors. A p value <0.05 was considered significant.

Results

Findings in the children with diabetes

This study included 91 children with diabetes and 86 healthy children. Among them, 73 (41.24%) were male, and 104 (58.76%) were female. Their average age was 11.13 ± 2.67 years (range: 5–18 years); average height was 146.94 ± 15.90 cm (range: 109.50–183 cm); average body weight was 40.82 ± 13.23 kg (range: 18–79 kg); average BMI was 18.37 ± 3.04 kg/m^2 (range: 13.52–35.11 kg/m^2); average AL was 23.87 ± 1.12 mm (range: 21.25–27.99 mm); and average SE was −1.51 ± 2.53 D (range: −10.75 to +3.0 D). All children with diabetes were diagnosed with T1DM, and all of them were treated with insulin injection. The average duration of diabetes was 4.04 ± 2.95 years, and the average HbA1c was (7.75 ± 2.31)%. The children with diabetes and the healthy controls were matched for sex, age, height, weight, BMI, SE and AL ($p > 0.05$). Significant differences were observed in β-PPA area between the two groups ($p < 0.05$, Fig. 3). However, no significant differences were observed in ODA, MA, MI, ODO, ODT, ODR and BP between the two groups ($p > 0.05$; Table 1).

Multiple forward stepwise linear regression analysis was carried out with PPA as the dependent variable, and diagnosis of DM, duration of diabetes, HbA1c level, height, weight, BMI, sex, age and AL as the independent variables. The results showed that diagnosis of DM was negatively associated with β-PPA area. Longer AL and higher BMI were positively associated with β-PPA area. (Table 2).

Findings in the adults with diabetes

This study included 444 patients with diabetes and 442 healthy adults. All adults with diabetes were diagnosed with T2DM. Of the 886 subjects, 391 were male (44.13%), and 495 were female (55.87%). Their mean age was 63.21 ± 5.66 years (range: 44–85 years); average height was 162.85 ± 7.89 cm (range: 142–188 cm); average body weight was 66.03 ± 10.48 kg (range: 37.7–104 kg); mean BMI was 24.86 ± 3.31 kg/m^2 (range: 15.43–40.37 kg/m^2); average AL was 23.18 ± 0.81 mm (range: 20.63–26.8 mm); and mean SE was 0.59 ± 1.32 D (range: −6.875 to +5.25 D). All adults with diabetes were diagnosed with T2DM, the average duration of diabetes was 6.41 ± 4.86 years, and the average HbA1c levels were (6.85 ± 1.15)%. According to the questionnaire in adults with diabetes, a total of 318 (71.6%) patients received medication, of which 299 were treated with oral hypoglycaemic drugs (44 with more than two oral drugs) and 19 with insulin injections. 126 (28.4%) used the diet control without oral drugs or insulin treatment.

The height, weight, BMI and SE of the adults with diabetes were significantly different from those of the healthy controls ($p < 0.05$). However, no significant differences were observed in sex, age and AL between the two groups ($p > 0.05$). Among the optic disc parameters, MA and ODO were significantly higher in the adults with diabetes than in the healthy controls ($p < 0.05$, Fig. 4). However, no significant differences were observed in the short AL, ODT and PPA between the two groups ($p > 0.05$; Table 3).

Multiple forward stepwise linear regression analysis was carried out with ODO as the dependent variable, and diagnosis of DM, sex, age, height, weight, BMI, AL, SE, HbA1c level, duration of DM and treatment or not as the independent variables. Optic disc ovality (ODO) was positively correlated with the BMI and diagnosis of DM. The ODO was larger in adults with diabetes than in the healthy controls, and for each unit of increase in the BMI, the ODO increased by 0.002 (Table 4).

Discussion

To our knowledge, this is the first study focusing on the early changes in ODM and PPS in children and adults with diabetes who have not yet developed DR or VI, and could more accurately reflect the effect of hyperglycaemia on ODM and PPS. This study is also the first to show that hyperglycaemia has different effects on ODM and PPS in adults and children. In children with diabetes, PPS was affected and β-PPA was less common and significantly smaller than that in healthy children, but no difference was observed in ODM. In adults with diabetes, ODM was affected and ODO was significantly higher than that in adults without diabetes, but no difference was observed in β-PPA.

β-peripapillary atrophy (β-PPA) was characterized by marked atrophy of the RPE and choroidal capillaries (Sun et al. 2018). Previous studies had found an obvious correlation between β-PPA and AL (Lee et al. 2018), and a similar result was obtained in this study. However, after the AL of diabetic children was matched with that of control children, we found that hyperglycaemia was an independent risk factor for β-PPA in children with diabetes, and this resulted in a decrease in β-PPA. Since the outer retinal layers are largely dependent on the choroid for their nutrition and oxygenation, we speculated that this effect is caused by choroidal vascular injury. A previous autopsy study showed that the percentage of choroid with focal choroidal capillary degeneration in patients with diabetes was more than four times higher than that in patients without diabetes (Cao et al. 1998). Previous studies also showed that an increase in β-PPA was significantly associated with a decrease in choroidal thickness (CT) (Sullivan-Mee et al. 2015). In addition, we had found that the parapapillary CT in children with diabetes without DR or VI was larger than that in healthy control children (Li et al. 2020).

In this study, we also found that the BMI was independent risk factor for the size of β-PPA, which had not been

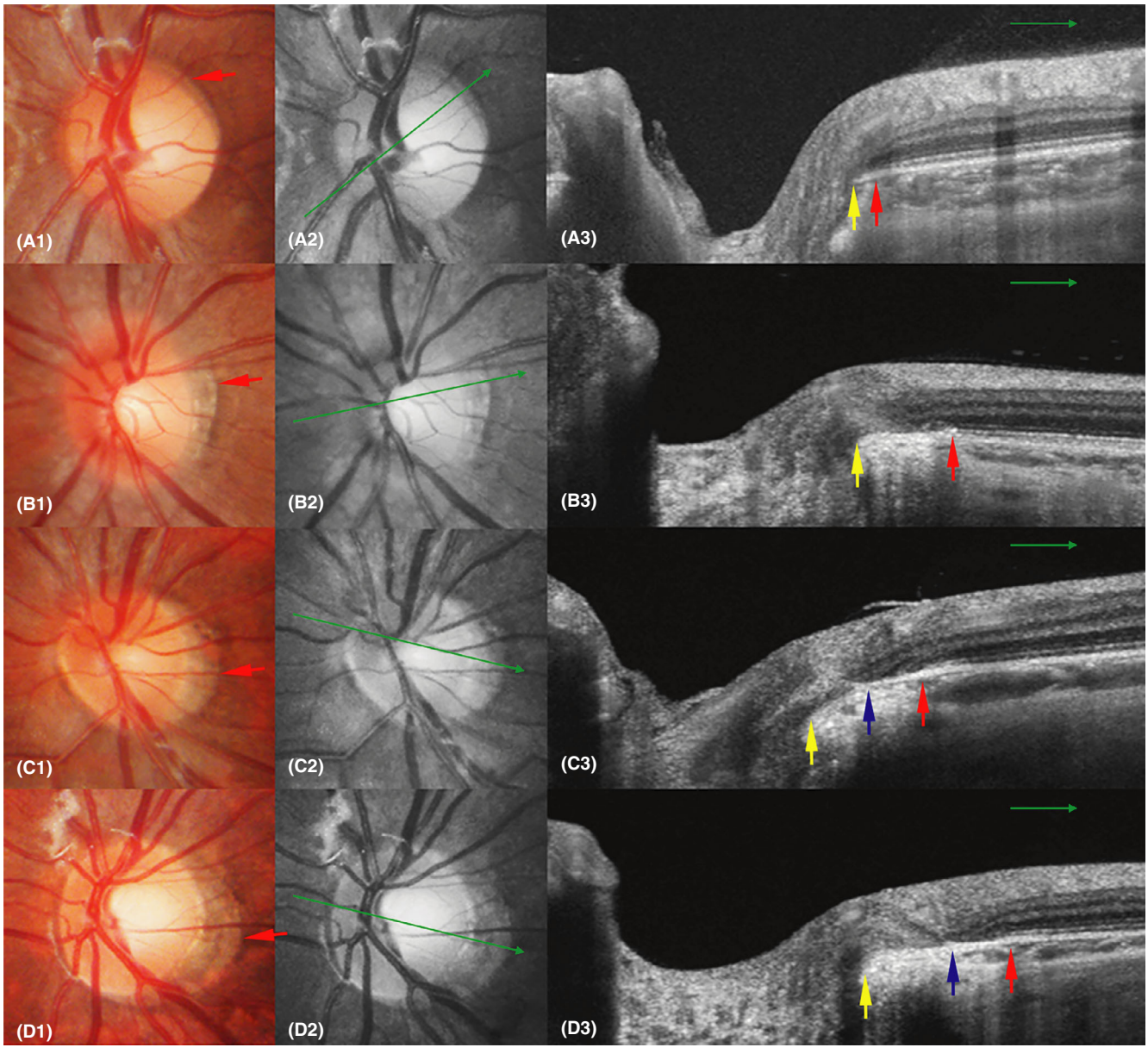

Fig. 3. Sample cases showing smaller peripapillary atrophy area in children with diabetes than in healthy children. (A, C) Fundus photographs of children with diabetes. (B, D) Fundus photographs of healthy controls. (A1, B1, C1, D1) Fundus photographs. (A2, B2, C2, D2) Infrared fundus images. (A3, B3, C3, D3) B-scan ss-OCT images. Green line with arrows represents the position of the radial B-scan. Red arrows and yellow arrows point to the retinal pigment epithelial termination (RPET) and optic disc border (ODB). Blue arrows point to the Bruch's membrane (BM) termination. (A) A 10-year-old girl diagnosed with diabetes for 3.5 years, axial length (AL) as 23.31 mm, body mass index (BMI) as 19.1 kg/m^2 and PPA area as 0.13mm^2. (B) A 10-year-old healthy girl, AL as 23.31 mm, BMI as 19.50 kg/m^2 and PPA area as 0.38 mm^2. (C) A 18-year-old boy diagnosed with diabetes for 3 years, AL as 27.99 mm, BMI as 20.22 kg/m^2 and PPA area as 0.66 mm^2. (D) A 13-year-old healthy boy, an AL as 27.37 mm, BMI as 19.53 kg/m^2 and PPA area as 1.57 mm^2.

previously reported. Some studies have reported that high-cholesterol diet can destroy the structure of RPE cells and Bruch membrane in mouse models of human atherosclerosis (Miceli et al. 2000; Ong et al. 2001). As RPE cells are key regulators of lipid metabolism in the retina, accumulation of large amounts of lipids in and around RPE cells might damage RPE cells (Fliesler & Bretillon 2010). Miceli et al. (2000) found that in mice fed a high-fat diet, the RPE atrophied, the number and size of autophagocytic and empty cytoplasmic vacuoles of RPE cells increased, and lipid-like droplets accumulated in the cytoplasm. Bruch's membrane was thickened, the elastic lamina was broken, and electron-dense particulate and vesicular structures accumulated within the inner and outer collagenous zones. This might be the reason for the increase in β-PPA area caused by the larger BMI.

In previous studies, ODO was different in different age groups, but decreased with age. The average ODO in newborns was 1.28 (Kim et al. 2019). Guo et al. (2018) showed that ODO in Chinese children was 1.18 (average age: 11.4 6 ± 0.5; range: 10–13). This was consistent with the data of healthy children in this study. A population-

Table 1. Demographic and optic disc parameters of the children enrolled in this study.

Variable	Children with diabetes	Healthy children	Statistics	p
Male	40 (44.0%)	33 (38.4%)	0.569	0.451*
Female	51 (56.0%)	53 (61.6%)		
Age (years)	11.31 ± 3.00	10.94 ± 2.27	0.847	0.397†
Height (cm)	146.10 ± 17.20	147.83 ± 14.45	−0.719	0.473‡
Weight (kg)	40.54 ± 13.77	41.11 ± 12.71	−0.286	0.776‡
BMI (kg/m^2)	18.39 ± 3.02	18.35 ± 3.09	0.097	0.923‡
axial length (mm)	23.81 ± 1.23	23.93 ± 0.99	−1.330	0.184†
SE (D)	−1.25 ± 2.64	−1.79 ± 2.39	0.828	0.157‡
ODA (mm^2)	2.10 ± 0.48	2.03 ± 0.45	0.954	0.341‡
MA (mm)	1.77 ± 0.21	1.74 ± 0.19	0.935	0.351‡
MI (mm)	1.49 ± 0.20	1.48 ± 0.19	0.484	0.629‡
ODO	1.19 ± 0.15	1.18 ± 0.10	0.595	0.553‡
With ODT	10 (10.99%)	13 (15.12%)	0.666	0.414*
Without ODT	81 (89.01%)	73 (84.88%)		
Deviation angle (°)	11.59 ± 11.59	10.09 ± 10.51	0.903	0.368‡
With ODR	37 (40.66%)	28 (32.56%)	1.249	0.264*
Without ODR	54 (59.34%)	58 (67.44%)		
β-PPA area (mm^2)	0.29 ± 0.43	0.46 ± 0.58	−2.275	0.023†
With β-PPA	43 (47.3%)	51 (59.3%)	2.578	0.108*
Without β-PPA	48 (52.7%)	35 (40.7%)		
With the BP	57 (62.6%)	60 (69.8%)	1.003	0.317*
Without the BP	34 (37.4%)	26 (30.2%)		

BMI = body mass index, BP = Bergmeister papilla, MA and MI = major and minor axis lengths, ODA = optic disc area, ODO = optic disc ovality, ODR = optic disc rotation, ODT = optic disc tilt ratio, PPA = peripapillary atrophy, SE = spherical equivalent.
* Chi-squared test.
† Mann-Whitney *U* test.
‡ Student's *t*-test.

Table 2. Stepwise linear regression analysis of predictors for β-PPA area in all the children.

			Unstandardized coefficients		SC		
	r^2	Independent Factor	*B*	SD	Beta	*t*	p
β-PPA area	0.342	Axial length	0.233	0.032	0.488	7.223	<0.01
		Body mass index	0.029	0.012	0.164	2.441	0.016
		Diagnosis of diabetes	−0.155	0.069	−0.144	−2.236	0.027

PPA = peripapillary atrophy, SC = standardized coefficients.

based study conducted in Singapore showed that ODO in healthy adults (average age: 54.7 years) was 1.1 (Bourne et al. 2008). A Japanese population study showed that adults (average age: 56.9 years) had ODO of 1.12 (Mataki et al. 2017). Another population survey conducted in Beijing showed that ODO of adults (average age: 63 years; range: 50–91 years) was 1.08 (Jonas et al. 2016). This was similar to the data of healthy adults included in the current study. Optic disc ovality (ODO) showed obvious changes after the occurrence of various eye diseases, especially glaucoma and high myopia. Kimura et al. (2014) analysed the ODO of 129 primary open-angle glaucoma (POAG) patients and 55 age-, gender- and AL-matched control subjects with high myopia and found that the ODO (convert the value of ODO to the ratio of maximum to minimum optic disc diameter) of POAG eyes with lamina cribrosa (LC) defects (n = 75) was significantly larger than that of POAG eyes without LC defects (n = 54), also significantly larger than that of controls. In this study, ODO of adults with diabetes (mean age: 63.36 ± 5.68 years) was 1.14, which was significantly larger than that of the healthy adults. Multiple linear regression analysis confirmed that ODO was significantly correlated with diabetes, and hence, we suspected that it might be associated with LC damage in diabetes. Advanced glycation end product (AGE) formation is increased in diabetes. Studies have demonstrated that AGEs could accumulate in the LC of donor eyes (Tezel et al. 2007). Advanced glycation end products (AGEs) can increase the production of reactive oxygen species, thereby initiating intracellular oxidative stress (Faria & Persaud 2017). Moreover, AGEs had a direct cytotoxic effect on neuron apoptosis (Marques et al. 2017). Therefore, we hypothesized that the increased ODO in diabetes might be due to the accumulation of AGEs that caused changes in the optic nerve head or LC. In addition, we found that the BMI was an independent factor affecting ODO. Previous studies report that obesity might lead to vascular endothelial dysfunction and autonomic nervous dysfunction (Yudkin et al. 2005; Cheung & Wong 2007),

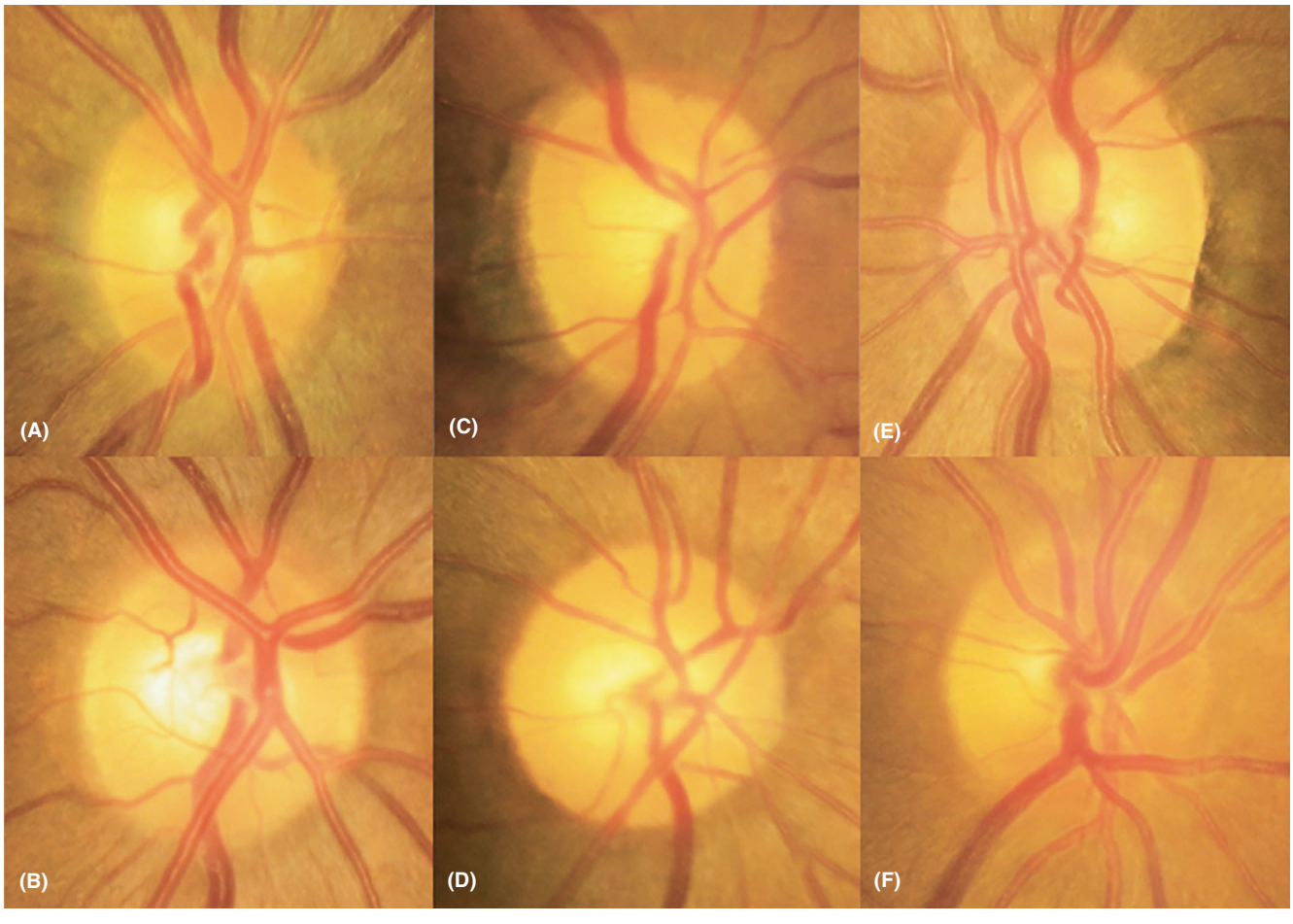

Fig. 4. Sample cases showing larger optic disc ovality (ODO) in adults with diabetes than in healthy adults. (A) A 51-year-old woman diagnosed with diabetes for 6.8 years, axial length (AL) as 22.78 mm, body mass index (BMI) as 30.23 kg/m^2 and ODO as 1.29. (B) A 53-year-old woman without diabetes, AL as 22.95 mm, BMI as 27.19 kg/m^2 and ODO as 1.08. (C) A 66-year-old woman diagnosed with diabetes for 5.8 years, AL as 23.51 mm, BMI as 28.51 kg/m^2 and ODO as 1.25. (D) A 67-year-old woman without diabetes, AL as 24.22 mm, BMI as 20.31 kg/m^2 and ODO as 1.06. (E) A 63-year-old woman diagnosed with diabetes for 1.8 years, AL as 22.58 mm, BMI as 27.55 kg/m^2 and ODO as 1.31. (F) A 63-year-old woman without diabetes, AL as 22.4 mm, BMI as 22.21 kg/m^2 and ODO as 1.08.

especially in patients with diabetes (Lim et al. 2004). Meanwhile, obesity was prone to be complicated by insulin resistance, which promoted oxidative stress response and the release of inflammatory factors. These physiological changes caused by obesity might lead to changes in the optic nerve by affecting the blood supply to the optic nerve and causing direct damage. Moreover, strong evidence suggests that obesity is associated with elevated IOP (Cheung & Wong 2007). Although no direct evidence suggests that obesity is associated with glaucomatous optic neuropathy, the elevated IOP caused by obesity could have affected the shape of the optic disc. These speculations need to be further explored.

Interestingly, we found that hyperglycaemia had different effects on ODM and PPS in children and adults. We considered this was mainly related to the individual differences between the two groups. All the children with diabetes were diagnosed with T1DM caused by the absolute lack of insulin, and blood glucose fluctuation was obvious and difficult to control; most of them had autoimmune diseases, and most had normal or reduced weight. In this study, no significant difference was observed in the BMI between children with diabetes and healthy controls, but choroidal thickening could occur in children with early diabetes (Li et al., 2020). We inferred this might increase the blood supply to the optic nerve tissue to some extent or slow the metabolism of RPE cells around the optic disc, making β-PPA area smaller in these children with diabetes than in healthy children. The MA, MI and ODA were not significantly different between the children with diabetes and healthy children. This might be due to the shorter duration of diabetes and the younger age, because of which optic nerve injury might not be obvious or be less (Pekel et al. 2018). In contrast, all of the adults with diabetes were diagnosed with T2DM caused by impaired insulin secretion and insulin resistance, often accompanied by obesity and a high BMI. These patients were older, their disease duration was generally longer, and the effects of long-term drug treatment or other factors on the body were very complex. The accumulation of AGEs in the optic nerve tissue caused irreversible optic nerve and LC injury, which might lead to the change in the position and shape of the optic disc, eventually leading to an increase in the MA and ODO. The increase in β-PPA in healthy adults might be due

Table 3. Demographic and optic disc parameters of the adults enrolled in this study.

	Adults with diabetes	Healthy adults	Statistics	p
Male	193 (43.47%)	198 (44.80%)	0.158	0.691*
Female	251 (56.53%)	244 (55.20%)		
Age (yrs)	63.36 ± 5.68	63.06 ± 5.65	0.783	0.434†
Height (cm)	163.49 ± 7.69	162.21 ± 8.03	2.433	0.015†
Weight (kg)	67.34 ± 10.32	64.70 ± 10.49	3.772	0.000†
BMI (kg/m^2)	25.19 ± 3.49	24.53 ± 3.08	2.388	0.017‡
SE (D)	0.45 ± 1.44	0.72 ± 1.18	−3.038	0.002‡
AL (mm)	23.22 ± 0.87	23.14 ± 0.75	0.828	0.408‡
ODA (mm^2)	1.77 ± 0.43	1.71 ± 0.37	1.723	0.085†
MA (mm)	1.51 ± 0.18	1.48 ± 0.16	2.286	0.022†
MI (mm)	1.33 ± 0.17	1.32 ± 0.15	0. 858	0.391†
ODO	1.14 ± 0.09	1.12 ± 0.06	3.334	0.001†
With ODT	8 (1.80%)	5 (1.13%)	1.324	0.250*
Without ODT	436 (98.20%)	437 (98.87%)		
β-PPA area (mm^2)	0.29 ± 0.43	0.24 ± 0.29	0.085	0.933‡
With β-PPA	231 (52.23%)	252 (57.01%)	2.221	0.136*
Without β-PPA	213 (47.97%)	190 (42.99%)		

AL = axial length, BMI = body mass index, MA and MI = major and minor axis lengths, ODA = optic disc area, ODO = optic disc ovality, ODT = optic disc tilt ratio, PPA = peripapillary atrophy, SE = spherical equivalent.
* Chi-squared test
† Student's *t*-test.
‡ Mann-Whitney *U* test.

Table 4. Stepwise linear regression analysis of predictors for optic disc ovality in all the adults.

			Unstandardized coefficients		SC		
Model	r^2	Independent factor	*B*	SD	Beta	*t*	p
Optic disc ovality	0.018	Body mass index	0.002	0.001	0.076	2.28	0.023
		Diagnosis of diabetes	0.016	0.005	0.104	3.099	0.002

SC = standardized coefficients.

to age and other factors leading to RPE cell apoptosis and choroidal vascular changes. This might be because the adults with diabetes included in this study had not yet developed DR or VI, and hence, RPE cells were not obviously damaged. In addition, a previous study confirmed the absence of a significant difference in CT between adult patients with T2DM and good glycaemic control and patients without diabetes (Torabi et al. 2019). We speculated that the above reasons might account for the insignificant difference in β-PPA area between the adults with diabetes and the healthy controls in this study.

This study had some limitations. First, this study was a cross-sectional study. We selected subjects for two age groups, those under 18 years old and those over 45 years old, to account for the typical changes in ODM and PPS. Therefore, we did not select the 19- to 44-year age group. The main type of diabetes in children is T1DM, whereas that in adults is T2DM. Therefore, the two age groups included in this study had different types of diabetes. This made it impossible to directly compare the influence of different age groups on ODM and β-PPA in early diabetes. Significant differences were observed in AL and BMI between children and adults with diabetes, and this might be related to them having different types of diabetes (Kahn et al. 2014; Santi et al. 2019) and might directly lead to significant differences in ODM and PPS between the two age groups in this study. Currently, we are conducting prospective cohort studies to observe the long-term changes in ODM and PPS in paediatric patients with diabetes with increasing age and progressing disease duration. Second, there was a lack of blood lipid reports of the study subjects, and the influence of hyperlipidaemia on optic disc morphology cannot be further analysed. In future studies, we will further explore the influence of hyperlipidaemia on optic disc morphology. Third, in adults, although no significant difference was observed in AL between those with diabetes and healthy controls, a significant difference was observed in SE. We believed this was related to the high incidence of cataracts in patients with diabetes (Memon et al. 2016), which resulted in lens-derived refractive changes. Considering no studies have reported direct changes in the optic disc caused by cataracts, the difference in SE between the two groups would not have affected the conclusions of this study. Finally, no objective and standardized methods are available for measuring ODA and β-PPA, as the accurate description of the edge of the optic disc and β-PPA area depends on the subjective judgement of the operator. Manual measurement errors might have occurred. However, although two-dimensional image

analysis was adopted in this study, in order to eliminate the influence of AL on the image size as much as possible, we corrected the measurements by applying Littmann's formula to ensure the measurements were closer to the real value. Moreover, owing to the consistency in the measurement method used, the difference between the two groups should be reliable. Planimetric fundus photography was widely used in the measurement and analysis of PPA, ODO and ODA (Xu et al. 2009; Kim et al. 2019; Hu et al. 2020); however, planimetric fundus photography analysis cannot reflect the spatial morphology; therefore, we hope that three-dimensional imaging technology will become available in the future to analyse the early changes in ODM and PPS around the disc affected by hyperglycaemia.

In conclusion, the results of this study showed that before the development of DR or VI and after eliminating the influence of AL, β-PPA area of children with diabetes was significantly smaller and ODO of adults with diabetes was significantly higher than those in the corresponding healthy controls. These changes were closely related to diabetes. These results could provide the basis for understanding the mechanism of hyperglycaemia in optic disc and peripapillary tissue injury.

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Correspondence:
Haidong Zou
Shanghai General Hospital
Shanghai Jiao Tong University School of Medicine
No.100 Haining Road
Shanghai 200080
China
Tel: +86-13311986528
Fax: +86-21-63240825
Email: zouhaidong@sjtu.edu.cn
Chenhao Yang
Department of Ophthalmology
Children's Hospital of Fudan University
No. 399 Wanyuan Road
Shanghai 201102
China
Tel: +86-18017590866
Fax: +86-21-64931901
Email: ychben@hotmail.com

[†]Contributed equally to this study.

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