Incidence, progression and regression of diabetic retinopathy in a northeastern Chinese population

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ABSTRACT

Aim To determine the incidence, progression and regression of diabetic retinopathy (DR), with corresponding risk factors, in a northeastern Chinese population of patients with type 2 diabetes.

Methods Among 2006 patients who completed baseline examinations in 2012–2013 and underwent re-examination after a mean interval of 21.2 months, 1392 patients with gradable fundus photographs for both baseline and follow-up examinations were included. Incidence was defined as new development of any DR among patients without DR at baseline. An increase of ≥2 scales (concatenating Early Treatment Diabetic Retinopathy Study levels of both eyes) in eyes with DR at baseline was defined as progression, while a reduction of ≥2 scales was defined as regression.

Results The age- and sex-standardised incidence, progression and regression were 5.8% (95% CI 4.7% to 6.9%), 26.8% (95% CI 24.8% to 28.8%) and 10.0% (95% CI 8.6% to 11.3%), respectively. In addition to poor blood glucose control, wider central retinal venular equivalent was associated with both incidence (relative risk (RR) 2.17, 95% CI 1.09 to 4.32, for ≥250 µm vs <210 µm) and progression (RR 2.00, 95% CI 1.02 to 3.96, for ≥250 µm vs <210 µm). Patients without insulin therapy (RR 0.64, 95% CI 0.43 to 0.97) and patients with wider central retinal arteriolar equivalent (RR 1.14, 95% CI 1.02 to 1.26, per 10 µm increase) were likely to exhibit DR regression.

Conclusion We determined the incidence, progression and regression of DR among northeastern Chinese patients with type 2 diabetes. Retinal vessel diameters, in addition to blood glucose level, influence the natural evolution of DR.

WHAT IS ALREADY KNOW ON THIS TOPIC

⇒ A wide range of incidence of diabetic retinopathy (DR) among Chinese patients with diabetes was reported. However, little was known about incidence of progression and regression, especially in the same study cohort.

WHAT THIS STUDY ADDS

⇒ We reported comprehensive incidences and risk factors for DR onset, progression and regression in a Chinese study cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This completed information on DR would be beneficial for further studies and making public health policies.

INTRODUCTION

Diabetes is a major public health issue worldwide. The number of people with diabetes has quadrupled in the past three decades, with staggering figures in both China (109.6 million) and India (69.2 million).[1] Diabetic retinopathy (DR) is a microvascular complication of diabetes which can potentially cause severe visual impairment among patients if appropriate intervention is not performed.[2] As the number of patients with diabetes increases, the number of individuals with DR will inevitably rise and has been projected to be 191.0 million worldwide in 2030[3] and 9.2 million in rural China.[4]

To better understand the natural evolution of DR, including its progression and regression, cohort studies are necessary. Thus far, most cohort data have been from Western populations, such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR),[5] the Blue Mountains Eye Study (BMES)[6] and the Los Angeles Latino Eye study.[7] There are limited longitudinal data, particularly regarding the incidence of regression, in Chinese populations. Three community-based studies have reported a wide range of incidences for newly developed DR among Chinese diabetic patients: from 1.81% person-year in a northeast population to 5-year incidence of 46.89% in eastern China.[8–10] It is unclear whether these disparate values are related to differences in study area, participant lifestyle or methodology. Moreover, the sample size has generally been small in previous studies (<1000).

Hyperglycaemia, hypertension and hyperlipidaemia were the major risk factors for DR onset or development in both high-income countries and China, and controlling[8–14] these factors could effectively reduce DR progression.[15–17] The Diabetes Control and Complications Trial has reported that intensive glycaemic control reduced the risk of DR developing or progressing to a clinically significant degree by 34%–76% in type 1 diabetes.[15] With regard to type 2 diabetes, a 4-year DR progression incidence had a significant reduction in the intensive glycaemic control group compared with the standard therapy group (7.3% vs 10.4%).[16] Similarly, it was shown that intensive blood pressure control (<150/85 mm Hg) and intensive dyslipidaemia therapy could reduce the DR progression by 34% (9-year follow-up) and approximately 4% (4 years follow-up), respectively.[16 17]

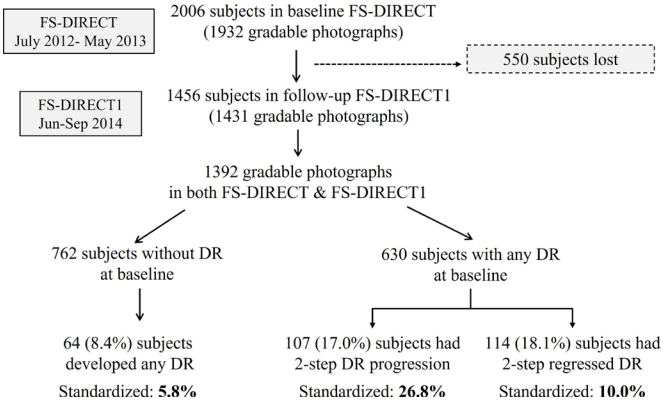

Figure 1 Flow of patient selection in FS-DIRECT. DR, diabetic retinopathy; FS-DIRECT, fushun diabetic retinopathy cohort study.

Accurate estimates of DR incidence, progression and regression in China, as well as their risk factors, could help to inform public health policy and resource allocation for screening and treatment. Therefore, we present an interim report of the Fushun Diabetic Retinopathy Cohort Study (FS-DIRECT).

MATERIALS AND METHODS

Study design and population

The rationale and methodology of the baseline study have been reported elsewhere.[18] Briefly, the FS-DIRECT is a community-based study conducted in Fushun City, Liaoning Province (in the northeast region of China). Baseline 2006 community-dwelling adults (aged ≥30 years) with diagnosed type 2 diabetes were enrolled using a multistage random sampling method from all 15 communities of Jiangjun Street, Fushun City, between July 2012 and May 2013. Participants were required to undergo fasting blood sample collection and ocular examination (slit-lamp exam, fundus photography and optical coherence tomography) at least 1 year later (between June 2014 and September 2014).

Five hundred and fifty (27.4%) participants were lost to follow-up. In total, 1456 (72.6%) participants were re-examined in the first follow-up period (FS-DIRECT1), with a mean follow-up interval of 21.2±3.2 (range 13.7–29.2) months. Among these 1456 participants, 1431 (98.3%) had gradable fundus photographs in FS-DIRECT1, while 1392 (95.6%) had gradable fundus photographs in both FS-DIRECT and FS-DIRECT1. Hence, data from these 1392 participants were used for further analysis. Figure 1 shows the flow of patient selection.

DR grading

In accordance with the baseline protocol,[18] six fundus fields were photographed after pupil dilation. DR was graded based on the fundus photographs using modified ETDRS criteria: no DR (levels 10–20); non-proliferative diabetic retinopathy (NPDR; mild (levels 31–37), moderate (levels 43–47 or severe level 53) or proliferative DR (levels 60–85). If the DR severity could not be graded in one eye, it was given a score equivalent to the score in the other eye.

The incidence of DR was defined as new development of any DR (level ≥31 in at least one eye) during follow-up among patients without DR at baseline. To assess the progression/regression of DR, we classified patients with DR into 12 scales (31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) according to the concatenating levels in both eyes; the eye with a higher level received greater weight in the classification system.[5 12] An increase of ≥2 scales in eyes with any DR at baseline was regarded as progression of DR, while a decrease of ≥2 scales was regarded as regression of DR.

Measurement of central retinal vessel diameter

Baseline central retinal vessel diameter was measured in fundus photographs using Integrative Vessel Analysis software V.1.3 (Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, Wisconsin, USA). The details of the measurement protocol have been described elsewhere.[19] Briefly, the six largest arterioles and venules passing completely through a circumferential zone, 0.5–1.0 disc diameter from the optic disc margin, were identified through automated assessment by Integrative Vessel Analysis software. The central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE) were automatically calculated by the software using the revised Parr-Hubbard formula.

Statistical analysis

Continuous variables with normal distributions are shown as means±SD; they were compared using independent t-tests. Categorical variables are shown as numbers (proportions); they were compared using the χ^2 test. Age-standardised and sex-standardised incidence, progression and regression of DR were estimated based on the Chinese population in the 2010 China Population Census.

The impacts of potential risk factors (eg, diabetes duration, glycosylated haemoglobin A1c (HbA1c) level and retinal vessel diameters) on incidence, progression, and regression of DR were primarily assessed using generalised additive models that had been adjusted for age and sex. Subsequently, multivariable-adjusted regression modelling was performed with the incidence/progression/regression of DR as the dependent variable and potential risk factors ($p<0.1$ in the previous analysis) as independent variables. Relative risk (RR) values were determined, along with 95% CIs. Statistical analyses were performed using Statistical Analysis System for Windows V.9.1.3. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

Table 1 compares patients with gradable fundus photographs at baseline and follow-up (n=1392) to patients without gradable photographs at either examination (n=614). Patients with gradable fundus photographs tended to have the following characteristics: younger age, higher level of education, less frequent proteinuria, earlier age of diabetes onset and wider CRVE. They also tended to have lower levels of fasting plasma glucose (FPG), serum creatinine, blood uric acid, total cholesterol and low-density lipoprotein.

Table 2 shows the incidence of DR, stratified according to various risk factors. Among 762 patients without DR at the baseline examination, 64 developed DR over a mean follow-up interval of 21.1±3.2 months, yielding a crude incidence of 8.4% (95% CI 6.4% to 10.4%). The corresponding age- and sex-standardised incidence was 5.8% (95% CI 4.7% to 6.9%) or 3.3% person-year. The crude incidences of DR were 8.7% (95% CI 5.6% to 11.7%) and 8.2% (95% CI 5.6% to 10.8%) for male and female patients, respectively (p=0.82). The corresponding age-standardised incidences were 5.4% (95% CI 3.0% to 7.9%) and 6.1% (95% CI 3.8% to 8.3%). For these 64 patients with newly diagnosed DR, the majority exhibited mild NPDR (n=60, 93.8%) followed by moderate NPDR (n=2, 3.1%) and proliferative diabetic retinopathy (PDR) (n=2, 3.1%). Sixteen

Table 1 Characteristics of patients with and without gradable fundus photographs at baseline and follow-up

Characteristics	Patients with gradable photographs (n=1392) Mean (±SD)/n (%)	Patients without gradable photographs (n=614) Mean (±SD)/n (%)	P value
Age (years)	61.2±8.5	64.1±9.7	<0.001
Male, n (%)	576 (41.4)	243 (39.6)	0.45
Income level, n (%)			
Low	522 (38.4)	209 (35.7)	0.41
Moderate	773 (56.8)	351 (60.0)	
High	66 (4.9)	25 (4.3)	
Education, n (%)			
Primary or lower	187 (13.7)	137 (23.4)	<0.001
Middle/high school	976 (71.3)	380 (65.0)	
College and above	206 (15.1)	68 (11.6)	
Current smoker, n (%)	296 (21.7)	129 (22.2)	0.80
Current drinker, n (%)	321 (23.5)	99 (17.0)	0.002
Diabetes treatment, n (%)			
No treatment	189 (13.9)	80 (13.8)	0.97
Oral	841 (61.8)	354 (61.3)	
Insulin	332 (24.4)	144 (24.9)	
Proteinuria, n (%)	440 (31.7)	227 (37.2)	0.02
Age of diabetic onset (years)	53.6±9.7	56.2±10.7	<0.001
Interval between treatment and diagnosis (years)	1.2±3.1	1.2±3.1	0.68
Duration of diabetes (years)	7.6±5.9	8.0±6.3	0.20
FPG (mmol/L)	9.2±3.3	9.7±3.7	0.01
HbA1c (%)	7.7±2.0	7.9±2.2	0.07
BMI (kg/m^2)	26.50±3.34	26.17±3.64	0.053
WHR	0.97±0.06	0.96±0.07	0.13
SBP (mm Hg)	148.2±22.5	147.1±25.3	0.36
DBP (mm Hg)	77.5±11.3	76.4±11.8	0.056
Serum creatinine (μmol/L)	83.6±18.8	88.0±21.2	<0.001
Blood urea nitrogen (mmol/L)	6.21±3.42	6.35±2.45	0.30
Blood uric acid (μmol/L)	306.9±84.2	315.7±94.8	0.049
Total cholesterol (mmol/L)	5.46±1.12	5.65±1.50	0.005
Total triglycerides (mmol/L)	2.21±1.68	2.18±1.62	0.73
LDL (mmol/L)	3.21±0.89	3.32±1.06	0.01
HDL (mmol/L)	1.50±0.37	1.45±0.37	0.01
CRAE (μm)	144.8±18.3	145.3±30.9	0.73
CRVE (μm)	227.9±28.7	221.0±37.0	<0.001

BMI, body mass index; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; WHR, waist:hip ratio.

(25.0%) patients exhibited bilateral DR (bilateral mild NPDR in 14 and bilateral moderate NPDR in 2). The multivariable-adjusted model showed that the incidence of DR was associated with longer diabetes duration (RR 1.95, 95% CI 1.09 to 3.50, for ≥10 years vs <5 years), higher HbA1c level (RR 2.95, 95% CI 1.54 to 5.67, for ≥9% vs <7%), higher systolic blood pressure (SBP) (RR 2.19, 95% CI 1.12 to 4.30, for ≥170 mm Hg vs <140 mm Hg), presence of proteinuria (RR 1.94, 95% CI 1.19 to 3.17) and wider CRVE (RR 2.17, 95% CI 1.09 to 4.32) for ≥250 μm vs <210 μm).

Among the 630 patients with DR at baseline, 107 (17.0%, 95% CI 14.1% to 19.9%) had ≥2 steps of DR progression over a mean follow-up interval of 21.6±3.0 months. The age-and sex-standardised incidence of progression was 26.8% (95% CI 24.8% to 28.8%) or 14.9% person-year. The crude incidences of progression were 19.8% (95% CI 14.9% to 24.7%) and 15.1% (95% CI 11.5% to 18.7%) for male and female patients, respectively (p=0.13). The corresponding age-standardised incidences were 24.5% (95% CI 19.2% to 29.8%) and 28.3% (95% CI 23.7% to 32.8%). When stratified according to severity, 23 (21.5%) patients exhibited mild NPDR with newly developed hard exudates or cotton wool spots (from ETDRS level of 31 to 37); 30 (28.0%) patients progressed to moderate NPDR; 24 (22.5%) patients progressed to severe NPDR; and 30 (28.0%) patients progressed to PDR. The multivariable-adjusted model showed that DR progression was associated with higher FPG (RR 1.73, 95% CI 1.00 to 3.00, for ≥15 mmol/L vs <10 mmol/L), higher serum creatinine level (RR 1.01, 95% CI 1.00 to 1.02, per 1 μmol/L) and wider CRVE (RR 2.00, 95% CI 1.02 to 3.96, for ≥250 μm vs <210 μm) (table 3).

One hundred fourteen patients had ≥2 steps of DR regression, yielding a crude incidence of 18.1% (95% CI 15.1% to 21.1%). The age- and sex-standardised incidence of regression was 10.0% (95% CI 8.6% to 11.3%) or 5.5% person-year. The crude incidences of regression were 16.2% (95% CI 11.7% to 20.7%) and 19.4% (95% CI 15.2% to 23.4%) for male and female patients, respectively (p=0.31). The corresponding age-standardised incidences were 9.2% (95% CI 5.7% to 12.8%) and 10.5% (95% CI 7.4% to 13.6%). When stratified according to severity, 15 (13.2%) patients regressed to moderate NPDR; 36 (31.6%) patients regressed to mild NPDR; and 63 (55.2%) patients regressed to no DR. The multivariable-adjusted model showed that DR regression was negatively associated with insulin use (RR 0.64, 95% CI 0.43 to 0.97) and higher education level (RR 0.47, 95% CI 0.31 to 0.69, for middle/high school level vs primary or lower), and positively associated with wider CRAE (RR 1.14, 95% CI 1.02 to 1.26, per 10 μm increase) (table 4).

DISCUSSION

In this prospective community-based study, we provided comprehensive data on the incidence, progression and regression of DR in a large cohort of patients with type 2diabetes. The age-standardised and sex-standardised incidence of DR was 5.8%, or 3.3% person-year. The incidence the present study was comparable with the incidences previously reported in Caucasian populations, such as a 5-year incidence of 22.2% in the BMES,[6] and a 6-year incidence of 22% in the UK Prospective Diabetes Study (UKPDS).[11] However, it was lower than the incidence among insulin-treated patients aged <30 years (10-year incidence of 89.3% in the WESDR).[5] With respect to Asian populations, the incidence in the present study was also similar to the incidences in population-based studies of Singapore Indians (6-year incidence of 21.89%[13] and Indians living in urban India (4-year incidence of 9.25%,[20] as well as the incidence in a hospital-based study of Korean patients (3.21% person-years[21]); it was slightly lower than the incidence in a hospital-based study of Japanese patients (5-year incidence of 22.2%.[22] With respect to Chinese populations (table 5), the incidence in the present study was higher than the incidences in a community-based study in northeastern China (1.81% person-year[10]) and a general population in Beijing (10-year incidence of 4.2%[14] ; it was lower than the incidences in Hong Kong (4.2-year incidence of 20.3%[23]), Taiwan (6.62% person-year[8]) and a community study in east China (5-year incidence of 46.89%).[9]

The present study found a very high incidence of DR progression (≥2 steps): 26.8% or 14.9% person-year. This incidence

Table 2 Incidence of diabetic retinopathy onset by different risk factors

	At risk (n)	Incidence, % (95% CI)	Age, sex-adjusted RR (95% CI)	P value	Multivariate RR (95% CI)	P value
Age (years)	–	–	0.99 (0.97 to 1.02)	0.62	0.99 (0.96 to 1.02)	0.55
Sex*						
Male	323	5.4 (3.0 to 7.9)	Reference		Reference	
Female	439	6.1 (3.8 to 8.3)	0.95 (0.59 to 1.53)	0.84	1.21 (0.72 to 2.02)	0.46
Duration of diabetes (years)						
<5	383	6.5 (4.1 to 9.0)	Reference		Reference	
5–10	237	8.4 (4.9 to 12.0)	1.32 (0.74 to 2.36)	0.34	1.13 (0.66 to 1.96)	0.65
≥10	142	13.4 (7.8 to 19.0)	2.13 (1.19 to 3.81)	**0.01**	1.95 (1.09 to 3.50)	**0.02**
FPG (mmol/L)						
<9	526	7.6 (5.3 to 9.9)	Reference		Reference	
9–12	150	8.0 (3.7 to 12.3)	1.05 (0.57 to 1.95)	0.87	0.57 (0.30 to 1.07)	0.08
≥12	81	14.8 (7.1 to 22.5)	1.95 (1.03 to 3.68)	**0.04**	0.72 (0.34 to 1.54)	0.40
HbA1c (%)						
<7	361	5.5 (3.2 to 7.9)	Reference		Reference	
7–9	273	9.2 (5.7 to 12.6)	1.65 (0.94 to 2.90)	0.08	1.68 (0.95 to 2.97)	0.07
≥9	123	15.5 (9.1 to 21.8)	2.79 (1.55 to 5.02)	**<0.001**	2.95 (1.54 to 5.67)	**0.001**
Current smoking						
No	575	7.7 (5.5 to 9.8)	Reference		Reference	
Yes	171	11.7 (6.9 to 16.5)	1.64 (0.96 to 2.80)	0.07	1.69 (0.96 to 2.95)	0.07
SBP (mmHg)						
<140	343	7.3 (4.5 to 10.0)	Reference		Reference	
140–170	331	8.2 (5.2 to 11.1)	1.15 (0.68 to 1.96)	0.60	1.05 (0.61 to 1.80)	0.85
≥170	88	13.6 (6.5 to 20.8)	2.00 (1.03 to 3.90)	**0.04**	2.19 (1.12 to 4.30)	**0.02**
Proteinuria						
No	567	6.7 (4.6 to 8.8)	Reference		Reference	
Yes	193	13.5 (8.7 to 18.3)	2.02 (1.26 to 3.23)	**0.003**	1.94 (1.19 to 3.17)	**0.01**
CRVE (μm)						
<210	207	6.8 (3.3 to 10.2)	Reference		Reference	
210–250	444	7.7 (5.2 to 10.1)	1.13 (0.61 to 2.08)	0.70	1.10 (0.59 to 2.04)	0.76
≥250	103	15.5 (8.5 to 22.5)	2.28 (1.15 to 4.52)	**0.02**	2.17 (1.09 to 4.32)	**0.03**
Total†	762	5.8 (4.7 to 6.9)	–	–	–	–

Bold values denote p<0.05.
*Age-standardised prevalence.
†Age-standardised and sex-standardised prevalence. Both were standardised to the year 2010 China population census data.
RR, relative risk; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin A1c; SBP, systolic blood pressure; CRVE, central retinal vein equivalent.

was higher than incidences in Caucasian populations (also ≥2 steps), such as a 5-year incidence of 15.1% in the BMES,[6] a 6-year incidence of 29% in the UKPDS[11] and a 10-year incidence of 76% among insulin-treated patients aged <30 years in the WESDR[5]; it was also higher than incidences in Singapore Indians (6-year incidence of 33.45%)[13] and in Indians living in urban India (4-year incidence of 12.61%).[20] With respect to Chinese populations, including studies with different definitions of DR progression, the present study had a higher incidence of DR progression than the incidences in Hong Kong (4-year incidence of 34.7% for ≥2 steps),[23] Beijing (5-year incidence of 35.3% in patients with known diabetes)[24] and Taiwan (4-year incidence of 30% in non-insulin-treated patients).[25]

The variations among studies in Chinese populations are presumably related to the use of different methodologies, particularly concerning the definition of DR. For example, fundus fluorescence angiography (FFA) was used to confirm the presence and severity of DR for suspected patients in the Beixinjing community of Shanghai.[9] The high sensitivity of FFA for DR diagnosis may have led the previous study to report the highest incidence of DR in a Chinese population (5 year incidence of 46.89%).[9] Additionally, the definition of DR in this study was more strictly (ETDRS level >31) than that in Beijing Eye Study and the study in Hong Kong (ETDRS≥20).[14 23 24] Age criterion for patients may have also influenced the observed incidence. Among previous investigations, the Beixinjing study included younger patients (≥19 years),[9] while the Fengyutan study was limited to older patients (≥60 years).[10] Two more points regarding the variations should be addressed. One is that we reported both the crude and age/sex-standardised incidences, while most previous studies only reported crude incidences.[8–10 14 23–25] The other one is that the Beijing Eye Study reported a low DR incidence because it focused on the general population rather than on patients with diabetes.[14]

Despite differences in ethnicity, methodology and age criterion, the present study demonstrated a high incidence of DR progression. There were several possible reasons for this finding. First, analysis of six fundus fields may be beneficial for detection of peripheral lesions. Only this study used six fundus fields, while most other longitudinal studies on Chinese used two fields or even a single field (table 5). Second, participants in our study tended to have more severe diabetes. Compared with previous investigations, participants in this study had a comparatively longer duration of diabetes (7.6 years vs 5.29 years in urban Indians[20] or 5.04 years in northeast Chinese with diabetes[10]), higher baseline FPG (9.2 mmol/L vs 8.20 mmol/L in urban Indians[20] or 5.14 mmol/L in northeast Chinese with diabetes[10]), and higher proportion of insulin use (24.4% vs

Table 3 Incidence of diabetic retinopathy progression by different risk factors

	At risk (n)	Incidence, % (95% CI)	Age, sex-adjusted RR (95% CI)	P value	Multivariate RR (95% CI)	P value
Age (years)	–	–	0.98 (0.95 to 1.00)	**0.03**	0.98 (0.96 to 1.01)	0.13
Sex*						
Male	253	24.5 (19.2 to 29.8)	Reference		Reference	
Female	377	28.3 (23.7 to 32.8)	0.81 (0.57 to 1.14)	0.22	1.09 (0.75 to 1.60)	0.65
FPG (mmol/L)						
<10	294	11.6 (7.9 to 15.2)	Reference		Reference	
10–15	176	16.5 (11.0 to 22.0)	1.38 (0.87 to 2.18)	0.17	1.23 (0.73 to 2.08)	0.44
≥15	158	27.2 (20.3 to 34.2)	2.17 (1.44 to 3.28)	**<0.001**	1.73 (1.00 to 3.00)	**0.049**
HbA1c (%)						
<7	183	12.0 (7.3 to 16.7)	Reference		Reference	
7–9	239	13.8 (9.4 to 18.2)	1.09 (0.66 to 1.81)	0.72	0.82 (0.48 to 1.41)	0.47
≥9	205	24.9 (19.0 to 30.8)	1.89 (1.20 to 2.99)	**0.006**	1.30 (0.74 to 2.29)	0.37
Income level						
Low	253	21.3 (16.3 to 26.4)	Reference		Reference	
Moderate	342	12.9 (9.3 to 16.4)	0.66 (0.45 to 0.95)	**0.03**	0.76 (0.53 to 1.10)	0.15
High	20	15.0 (–0.6 to 30.6)	0.80 (0.28 to 2.34)	0.69	1.17 (0.41 to 3.32)	0.77
Serum creatinine (µmol/L)	–	–	1.01 (1.00 to 1.02)	0.07	1.01 (1.00 to 1.02)	**0.01**
Proteinuria						
No	381	15.0 (11.4 to 18.5)	Reference		Reference	
Yes	247	20.2 (15.2 to 25.3)	1.34 (0.95 to 1.88)	0.10	1.18 (0.83 to 1.68)	0.36
CRAE (µm)						
<140	223	13.9 (9.4 to 18.4)	Reference		Reference	
140–150	158	17.7 (11.8 to 23.7)	1.29 (0.81 to 2.06)	0.28	1.13 (0.70 to 1.84)	0.61
≥150	244	19.7 (14.7 to 24.7)	1.50 (0.99 to 2.27)	0.06	1.38 (0.90 to 2.11)	0.14
CRVE (µm)						
<210	103	9.7 (4.0 to 15.4)	Reference		Reference	
210–250	337	15.7 (11.8 to 19.6)	1.54 (0.81 to 2.91)	0.18	1.43 (0.73 to 2.81)	0.30
≥250	185	23.8 (17.6 to 29.9)	2.28 (1.21 to 4.33)	**0.01**	2.00 (1.02 to 3.96)	**0.045**
Total†	630	26.8 (24.8 to 28.8)	–	–	–	–

Bold values denote p<0.05.
*Age-standardised prevalence.
†Age and sex-standardised prevalence. Both were standardised to the year 2010 China population census data.
CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin A1c; RR, relative risk.

8.25% in Singapore Indians[13] or 14.0% in the Japan Diabetic Complication Study.[26] Furthermore, a subset of patients began to use insulin after the baseline examination, which was hypothesised to have dual influence on the inner blood–retinal barrier.[27] Third, participants in this study generally had more severe systemic comorbidities. Compared with previous investigations, participants in this study had higher SBP (148.1 mm Hg vs 138.84 mm Hg in Singapore Indians[13] or 122.9 mm Hg in northeast Chinese with diabetes[10]) and a higher proportion of metabolic syndrome (88.0% vs 79.5% in Koreans[28] or 73.8% in Indians[29]) which were associated with the presence of DR among female participants in this study cohort.[30]

The concomitant low incidence of DR onset and high incidence of progression in the same population are suggestive of distinct aetiologies for DR onset and progression, although the exact mechanisms are unclear. Another explanation may be due to different systemic conditions between these two subgroups. For example, patients with DR had an apparently higher HbA1c level (mean 8.2% vs 7.3%) and SBP (mean 152.8 mm Hg vs 144.4 mm Hg) than patients without DR. Poor blood glucose control is a critical risk factor for DR onset and progression in this population, as previously reported.[11–13] For example, patients with HbA1c of ≥9% were nearly threefold more likely to develop DR than patients with HbA1c of <7%; patients with FPG of ≥15 mmol/L were 1.73-fold more likely to exhibit DR progression in our study. Another important risk factor for both DR onset and progression in our study was the CRVE: patients with CRVE of ≥250 µm had an approximately twofold greater risk of DR onset or progression than did patients with CRVE of <210 µm. Among African–Americans with type 1 diabetes, Roy *et al* found that larger CRVE was an independent indicator of progression to either PDR (levels 10/10 through 65/65) or PDR with high-risk characteristics (levels 71+/<71 or worse).[31] Similar results were found in the WESDR, such that a 10 µm increase in CRVE was associated with 6-year incidence of DR, progression of DR, incidence of PDR and incidence of macular oedema.[32] The reason may be the increasing retinal blood flow (law of Hagen-Poiseuille),[33] increasing capillary leakage (Starling and Laplace's law),[34] or chronic retinal hypoxia and inflammation.[35]

The phenomenon of DR regression has been observed in clinical practice, and a high-quality randomised placebo-controlled trial suggested that the angiotensin receptor blocker candesartan could promote DR regression in patients with type 2 diabetes.[36] However, the natural incidence of regression has rarely been reported.[9 20 23 37] Among studies with different definitions, the incidence of DR regression has ranged from 4 years of 1.79% in urban Indians,[20] 4.2 years of 13.2% in Hong Kong[23] and 5 years of 24.12% in the Beixinjing community of Shanghai (table 5).[9] The present study reported a high standardised incidence of 10.0% (or 5.5% person-year). However, when using a similar definition to that of the Beixinjing

Table 4 Incidence of diabetic retinopathy regression by different risk factors

	At risk (n)	Incidence, % (95% CI)	Age, sex-adjusted RR (95% CI)	P value	Multivariate RR (95% CI)	P value
Age (years)	–	–	1.03 (1.01 to 1.05)	**0.001**	1.01 (0.99 to 1.03)	0.52
Sex*						
Male	253	9.2 (5.7 to 12.8)	Reference		Reference	
Female	377	10.5 (7.4 to 13.6)	1.13 (0.80 to 1.60)	0.49	0.97 (0.68 to 1.37)	0.86
Duration of diabetes (years)	–	–	0.97 (0.95 to 1.00)	**0.03**	0.99 (0.96 to 1.02)	0.42
FPG (mmol/L)	–	–	0.95 (0.90 to 1.00)	0.06	0.97 (0.90 to 1.03)	0.33
HbA1c (%)	–	–	0.92 (0.85 to 1.01)	0.08	0.97 (0.87 to 1.08)	0.56
Insulin						
No	394	22.1 (18.0 to 26.2)	Reference		Reference	
Yes	225	12.0 (7.8 to 16.2)	0.58 (0.39 to 0.87)	**0.008**	0.64 (0.43 to 0.97)	**0.04**
Education						
Primary or lower	92	37.0 (27.1 to 46.8)	Reference		Reference	
Middle/high school	444	14.4 (11.1 to 17.7)	0.44 (0.29 to 0.65)	**<0.001**	0.47 (0.31 to 0.69)	**<0.001**
College and above	85	18.8 (10.5 to 27.1)	0.55 (0.31 to 0.98)	**0.04**	0.59 (0.34 to 1.03)	0.07
CRAE (10 µm)	–	–	1.12 (1.01 to 1.24)	**0.04**	1.14 (1.02 to 1.26)	**0.02**
Total†	630	10.0 (8.6 to 11.3)	–	–	–	–

Bold values denote p<0.05.
*Age-standardised prevalence.
†Age and sex-standardised prevalence. Both were standardised to the year 2010 China population census data.
CRAE, central retinal artery equivalent; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; RR, relative risk.

community study, only 63 participants (crude 10.0%, standardised 5.3%) regressed to no DR in the present study. Furthermore, we found that patients without insulin usage and with wider CRAE were more likely to exhibit DR regression. Regarding insulin use, patients with insulin use may exhibit more severe diabetes-related conditions (including retinopathy), but there is increasing research (as well as the baseline data of FS-DIRECT) to suggest that insulin usage might contribute to diabetic macular oedema onset and DR progression.[27 38 39] The underlying mechanism may involve its similar mediated effects for growth hormones (which have demonstrated strong relation with DR progression) and proliferation effect on retinal cells (eg, glia, retinal pigmental epithelial cells and fibroblast-like cells), when the inner blood–retinal barrier was impaired.[27] Similarly, patients with narrower CRAE may exhibit more severe DR or lower oxygen saturation.[40 41] It should be noted that baseline DR severity was not associated with progression or regression of DR (data not shown).

A notable strength of this study was its large sample size and use of standard examinations (eg, six fundus fields and use of the ETDRS photography grading protocol to assess DR). Another strength was that we provided comprehensive follow-up data regarding DR incidences, as well as their corresponding risk factors. However, there were some important limitations. First, the mean follow-up interval of 21.3 months was insufficient to fully characterise this complex and almost lifetime evolving disease. Second, questionnaires were not collected at the follow-up visit. Hence, important factors (eg, current condition of medication) were unknown.

Table 5 Summary of incidence and progression of DR in Chinese populations

Name/place of study	Age (years)	Sample size	Design	Follow-up years	Photography	Classification	Incidence (%)	Progression (%)	Regression (%)
Fengyutan community, Shenyang (10)	60–84	548	CB	4	Not mentioned	ETDRS	1.81 person-year	–	–
Beijing Eye Study (18)	≥40	2602	PB	10	Two fields	ETDRS	4.2	–	–
Beixinjing community, Shanghai (9)	≥19	778	CB	5	Two fields (screening), FFA (for suspect)	ICDR	46.89	–	24.12
Beijing Eye Study (20)	≥40	170	PB	5	Two fields	ETDRS	–	35.3	–
Hong Kong (19)	20–77	354	HB	4.2	Two fields	ETDRS	20.3	34.7	13.2
Kinmen, Taiwan (8)	≥30	725	CB	2.56	Indirect ophthalmoscopy and single field	DRDSC	6.62 per year	–	–
Taiwan (21)	≥40	471	Healthcare centres	4	Direct/indirect ophthalmoscopy	No DR, BDR, PPDR, PDR	19.2	30	–
FS-DIRECT	≥30	1389	CB	1.8	Six fields	ETDRS	5.8*	26.8*	10.0*

*Data presented as age-standardised and sex-standardised.
BDR, background diabetic retinopathy; CB, community-based; DR, diabetic retinopathy; DRDSC, diabetic retinopathy disease severity scale; FFA, fundus fluorescence angiography; FS-DIRECT, fushun diabetic retinopathy cohort study; HB, hospital-based; ICDR, international clinical diabetic retinopathy and diabetic macular oedema disease severity scale; PB, population-based; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy.

In conclusion, this study reported comprehensive incidences and risk factors of DR onset, progression and regression among north-eastern Chinese patients with type 2 diabetes. Poor blood glucose control and wide CRVE were risk factors for both DR onset and progression, while wide CRAE and a lack of insulin therapy were factors associated with DR regression.

Contributors YW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: ZL, LW and YW. Acquisition, analysis or interpretation of data: ZL, LW, DL and GZ. Drafting of the manuscript: ZL and NM. Critical revision of the manuscript for important intellectual content: all authors. Administrative, technical or material support: YW, YL and FW. Study supervision: YW. YW is the guarantor.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Fushun Eye Hospital Ethics Committee (ID number FSKJHT201025). The participants gave informed consent to participate in the study before taking part. Both baseline and follow-up studies were conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants; patients who were unable to read or write were asked to indicate consent using a right forefinger stamp.

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