• Investigation •

Influencing factors for peripheral and posterior lesions in mild non-proliferative diabetic retinopathy—the Kailuan Eye Study

Mo-Chi Yang[1,2], Xiao-Bo Zhu[3], Ya-Xing Wang[4], Shou-Ling Wu[5], Qian Wang[1], Yan-Ni Yan[1], Xuan Yang[1], Jing-Yan Yang[1], Meng-Xi Chen[1], Ya-Hui Lei[1], Wen-Bin Wei[1]

[1]Beijing Tongren Eye Center, Beijing Key Laboratory of Intraocular Tumor Diagnosis and Treatment, Beijing Key Laboratory of Ophthalmology and Visual Sciences, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China
[2]Department of Ophthalmology, General Hospital of Ningxia Medical University, Yinchuan 750004, Ningxia Hui Autonomous Region, China
[3]Dongfang Hospital Beijing University of Chinese Medicine, Beijing 100078, China
[4]Beijing Institute of Ophthalmology, Beijing Key Laboratory of Ophthalmology and Visual Sciences, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China
[5]Department of Cardiology, Kailuan General Hospital, Tangshan 063000, Hebei Province, China
Correspondence to: Wen-Bin Wei. Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, No.1 Dong Jiao Min Xiang, Dong Cheng District, Beijing 100730, China. weiwenbintr@163.com
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Abstract

● **AIM:** To explore the influencing factors of diabetes type 2 patients with mild non-proliferative diabetic retinopathy (NPDR) in the Kailuan area of Tangshan, Hebei Province, China.

● **METHODS:** In this non-interventional, retrospective study, 683 patients with type 2 diabetes were included in the Kailuan Diabetic Retinopathy Study involving participants with diabetes in the community-based longitudinal Kailuan Study. Based on the undilated ultra-wide field (200°; UWF) images and partial dilated digital fundus images, the diabetic retinopathy (DR) of the surveyed population was graded. Interobserver agreement was estimated by using Cohen's Kappa statistics. The main outcome indicators included gender, age, weight, height, body mass index, blood pressure, circumferences of neck, waist and hip, current smoking, levels of fasting plasma glucose (FPG), hypersensitive C-reactive protein, creatinine, and cholesterol, *etc*. According to different lesions' locations of patients with mild NPDR, logistic regression models were used to estimate the odds ratios (ORs) and their 95%CIs of each risk factor.

● **RESULTS:** The study group of 683 patients included 570 males and 113 females. The mean age of the patients was 62.18±9.41y. Compared with dilated fundus examinations, there was fair agreement with the level of DR identified on UWF images in 63.91% of eyes (k=0.369, 95%CI, 0.00-0.00). Detected by UWF images, there were 98 patients with mild NPDR having peripheral retinal lesions, 35 patients with mild NPDR having posterior lesions, 44 patients with mild NPDR whose lesions were detected both in and out the standard two fields area, and 336 patients with non obvious DR. Parameters that conferred a statistically significant increased risks for mild NPDR with having peripheral retinal lesions were neck circumstance (OR, 1.124; 95%CI, 1.044-1.211), and with posterior lesions were FPG (OR, 1.052; 95%CI, 1.007-1.099).

● **CONCLUSION:** UWF is an effectiveness means of DR screening. Moreover, it is necessary to evaluate peripheral diabetic retinal lesions which can help to estimate the severity of DR. The phenomenon that nonuniform and inhomogeneous distribution of DR lesions has been found. And the influencing factors in mild NPDR are differing by different lesions' locations.

● **KEYWORDS:** diabetic retinopathy; ultra-wide field image; neck circumference; peripheral lesions; fasting plasma glucose; posterior pole lesions

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INTRODUCTION

Diabetes mellitus (DM) has been impacting on worse general health and poor quality of life, and it has

emerged as an important clinical and public health problem throughout the world. Since last decade, the prevalence of DM has reached an epidemic proportion[1-3]. In China, the weighted prevalence of total diagnosed diabetes has been increasing from 9.7% in 2007 and 2010, to 10.4% in 2013, and to 11.2% in 2017[4], and the total number of patients with type 2 DM reaches almost 114 million which accounts one in three globally[5]. Diabetic retinopathy (DR) is the most common microvascular complications of diabetes and is prior to bring about blindness in diabetic patients. Without treatment, 50% of patients with proliferative diabeticretinopathy (PDR) will be blinded within 5y[6]. In the past 10y, the prevalence of DR in China has increased significantly. In a multi-hospital-based population across China, the prevalence of DR was 27.9%[7]. Shanghai Community Survey showed that the cumulative incidence rate and progression rate of DR was 46.89% and 32.23% respectively between 5y. In recent years, a large number of studies reveal that the severity of peripheral retinopathy in diabetic patients has a major impact on the extent as much as progress of DR. Furthermore, the early control of DR is of great significance. Silva *et al*[8] revealed the increased risk of DR progression were associated with the presence and growing extent of predominantly peripheral lesions over 4y. So the peripheral lesions for the severity of DR should not be ignored. This study is a cross-sectional, prospective, based on epidemiological investigations, and assess the lesions of DR by color fundus photographs of two fields (macular and disc field) and ultra-wide field (200°; UWF) imaging.

SUBJECTS AND METHODS

Ethical Approval The Kailuan Diabetic Retinopathy Study is a retrospective cohort study which is based on the participants of the Kailuan Study. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all participants gave informed written consent.

A total of 683 patients with type 2 DM were included in the Kailuan rehabilitation hospital service center in Tangshan City, Hebei Province, China between October 2016 and December 2016. Detailed history was taken using a standardized questionnaire. Age, gender, current smoking (no/yes) were elicited from the administrated standardized questionnaire. The diagnostic criterion for diabetes was any measurement of the fasting plasma glucose (FPG) concentration of ≥7.0 mmol/L, or a self-reported history of diabetes, or a history of medication with hypoglycemic agents. A venous blood collection was drawn on the day of each examiner's examination to estimate several levels of assay index, including FPG, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, total cholesterol, uric acid, hypersensitive C-reactive protein, glutamate pyruvate transaminase, total bilirubin, creatinine, urea, red blood cell count, white blood cell count, blood platelet count, hemoglobin, neutrophil cell count, and urinary protein. Other physical examinations include heart rate, blood pressure, weight, height, waist circumference, hip circumference, and neck circumference. Body weight and height were measured using standard technique and body mass index (BMI) was calculated. BMI was calculated as weight (kg)/height (m) squared, and waist-hip ratio was calculated as waist circumference (m)/hip circumference (m). Glomerular filtration rate (GFR) was assessed by taking the modified Modification of Diet in Renal Disease (MDRD) formula for Chinese patients[9]: eGFR (mL/min/1.73m^2)=175 × Scr$^{-1.234}$ × age$^{-0.179}$ × 0.79 (if female).

Screening Processand Grading All patients underwent an anterior segment examination of eyeball, dilated fundus examination, and measurement of intraocular pressure (IOP). IOP was tested by non-contact tonomter. An ophthalmic examination was performed by an experienced ophthalmologist with a holding type slit-lamp in the clinic. The patients with abnormal IOP (more than 21 mm Hg) or shallow anterior chamber judged by slip-lamp would not be dilated the pupils. Patients underwent a nonmydriatic UWF laser photography and two standard horizontal field mydriatic digital photography (one centered on the fovea and the other on the disc), using a 200 degree UWF scanning laser ophthalmoscope in United Kingdom and a 45 degree Canon CR6 retinal camera in Norwich respectively. The certified imager repeated imaging up to two times during the imaging session if the imager considered the images to be of suboptimal quality. The imager stored all images using proprietary software and images were available for review using proprietary Optos image review software (Optos V2 Vantage Dx Review version 2.5.0.135; Optos plc, Dunfermline, Scotland, United Kingdom).

All two methods of examination for DR were graded independently. The ophthalmoscopic assessments were completed twice at the time of examination by two experienced ophthalmologists, respectively. The digital and film graders were masked regarding both each subject's history of DM and visual acuity, noting the underlying cause of the discrepancy and explanation (grader error, image quality, or field coverage). Image quality for the two-field digital photography was determined using the following criteria: Assessable—possible to see the small vessels of the temporal arcades with reasonable clarity. Not assessable—the large vessels of the temporal arcades are blurred or more than one third of the picture is blurred unless sight threatening retinopathy is detected in the remainder. Insufficient image quality for UWF images was stated as laying over at most the central 60° and without both the optic disc and the macula in good quality.

Grading was performed to determine the presence and severity of the following lesions: microaneurysm (Ma), blot

or flame shaped hemorrhage (H), hard exudate, cotton wool spot, intraretinal microvascular abnormalities (IRMA), new vessel (NV) formation or evidence of laser treatment for DR at baseline. Images that were classified as ungradable were excluded from the analysis. The International Clinical Diabetic Retinopathy (ICDR) severity scale was used for grading[10]. DR was categorized as non-obvious retinopathy, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, PDR and after laser photocoagulation. By using UWF imaging in this report, we sought to explore the issue in a case-control study to find the risk factors for early DR in Kailuan area of Tangshan City in China. In our study, lesions locating outside the standard two-field photograph fields simulated without the dashed line on UWF images were defined as peripheral retinal lesions. Besides, lesions locating in the two-field retina area simulated within the dashed line on UWF images were defined as posterior pole lesions.

Statistical Analysis Inter-observer agreement was evaluated by using Cohen's Kappa statistics[11]: <0.20 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1.00 excellent agreement.

The results were expressed as mean±standard deviation or as mean and the 95% confidential interval (CI). All subjects consisted three groups. With mild NPDR, ones only having peripheral retinal lesions which locate outside the two-field retina area simulated within the dashed line (Figure 1) or only having posterior pole lesions were defined as cases respectively and subjects with no DR were defined as controls. The Fisher's exact, Chi-squared and Student's *t*-tests were used to compare means and percentages between each independent groups. And the first two independent groups participants with mild NPDR were analyzed with all of the predictors together in a multivariate logistic regression model using stepwise forward selection procedure with an entry probability of 0.05 and a removal probability of 0.10 respectively. Logistic regression models were used to estimate the odds ratios (ORs) and their 95% CIs of each risk factor. A *P*-value smaller than 0.05 was considered significant. All analyses were performed by SPSS software version 22.0 (SPSS Inc., IBM, NC, USA).

RESULTS

Characteristics of the Study Population Retinal images from 1366 eyes (683 patients) were evaluated, including 27 eyes with photocoagulation. Among these 683 patients, 570 were males (83.5%) and 113 were females (16.5%). Meanwhile, the range of age was from 28 to 83, with the average age was 62.18±9.41 years old.

Characteristics of Diabetic Retinopathy Compared with dilated fundus examinations, there was fair agreement with the level of DR identified on UWF images in 63.91% of eyes (k=0.369, 95%CI, 0.00-0.00; Table 1).

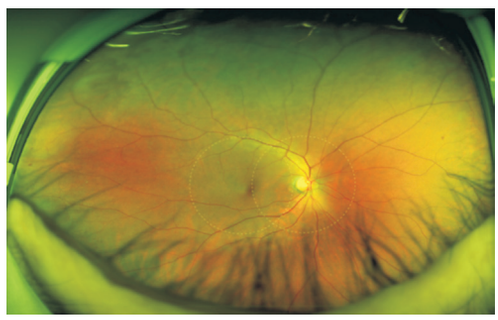

Figure 1 The UWF image of the right eye whose lesion (H/Ma) locate outside the two-field retina area (simulated within the dashed line) with mild NPDR.

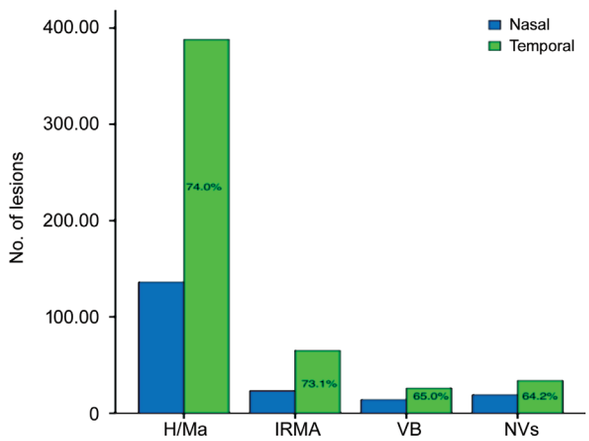

Figure 2 DR lesions in nasal and temporal retinal fields H/Ma: Hemorrhage and/or microaneurysm; IRMA: Intraretinal microvascular abnormality; VB: Venous beading; NVs:New vessels.

Table 1 Severity level of diabetic retinopathy in ultra-wide field images and two standard 45° photographs (eyes) *n* (%)

Parameters	Two-field images	UWF images
No obvious DR	944 (69.1)	760 (55.6)
Mild NPDR	158 (11.6)	304 (22.3)
Moderate NPDR	151 (11.1)	180 (13.2)
Sever NPDR	69 (5.0)	73 (5.3)
PDR	17 (1.2)	22 (1.6)
Treated by laser	27 (2.0)	27 (2.0)
Total	1366 (100)	1366 (100)

Simple kappa statistic: 0.369 (95%CI, 0.00-0.00); Perfect agreement: 63.9%.

Approximately a half of H/Ma, IRMA and NVs were located predominantly outside the two-field photograph fields. The distribution of DR lesions revealed inhomogeneous on the UWF images. Imaginary vertical lines through the center of the optic disc divide the image into the nasal side and the temporal side. It was found that all kinds of DR lesions [H/Ma, IRMA, venous beading (VB) and NVs] were nearly less predominant in the nasal half of the retina than in the temporal fields. In the visible range, there were 74.0% of H/Ma, 73.1% of IRMA, 65.0% of VB and 64.2% of NVs in the temporal fields respectively (Figure 2).

In the study cohorts, there were 672 eyes of 336 patients (49.2% of total patients) with non-obvious retinopathy and 304 eyes of 152 patients (11.1% of total patients) with mild NPDR. There were 68 eyes of 35 patients (2.6% of total patients, 22.4% of total eyes with mild NPDR) with mild NPDR just having posterior pole lesions. In contrast, 197 eyes of 98 patients (7.2% of total patients) with mild NPDR just having peripheral lesions. In addition, 44 patients with mild NPDR having both peripheral lesions and posterior pole lesions.

Multivariate Analysis of the Risk of Mild NPDR Table 2 shows descriptive statistics and the frequencies of the potential prognosticators, along with *P*-values summarizing the univariate associations of each prognosticator for the DR cases stratified by DR type respectively (non-obvious DR *vs* mild NPDR with peripheral lesions and non-obvious DR *vs* mild NPDR with posterior pole lesions).

In multivariable logistic regression analysis, neck circumference (*P*=0.026; OR:1.124; 95%CI:1.044, 1.211) seemed to have a significantly associated with mild NPDR just having peripheral lesions. By contrast, FPG (*P*=0.022; OR:1.052; 95%CI: 1.007, 1.099) seemed to have a significantly associated with mild NPDR just having posterior polar lesions (Table 3).

DISCUSSION

DM is a large public health problem which is reported to affect one in 11 adults worldwide, with significant morbidity and mortality worldwide[12]. World Health Organization (WHO) projects that diabetes will be the seventh leading of cause death by 2030 and this would increase disproportionately more in developing countries[13]. Moreover, DM is estimated to be the cause of blindness in 4.8% of the 37 million people who are blind throughout the world[14].

Type 2 diabetes is a fast-growing public health challenge in China. Nationally in China, the representative survey of adults in 2013 was estimated that 10.9% of Chinese adults have diabetes[15]. In addition to the deleterious effects of the disease itself, its long-term complications can conspicuously decrease the quality of life of diabetes patients. So, the impact on the health care system for the patient with DM is an urgent public health matter. And the sooner the disease is discovered, the better the complications can be controlled.

It has been found that the microcirculatory system of the retina has the same anatomical and physiological characteristics as the microcirculatory system of the brain, coronary artery and other organs[16]. There are a number of population-based epidemiological surveys showing that retinal vascular abnormalities are closely related to systemic blood vessels, such as the heart, brain, and kidney vessels[17-20], suggesting that retinal vascular abnormalities can be considered as a crucial clinical indicator in a risk assessment for systemic diseases[21-22]. Therefore, before the serious complications of diabetes take place, the slight changes of retinal blood vessels may predict the transformation of microcirculation. So to discover diabetic retinopathy at early stage is meaningful for control of diabetes and systemic microcirculation.

Over the decades of years, a variety of techniques can be used to detect and grade DR, including direct and indirect ophthalmoscopy, stereoscopic color film fundus photography, fluorescein angiography, and mydriatic or nonmydriatic digital color or monochromatic photography. It has proven to be beneficial to use a screening tool like digital non-mydriatic fundus imaging for detection of early DR changes by an endocrinologist, or any physician treating diabetes who can refer to an ophthalmologist for screening[23-25]. It is known that many primary care physicians are used to screen and monitor DR by two-field fundus photographic pictures in China. However, the peripheral lesions are easy to be ignored. Although it has been known that the Early Treatment Diabetic Retinopathy Study (ETDRS) 7-field photography is the gold standard for DR in terms of diagnosis and classification[26], it is seems time consuming to realize the large number of community screening for DR in a limit time and hard for both patient and photographer through the clinical practices.

Recent technological advantages have also resulted in the availability of UWF scanning laser ophthalmoscopy techniques for imaging, which can obtain a 200° UWF image at a time, covering about 82% of the retina range. Meanwhile, taking into account the advantages of it such as nonmydriatic, fast, safety and non-contact, it is convenient for physicians to detect community-based DR in large populations. So it has become the most effective and reliable way to observe peripheral retinopathy. In this study we used the UWF scanning laser ophthalmoscopy (Optos 200TX) to screen for DR in a large sample population with type 2 DM of Kailuan area of Tangshan City. UWF images were evaluated to impact on the grading of DR (36.09% of eyes with DR) in 493 eyes, not only because of inadequate two-field photograph quality and just almost having peripheral lesions, also because it can obtain a better retinal image for a patient with a certain degree of cataract, for the red or green laser of the UWF scanning laser ophthalmoscope system can reduce the light scattering when entering the anterior segment of the eye. Neither UWF image nor two-field fundus photographic picture ungradable was included in our study. However, we found that compared with UWF images, there were almost 2 times number of two-field fundus pictures ungradable because of the opaque refractive medium. Except for heavy-cloudy cataracts, uncooperative and eyelashes and eyelids blocking were the main reasons for ungradable UWF images.

Table 2 Differences between the group of diabetic participants with mild NPDR having peripheral retinal lesions and posterior pole lesions compared respectively with the group of diabetic participants with no obvious diabetic retinopathy in the Kailuan Diabetic Retinopathy Study

Parameters	No obvious DR	Mild NPDR with peripheral retinal lesions	Mild NPDR with posterior lesions
n	336 (49.2%)	98 (14.3%)	35 (5.1%)
Gender			
Male	268 (39.2%)	80 (11.7%)	29 (10.0%)
Female	68 (10.0%)	18 (2.6%)	6 (0.9%)
Age (y)	59.85±10.38	59.37±9.55	59.14±8.06
Smoking			
No	248 (36.3%)	62 (9.1%)[a]	26 (3.8%)
Yes	84 (12.3%)	35 (5.1%)	8 (1.2%)
Mean systolic blood pressure (mm Hg)	142.02±18.33	143.43±18.83	149.82±21.93
Mean diastolic blood pressure (mm Hg)	83.26±9.95	83.97±10.59	85.10±13.91[b,c]
Height (cm)	168.72±6.78	169.24±7.84	167.51±7.33
Body weight (kg)	74.55±11.66	75.99±10.77	73.77±13.91
Waist circumference (mm)	89.13±10.07	91.56±9.81	90.57±9.35
Neck circumference (mm)	38.49±2.26	39.09±3.18[a]	38.53±1.99
Hip circumference (mm)	99.26±10.67	101.18±11.20	99.17±11.02
Mean ventricular rate (beats/min)	75.19±12.98	75.12±11.55	76.60±12.16
Mean fasting blood glucose (mmol/L)	9.31±6.53	9.66±6.92	12.62±2.24
Mean high-density lipoprotein cholesterol concentration (mmol/L)	1.32±0.44	1.36±0.49	1.25±0.23
Mean low-density lipoprotein cholesterol concentration (mmol/L)	2.84±0.77	2.76±0.83	2.54±0.84
Mean triglyceride (mmol/L)	2.47±5.72	2.18±2.06	2.67±3.27[c]
Mean total cholesterol concentration (mmol/L)	5.54±1.18	5.48±1.34	5.61±1.47
Mean uric acid concentration (μmol/L)	324.52±102.18	333.16±91.57	336.23±92.84
Mean hypersensitive C-reactive protein concentration (mg/L)	3.63±6.60	4.08± 10.28	4.02±5.17
Mean total protein concentration (g/L)	79.07±43.39	75.69±5.44	76.54±4.34
Mean glutamate pyruvate transaminase (U/L)	25.51±21.09	26.63±23.83	20.83±9.81
Mean total bilirubin (μmol/L)	16.08±5.79	16.71±5.48	16.81±5.39
Mean direct bilirubin (μmol/L)	4.73±2.86	4.90±1.95	4.90±1.53
Mean creatinine (mmol/L)	77.83±57.79	67.41±15.22	69.25±24.70
Mean urea (mmol/L)	6.18±4.20	6.10±1.77	6.35±1.58
Mean red blood cell count (10^{12}/L)	4.85±0.44	4.81±0.40	4.89±0.43
Mean white blood cell count (10^9/L)	6.70±1.58	6.45±1.58	6.86±1.95
Mean blood platelet count (10^9/L)	242.43±66.28	239.24±67.73	218.00±48.22[c]
Mean hemoglobin (g/L)	151.00±16.74	151.19±15.61	153.23±13.30
Mean neutrophil cell count (10^9/L)	4.49±5.17	4.20±3.95	4.20±1.68
Mean waist-hip ratio	0.90±0.11	0.91±0.52	0.92±0.05
Meanbody mass index (kg/m^2)	26.17±3.52	26.55±2.89	26.22±4.15[e]
Urinary protein			
-	292 (42.8%)	84 (12.9%)	27 (4.0%)
Trace	13 (1.9%)	4 (0.6%)	1 (0.1%)
+-	76 (1.0%)	0	1 (0.1%)
+	10 (1.5%)	6 (0.9%)	1 (0.1%)
++	12 (1.8%)	3 (0.4%)	3 (0.4%)
+++	2 (0.3%)	1 (0.1%)	2 (0.3%)
Fatty liver			
No	109 (16.0%)	33 (4.8%)	12 (1.8%)
Light	104 (15.2%)	27 (4.0%)	12 (1.8%)
Moderate	97 (14.2%)	31 (4.5%)	10 (1.5%)
Heavy	26 (3.8%)	7 (1.0%)	1 (0.1%)
eGFR (mL/min/1.73 m^2)	48.10±35.52	48.08±15.05	45.19±13.04

[a]*P*<0.05 *vs* no obvious DR; [b]*P*<0.05 *vs* no obvious DR; [c]*P*<0.05 *vs* mild NPDR with peripheral retinal lesions.

Table 3 Associations (multivariable logistic regression analysis) of biologic risk factors with mild NPDR having peripheral and posterior retinal lesions respectively

Parameters	B	OR	95%CI for OR	*P*
Neck circumference (mm)	0.117	1.124	1.044, 1.211	0.002
FPG (mmol/L)	0.051	1.052	1.007, 1.099	0.022

FPG: Fasting plasma glucose.

The two technologies showed consistent for DR grading (Kappa=0.369, $P<0.001$). So it has an advantage for detecting DR by UWF images over by two-field fundus photographic pictures. Throughout all UWF images with DR lesions, peripheral lesions in the nasal half of the retina were less than in the temporal half. The phenomenon that nonuiform and inhomogeneous distribution of DR lesions has been found by some experimental research[27-28]. Furthermore, Silva *et al*[29] demonstrated that peripheral DR pathology primarily in the temporal and superior quadrants by using Optomap UWF scanning laser ophthalmoscope images.

In our study, interestingly, patients with mild NPDR whose lesions visibly sited in different retina area with inhomogeneous distribution. Some lesions were found outside the two-field retina area rather than in the posterior pole area, vice versa. The implied implications and pathogenesis are not clear. It may be associated with the the protective mechanism of retinal oxygenation, which was unavailable in the peripheral retinal arterioles rather than in the posterior pole retinal areas. Owing to the regionally different disturbance of diameter caused by increased blood pressure, distribution of DR lesions are regionally different[30].

As we known, the occurrence and advancement of DR is known to be caused by the combined effects of multiple factors in the whole body, including duration of diabetes[31-33], systolic blood pressure[34], anemia[35-36], hyperlipidemia[37-39], renal dysfunction[40], high HbAlc[41] *etc*. The results of each study are not completely consistent, and are related to the research objects and geographical differences. However, what made the nonuiform distribution of lesions with mild NPDR happen?

Interestingly, we found that the influnerence factors for patient with mild NPDR were different in the light of different lesions' location. On one hand, we carried out an analysis of the risk factors for these ones with mild NPDR who are often easily neglected and not taken seriously on account of being misdiagnosis as usual. As far as we known, there are few reports on the factors affecting the peripheral lesions preceded at the early-stage of DR: mild NPDR. On the other hand, we did an analysis of the risk factors for those ones whose lesions chiefly and obviously located in the posterior pole area. Compared with the group of mild NPDR with peripheral lesions in our study, the group of mild NPDR with posterior lesions had higher diastolic blood pressure, higher triglyceride, lower blood platelet count and lower BMI. Also, these patients were more smoking and had longer neck circumference compared with no DR patients. Statistically, neck circumstance was the independent risk factor in the multivariable model for the mild NPDR that lesions located obviously outside posterior pole area. On contrary, FPG was the independent risk factor in the multivariable model for the mild NPDR with lesions occurred predominantly in the two-field retina area. It was found that BMI and age were not the significant risks. The result is similar with a multi-hospital-based cross-sectional study[42], although several previous studies presented the two had certain relationship[43-45].

Previously, several studies revealed neck circumference as a cardiometabolic possiblerisk factor[46-47]. Neck circumference were showed positively related to the metabolic syndrome risk factors, such as insulin resistance and abdominal visceral fat, manifesed a positively mutual relationship with triglycerides, FPG, fasting insulin, and showed a moderate negative correlation with insulin sensitivity[46,48]. Further investigations with prospective design are required to confirm these findings. Although more and more research pay close attention to the relationship between neck circumference with DM, the relationship between DR and neck circumference was rare reported. Some research[49-50] provided a positive correlation of neck circumference with metabolic syndrome in patients with type 2 diabetes. The result from a study from Khalangot *et al*[51] revealed neck circumference was a novel risk factor of diabetes during screen-based research of glycaemia and glucose tolerance. Our study showed positively relation of neck circumference with mild NPDR having peripheral lesions. Ischemia has been known as a critical component of DR, which has been associated with the advancement and progress of both microvascular and macrovascular complications[52]. In a study[53] based on population of Amerindians, smaller neck circumference was associated with lower carotid intima-media thickness but BMI was associated. These with mild obstructive sleep apnea (OSA) had shorter neck circumference and longer ocular axial length than those with either moderate or severe OSAS[54]. These findings support the result of our study that an increase of neck circumference may lead to an aggravation of retinal hypoxia and ischemia especially in peripheral

area for the patients with diabetic. The results from Korean indicated a negative impact on large neck circumference (the mean±SD of neck circumference; ranges) was 37.6±2.0 (31.8-45.3) cm in men and 32.9±1.8 (23.0-40.0) cm in women in the development of DM and the mean±SD of neck circumference (ranges) was 37.6±2.0 (31.8-45.3) cm in men and 32.9±1.8 (23.0-40.0) cm in women[55]. In our study, compared with the mean±SD of neck circumference was 38.49±2.26 cm in patient with non-obvious DR, 39.09±3.18 cm in the patient with mild NPDR having peripheral retinal lesions obviously (F=4.227, P=0.40). It revealed the patients with early stage of DR whose lesions (H/Ma) located mainly outside the posterior pole retina might have larger neck circumference than the ones suffered from DM with non-obvious DR. We deemed that neck circumference may be an important predictor of early stage of DR and H/Ma located outside posterior pole retina might be a sign of cardiometabolic alter, which is a novel, easily measured index.

Excessive high glucose levels were widely considered by researchers as a big risk of vascular diseases and all-cause mortality[56-57]. Additionally, the prevalence of retinopathy was found having an association with FPG[58-61]. In China, some studies' conclusion was analogous to those results[60,62]. Similarly, in our study, the patients with mild NPDR whose lesions located in the posterior pole area have higher FPG. However, FPG was not the risk factor for the patients with mild NPDR having peripheral retinal lesions. It is possible that presence of H/Ma in posterior pole identifies an individual with an increased microvascular susceptibility to glycemia. The presence of retinopathy lesions at baseline was related to be a two-fold increased risk of progression of FPG and suggested that an assessment of retinopathy could be of value in initial assessments of risk of metabolic worsening in early diabetes, adding information beyond the risk associated with age and glycemia[63]. And retinopathy in newly diagnosed type 2 diabetes was associated with elevated fasting and postprandial glucose[64]. It is deemed that detection of early DR, especially in posterior pole retinal area, may beneficial to prevent progressive metabolic worsening and promote individualized therapy in early diabetes further. Clinically, in patients with DR, we also found the ones with high FPG whose lesions of DR located in the posterior pole retina are more severe than those patients with normal FPG controlled.

Our study has some limitations. Although the designed project actually contains nearly 1200 people, the complete data were not available for a significant proportion of the subjects (almost 30%) who were thus not included in these analyses, which might cause some systematic error. Furthermore, some indicators (such as glycosylated hemoglobin, duration of DM) were not recorded. In addition, some data are not included (such as peripheral neuropathy, urinary albumin excretion and time of insulin intervention). The missing information of ex-smoker or never smoked was too much to include into the statistical analysis, although those who reported not current smoking were further classified as ex-smoker or never smoked in our questionnaire. Compared with other studies, our population had little prevalence of microvascular complications[65-67]. It might because the subjects of our study were health-examined individuals, who were different from the hospital patients. On the analysis side, the presence of goiter and quantitative parameters of thyroid gland were not considered in our study, which affected the results of neck circumference. The selection criteria could limit the generalisability of the study. All above may create a potential selection bias. Despite these limitations, our study has many strengths, including the large sample size of individuals with DM, standardized laboratory assessment of serum samples and imaging data. To the best of our knowledge, this was the first time that a wide-angle laser retinal imaging system had been used in the screening of DR in community of China, and this is the first reporting the risk factors for patients with mild NPDR in light of different lesions' locationin a Chinese population. These observations may be of value in future investigations.

In summary, the present study has shown the effectiveness of DR screening using UWF scanning laser ophthalmoscope system, especially for reducing the burden of DR screening and enhancing early detection of treatable DR in large group people suffered from DM. As we known, clinically, retina outside the two-field area is often easily overlooked, and it has been found that lesions in peripheral retina could affect the grading of DR. The phenomenon that nonuiform and inhomogeneous distribution of DR lesions has been found. Meanwhile our data showed different influence factors for patient with mild NPDR on the basis of different lesions' location. In view of current study, we deem that the pathogenesis of retinopathy is dissimilar from distribution of lesions for patients with NPDR. In detail, the patients with peripheral lesions might have larger neck circumference and should pay more attention to cardiometabolic or macrovascular complications, while the patients with posterior pole lesions might get along with higher FPG in advanced stage DM. Clinically, they all could give tips for the analysis of the severity of a patient's systematic diseases. Further investigations with prospective design are required to confirm these findings.

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