• Investigation •

The relationship between insulin resistance/β-cell dysfunction and diabetic retinopathy in Chinese patients with type 2 diabetes mellitus: the Desheng Diabetic Eye Study

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Abstract

• AIM: To investigate the relationship between insulin resistance (IR)/β-cell dysfunction and diabetic retinopathy (DR) in Chinese patients with type 2 diabetes mellitus (T2DM), and to explore further whether there were differences in the relationship among diabetic patients with higher and lower body mass index (BMI).

• METHODS: Cross-sectional study. A total of 1466 subjects with T2DM were recruited in a local Desheng Community of urban Beijing from November 2009 to June 2012 for the cohort of Beijing Desheng Diabetic Eye Study. Standardized evaluation was carried out for each participant, including questionnaire, ocular and anthropometric examinations, and laboratory tests. Seven fields 30° color fundus photographs were used for DR grading according to the Early Treatment Diabetic Retinopathy Study protocols. Homeostatis Model Assessment (HOMA) method was employed for IR and β-cell function assessment.

• RESULTS: After excluding those participants who were treated with insulin (*n*=352) or had missing data of fasting insulin (*n*=96), and further excluding those with poor quality of retinal photographs (*n*=10), a total of 1008 subjects were included for the final analysis, 406 (40.3%) were men and 602 (59.7%) were women, age ranging from 34 to 86 (64.87±8.28)y. Any DR (levels 14 and above) was present in 278 (27.6%) subjects. After adjusting for possible covariates, the presence of any DR did not correlate with HOMA IR [odds ratio (OR) 1.51, 95% confidence interval (CI) 0.87-2.61, *P*=0.14] or HOMA β-cell (OR 0.71, 95%CI 0.40-1.26, *P*=0.25). After stratification by BMI, the presence of any DR was associated positively with HOMA IR (OR 2.46, 95%CI: 1.18-5.12, *P*=0.016), and negatively with HOMA β-cell (OR 0.40, 95%CI: 0.19-0.87, *P*=0.021) in the group of patients with higher BMI (≥25 kg/m^2). In the group of patients with lower BMI (<25 kg/m^2), the presence of any DR was not associated with HOMA IR (OR 1.00, 95%CI: 0.43-2.33, *P*=1.00) or HOMA β-cell (OR 1.41, 95%CI: 0.60-3.32, *P*=0.43).

• CONCLUSION: The data suggest that higher IR and lower β-cell function are associated with the presence of DR in the subgroup of diabetic patients with higher BMI. However, this association is not statistically significant in diabetic patients with lower BMI.

• KEYWORDS: type 2 diabetes mellitus; diabetic retinopathy; insulin resistance; β-cell function; body mass index

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INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus and the leading cause of blindness in working age adults, accounting for 8% of the legal blindness in China[1]. Despite intensive studies, the precise mechanism still remains obscure. Longer duration of diabetes[2-3] and poor glycemic control[4] are established risk factors for the development and progression of DR. Early detection and timely treatment of DR could effectively reduce the risk of severe vision loss[5].

Insulin resistance (IR) and pancreatic β-cell dysfunction are two primary determinants of glucose metabolism disorder in type 2 diabetes mellitus (T2DM)[6-7]. The consequent hyperglycemia is closely associated with microvascular complications[8]. Improved understanding about the role of IR and β-cell dysfunction in DR may provide insights for

DR prevention at the early stage of T2DM. Several studies have explored the associations between IR/β-cell dysfunction and DR in diabetic patients[9-14]. To date, the relative role of impaired IR and β-cell insulin secretion in the development of DR still remains controversial. In addition, the contributions of IR and β-cell dysfunction to T2DM may be different for obese and non-obese patients as previously reported[15-16]. However, whether the role of IR and β-cell dysfunction in DR differs for obese and non-obese patients is not clear.

The present study aimed to investigate the relationship between IR/β-cell dysfunction and DR in a community-based cohort of Chinese patients with T2DM, and to further explore whether there were differences in the relationship among patients with higher and lower body mass index (BMI).

SUBJECTS AND METHODS

Patient Recruitment and Selection Criteria Patients with T2DM aged 30y or above, as identified from an age-related eye disease screening program in the Desheng Community of urban Beijing, were recruited for the cohort of Beijing Desheng Diabetic Eye Study between November 2009 and June 2012 by using posters, pamphlets, and phone calls. The details of the study have been described elsewhere[17]. Cross-sectional baseline data was used for the current study.

Diabetes was defined as either a history of physician diagnosed T2DM being treated with insulin, oral hypoglycemic agents, or diet only, or by a fasting plasma glucose (FPG) concentration of 7.0 mmol/L (126 mg/dL) or more in at least two previous examinations or a random plasma glucose concentration of ≥11.1 mmol/L (200 mg/dL). The duration of diabetes was defined as the interval between the first definite diagnosis and the time of enrollment into the study. Participants who were treated with insulin, with severe media opacity preventing the classification of retinopathy, with shallow anterior chamber or angle-closure glaucoma preventing mydriasis were excluded for the current study.

The study protocol was approved by the Ethics Committee of the Beijing Tongren Hospital (No.TRECKY2009-07) and adhered to the Helsinki Declaration of medical research. Verbal and written informed consent from the subjects was obtained prior to any investigations.

Questionnaire, Anthropometric and Laboratory Measurements A comprehensive interview using an interviewer-guided questionnaire was conducted by trained staffs collecting data related to potential risk factors for DR, including basic demographic and lifestyle information (such as age, sex, income, educational level, smoking history), and medical history (such as medication, the use of insulin, and history of systemic diseases). Persons currently smoking more than one cigarette/cigar/pipe a day for at least one year were defined as current smokers. Anthropometric parameters included body weight and height, waist circumference and hip circumference. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in a resting state three times with 5min apart. Hypertension was diagnosed when SBP≥140 mm Hg and/or DBP≥90 mm Hg according to World Health Organization criteria[18], or history of hypertension diagnosed by a doctor, and/or reporting of anti-hypertensive treatment. Height and weight were measured with subjects in light clothing and not wearing shoes by a trained observer. The waist circumference was taken by placing a non-stretchable measuring tape horizontally on the midpoint between the lower part of the 12th rib and the top of the iliac crest, under the mid-axillary line. To the hip circumference, a similar tape was positioned to the maximum circumference around the buttocks, with the subject standing straight, keeping hands by the sides, and facing palms inward. BMI was calculated as weight divided by height squared (kg/m^2). Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

Overnight fasting blood samples were collected for measurements of FPG, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), creatinine, uric acid, total cholesterol (TC), triglycerides (TG), high-density cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) and fasting insulin (FINS). The samples were allowed to stand at room temperature for 30min for coagulation and serum was obtained by centrifugation. The level of FINS was measured through radioimmunoassay using an automated system (Hitachi analyzer 7080, Japan). A first-void, midstream morning spot urine sample was collected, and albuminuria was measured by immunonephelometry (Roche/Cobas C501 analyzer, Ibaraki, Japan), and high albuminuria was defined as ≥20 mg/L[19].

Diabetic Retinopathy Grading One trained ophthalmologist (Yang XF) graded all the images in a masked manner at the University of Wisconsin Fundus Photographic Reading Center, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) standard classification. Retinopathy was considered present if any characteristic lesions as defined by the ETDRS severity grading scale were present, including microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading and new vessels[20]. A retinopathy severity score was assigned for each eye according to the ETDRS Diabetes Retinopathy Severity Scale and the score of the worse eye was used for analysis. Eyes were graded according to the following criteria: no DR (NDR, level 10) or any DR (levels 14 and above). Any DR was further divided into mild (levels 14-35), moderate (levels 43-47), and severe DR (level 53 and above). Grading reproducibility was assessed by regrading 5% of the eyes by a senior grader at the University of Wisconsin Fundus Photograph Reading Center. Exact agreement on retinopathy level was 86% and Weighted Kappa was 0.82[21], which are

in agreement with published reproducibility from the reading center[22].

Assessment of Insulin Resistance and β-cell Function The Homeostatis Model Assessments (HOMA) were employed for evaluating IR (marked as HOMA IR) and β-cell function (marked as HOMA β-cell)[23]. The detailed calculation was done by the following formula: HOMA IR=FPG (mmol/L)× FINS (mU/L)/22.5, HOMA β-cell=20×FINS (mU/L)/[FPG (mmol/L)-3.5][23]. Since the HOMA model is not suitable for T2DM cases treated with insulin[12], these were excluded from the present study.

Statistical Analysis Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as numbers (%) for categorical variables, mean±standard deviation (SD) for normally distributed variables. Variables with a skewed distribution were expressed as medians, the lower and upper quartiles. Differences in clinical characteristics of participants with or without DR were compared using independent sample *t*-tests or Mann-Whitney *U* test for continuous variables as appropriate, and Chi-square test for categorical variables. Selected indexes of the population stratified by HOMA IR or HOMA β-cell quartiles were analyzed with ANOVA or Kruskal-Wallis *H* test for continuous variables as appropriate and Chi-squared tests for categorical variables. Multiple logistic regression model was adopted to investigate whether HOMA IR and HOMA β-cell were independently associated with the presence of DR after adjusting for the potential confounding factors. Results were expressed as odds ratio (OR), 95% confidence intervals (CI) and *P* value. *P* value less than 0.05 was considered as statistically significant.

RESULTS

A total of 1466 subjects with T2DM were recruited from a local Desheng Community of urban Beijing for the cohort of Beijing Desheng Diabetic Eye Study. After excluding those participants who were treated with insulin (*n*=352) or had missing data of FINS (*n*=96), and further excluding those with poor quality of retinal photographs (*n*=10), a total of 1008 subjects were included for the final analysis. Of the 1008 subjects, 406 (40.3%) were men and 602 (59.7%) were women, mean age was 64.87±8.28y, ranging from 34 to 86y. Any DR (levels 14 and above) was diagnosed in 27.6% (*n*=278) subjects, of which 253 (25.1%) had mild (levels 14-35), 12 (1.2%) had moderate (levels 43-47), and 13 (1.3%) had severe (levels 53 and above) DR.

Baseline characteristics of the study population were shown in Table 1. Compared with the group of NDR, persons diagnosed with any DR were more likely to be male (*P*=0.004), had a lower level of monthly income (*P*=0.03), longer duration of diabetes (*P*<0.001), younger age when DM onset (*P*<0.001), more likely to be current smoker (*P*=0.01) and have high albuminuria (*P*=0.004). Moreover, DR persons were found to have higher levels of SBP (*P*=0.002), DBP (*P*=0.036), creatinine (*P*=0.01), FPG (*P*<0.001), HbA1c (*P*<0.001) and HOMA IR (*P*=0.028), but lower levels of CRP (*P*=0.048), TG (*P*=0.045) and HOMA β-cell (*P*=0.005).

Table 2 showed the selected parameters of the study participants stratified by quartiles of HOMA IR value. In unadjusted analyses of quartiles, increased HOMA IR was associated with higher levels of BMI (*P*<0.001), WHR (*P*<0.001), SBP (*P*=0.002), DBP (*P*<0.001), CRP (*P*<0.001), FPG (*P*<0.001), TG (*P*<0.001), HbA1c (*P*<0.001), FINS (*P*<0.001), high albuminuria (*P*=0.032), and lower HDL-C (*P*<0.001).

Table 3 showed the selected parameters of the study participants stratified by quartiles of HOMA β-cell value. In unadjusted analyses of quartiles, decreased HOMA β-cell was associated with younger age when DM onset (*P*<0.001), longer T2DM duration (*P*<0.001), current smoking (*P*=0.001), lower levels of BMI (*P*<0.001), WHR (*P*=0.011), FINS (*P*<0.001), creatinine (*P*<0.001), uric acid (*P*<0.001), and higher levels of SBP (*P*=0.01), DBP (*P*=0.002), CRP (*P*=0.034), FPG (*P*<0.001), TC (*P*<0.001), LDL-C (*P*=0.021), and HbA1c (*P*<0.001).

Table 4 showed the independent associations between baseline HOMA IR/HOMA β-cell and the presence of any DR by multiple logistic regression. After adjusting for confounding factors including established risk factors and variables with *P*≤0.2 as shown in Table 1 (sex, monthly income, education, DM duration, age when DM onset, current smoking, BMI, SBP, DBP, CRP, creatinine, TG, HbA1c, high aluminuria), when all participants were pooled together, the presence of any DR was not correlated with HOMA IR (OR 1.51, 95%CI: 0.87-2.61, *P*=0.14) or HOMA β-cell (OR 0.71, 95%CI 0.40-1.26, *P*=0.25).

According to the cut-off value of obesity for Asians (BMI≥25 kg/m^2)[24], the subjects were divided into groups of BMI≥25 kg/m^2 (*n*=528) and BMI<25 kg/m^2 (*n*=480) (Table 4), and any DR was diagnosed in 151 (28.6%) and 127 (26.5%) subjects respectively. The level of HOMA IR were significantly different between the group of patients with BMI≥25 kg/m^2 and BMI<25 kg/m^2 (median: 4.82 *vs* 2.98, *P*<0.001), and HOMA β-cell were also significantly different between the two groups (median: 73.70 *vs* 56.64, *P*<0.001). In the group of BMI≥25 kg/m^2, the presence of any DR was associated positively with HOMA IR (OR 2.46, 95%CI: 1.18-5.12, *P*=0.016) and negatively with HOMA β-cell (OR 0.40, 95%CI: 0.19-0.87, *P*=0.021) after adjustment for covariates. In the group of BMI<25 kg/m^2, the presence of any DR was not associated with HOMA IR (OR 1.00, 95%CI: 0.43-2.33, *P*=1.00) or HOMA β-cell (OR 1.41, 95%CI: 0.60-3.32, *P*=0.43) after adjustment.

Table 1 Characteristics of the study participants with type 2 diabetes mellitus

Variables	NDR (*n*=730)	Any DR (*n*=278)	*P* (any DR *vs* NDR)
Age (y)	65.03±8.21	64.44±8.48	0.32
Sex (male, %)	274 (37.5)	132 (47.5)	0.004
Monthly income lower than 2000 CNY, *n* (%)	224 (30.7)	105 (37.8)	0.03
Education lower than high school, *n* (%)	288 (39.5)	128 (46.0)	0.06
DM duration (y)	6.66±5.17	9.08±6.20	<0.001
Age when DM onset (y)	58.37±8.61	55.36±9.72	<0.001
Current smoking, *n* (%)	89 (12.2)	51 (18.3)	0.01
BMI (kg/m^2)	25.52±3.73	25.51±3.51	0.97
WHR	0.92±0.07	0.92±0.07	0.66
SBP (mm Hg)	133.53±16.33	137.10±16.75	0.002
DBP (mm Hg)	78.10±9.64	79.55±10.22	0.036
CRP (mg/dL)	0.12 (0.05, 0.23)	0.10 (0.05, 0.21)	0.048
Creatinine (mg/dL)	67.97±16.82	71.31±21.76	0.01
Uric acid (μmol/L)	294.47±77.92	291.91±78.30	0.64
FPG (mmol/L)	7.22±1.97	8.05±2.53	<0.001
TG (mmol/L)	1.44 (0.99, 2.05)	1.32 (0.90, 1.98)	0.045
TC (mmol/L)	4.99±0.98	5.05±1.11	0.42
HDL-C (mmol/L)	1.23±0.28	1.25±0.30	0.39
LDL-C (mmol/L)	3.02±0.82	3.07±0.89	0.42
HbA1c (%)	6.50±1.12	7.07±1.55	<0.001
FINS (mU/L)	12.22 (7.31, 18.77)	11.73 (7.62, 19.43)	0.64
High albuminuria, *n* (%)	94 (12.9)	55 (19.8)	0.004
HOMA IR	3.70 (2.16, 6.11)	4.11 (2.37, 6.87)	0.028
HOMA β-cell	72.70 (41.31, 119.76)	58.42 (35.77, 107.14)	0.005

CNY: China Yuan; BMI: Body mass index; WHR: Waist and hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein; FPG: Fasting plasma glucose; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; HbA1c: Glycosylated hemoglobin A1c; FINS: Fasting insulin; HOMA IR: Homeostasis model assessment of insulin resistance; HOMA β-cell: Homeostasis model assessment of β-cell function. The data were expressed as numbers (%) for categorical variables, mean±standard deviation (SD) for normally distributed variables. While variables with a skewed distribution, including Triglycerides, FINS, HOMA IR and HOMA β-cell were expressed as medians, and the lower and upper quartiles. Differences between any DR (diabetic retinopathy) and NDR (no diabetic retinopathy) groups were compared using independent *t*-test or the Mann-Whitney *U* test as appropriate. Differences between proportions were analyzed using Chi-squared test. $P<0.05$ was considered statistically significant.

DISCUSSION

The baseline cross-sectional data from the cohort of Beijing Desheng Diabetic Eye Study suggest that the presence of any DR is associated with higher IR and lower β-cell function in the group of patients with higher BMI (≥25 kg/m^2), but this association was not found in the group of patients with lower BMI (<25 kg/m^2).

T2DM is characterized by peripheral and hepatic IR and/or pancreatic β-cell dysfunction[25]. IR is defined as an inadequate physiological response of peripheral tissues to insulin action, resulting in metabolic and hemodynamic disturbances[26]. IR was also associated with endothelial dysfunction, increased inflammation and cardiovascular disease[27-29]. Meanwhile, pancreatic β-cells can increase the production of insulin to compensate for IR appropriately, and its dysfunction was central to the development and progression of T2DM[30] and microalbuminuria[29]. In our univariate analysis, higher IR and lower β-cell function were associated with a cluster of metabolic abnormalities including obesity, hypertension, dyslipidemia, hyperglycemia and inflammation, which were conventional risk factors for DR.

IR and/or β-cell dysfunction had also been suggested to be related to DR for T2DM patients[9,12,14]. For example, a hospital-based study showed that the presence of DR was associated with a greater tissue resistance to insulin action instead of inadequate insulin secretion[9]. Moreover, a cohort study of newly diagnosed T2DM patients showed that DR was associated with β-cell failure rather than IR[14], and a community-based study suggested that DR was both associated with IR and β-cell dysfunction in T2DM[12]. In this current study, however, we failed to find the association between IR/β-cell dysfunction and the presence of DR after adjusting for

Table 2 Characteristics of the participants with type 2 diabetes mellitus divided by quartiles of HOMA IR

Variables	HOMA IR				*P*
	1st quartile (0.08-2.21) (*n*=253)	2nd quartile (2.22-3.84) (*n*=252)	3rd quartile (3.85-6.27) (*n*=253)	4th quartile (6.28-55.19) (*n*=250)	
Age when DM onset (y)	57.56±8.39	57.39±9.04	57.30±9.24	57.92±9.43	0.88
Sex (male, %)	102 (40.3)	108 (42.9)	96 (37.9)	100 (40.0)	0.24
DM duration (y)	8.97±5.63	7.66±5.62	6.56±5.37	6.12±5.27	<0.001
Current smoking, *n* (%)	32 (12.6)	41 (16.3)	32(12.6)	35 (14)	0.60
BMI (kg/m^2)	24.18±3.76	24.90±3.51	26.07±3.31	26.92±3.49	<0.001
WHR	0.90±0.08	0.92±0.07	0.92±0.07	0.94±0.06	<0.001
SBP (mm Hg)	131.19±15.01	134.85±17.38	136.02±16.07	136.04±17.14	0.002
DBP (mm Hg)	76.26±9.39	78.55±9.73	79.38±9.00	79.81±10.77	<0.001
CRP (mg/dL)	0.09 (0.04, 0.17)	0.09 (0.04, 0.21)	0.13 (0.06, 0.24)	0.16 (0.07, 0.30)	<0.001
Creatinine (mg/dL)	68.29±15.64	69.04±21.45	68.68±16.82	69.57±19.11	0.88
Uric acid (μmol/L)	284.05±76.65	296.67±79.58	297.96±71.41	296.41±83.54	0.15
FPG (mmol/L)	6.33±1.42	7.20±1.77	7.36±1.79	8.92±2.67	<0.001
TG (mmol/L)	1.11 (0.78, 0.58)	1.36 (0.96, 1.95)	1.49 (1.07, 2.15)	1.79 (1.22, 2.33)	<0.001
TC (mmol/L)	4.92±0.99	5.01±1.03	4.99±0.94	5.09±1.10	0.35
HDL-C (mmol/L)	1.33±0.32	1.23±0.30	1.20±0.27	1.17±0.23	<0.001
LDL-C (mmol/L)	2.94±0.82	3.06±0.88	3.05±0.81	3.10±0.87	0.19
HbA1c (%)	6.14±0.80	6.47±1.01	6.68±1.12	7.37±1.70	<0.001
FINS (mU/L)	5.39 (4.28, 6.79)	9.63 (7.97, 11.43)	15.45 (13.32, 18.27)	24.30 (20.26, 31.59)	<0.001
High albuminuria, *n* (%)	24 (9.5)	38 (15.1)	41 (16.2)	46 (18.4)	0.032

HOMA IR: Homeostasis model assessment of insulin resistance; BMI: Body mass index; WHR: Waist and hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein; FPG: Fasting plasma glucose; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; HbA1c: Glycosylated hemoglobin A1c; FINS: Fasting insulin. While variables with a skewed distribution, including CRP, TG and FINS, were expressed as medians, the lower and upper quartiles. Groups were compared using ANOVA or Kruskal-Wallis *H* test as appropriate. $P<0.05$ was considered statistically significant.

Table 3 Characteristics of the participants with type 2 diabetes mellitus divided by quartiles of HOMA β-cell

Variables	HOMA β-cell				*P*
	1st quartile (2.11-39.71) (*n*=252)	2nd quartile (39.72-69.03) (*n*=252)	3rd quartile (69.04-115.83) (*n*=252)	4th quartile (115.84-740.35) (*n*=252)	
Age when DM onset (y)	54.70±8.94	57.26±8.75	58.38±8.68	59.82±8.98	<0.001
Sex (male, %)	109 (43.3)	105 (41.7)	104 (41.3)	88 (34.9)	0.24
DM duration (y)	8.97±5.63	7.66±5.62	6.56±5.37	6.12±5.27	<0.001
Current smoking, *n* (%)	51 (20.2)	40 (15.9)	21 (8.3)	28 (11.1)	0.001
BMI (kg/m^2)	24.68±3.77	25.35±3.17	25.95±3.84	26.07±3.71	<0.001
WHR	0.91±0.08	0.92±0.06	0.93±0.07	0.92±0.07	0.011
SBP (mm Hg)	135.78±15.15	136.38±16.80	134.05±17.09	131.87±16.70	0.010
DBP (mm Hg)	80.07±9.40	79.01±10.40	78.13±9.58	76.78±9.65	0.002
CRP (mg/dL)	0.12 (0.06, 0.24)	0.11 (0.06, 0.22)	0.11 (0.05, 0.24)	0.09 (0.04, 0.22)	0.034
Creatinine (mg/dL)	65.50±15.35	67.90±20.59	69.10±17.96	73.07±18.46	<0.001
Uric acid (μmol/L)	275.13±75.89	292.46±75.37	300.50±79.90	306.96±77.51	<0.001
FPG (mmol/L)	8.98±2.82	7.72±1.79	6.94±1.42	6.16±1.19	<0.001
TG (mmol/L)	1.28 (0.89, 1.92)	1.39 (1.01, 2.04)	1.48 (1.02, 2.04)	1.46 (0.99, 2.07)	0.05
TC (mmol/L)	5.19±1.03	5.04±1.06	4.94±0.95	4.84±0.98	<0.001
HDL-C (mmol/L)	1.26±0.29	1.22±0.30	1.23±0.28	1.24±0.28	0.40
LDL-C (mmol/L)	3.18±0.83	3.02±0.84	2.98±0.82	2.97±0.87	0.021
HbA1c (%)	7.36±1.79	6.74±1.12	6.40±0.90	6.14±0.69	<0.001
FINS (mU/L)	5.73 (4.44, 8.36)	10.27 (7.41, 13.96)	14.45 (10.32, 19.29)	22.92 (16.88, 29.58)	<0.001
High albuminuria, *n* (%)	42 (16.7)	34 (13.5)	42 (16.7)	31 (12.3)	0.51

HOMA β-cell: Homeostasis model assessment of β-cell function; BMI: Body mass index; WHR: Waist and hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein; FPG: Fasting plasma glucose; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; HbA1c: Glycosylated hemoglobin A1c; FINS: Fasting insulin. While variables with a skewed distribution, including CRP, TG and FINS, were expressed as medians, the lower and upper quartiles. Groups were compared using ANOVA or Kruskal-Wallis *H* test as appropriate. $P<0.05$ was considered statistically significant.

Table 4 Multiple logistic regression of association between HOMA IR/β-cell and diabetic retinopathy

Variables	Any DR (yes *vs* no)		
	OR	95%CI	*P*
Total (*n*=1008)			
HOMA IR			
1st quartile (0.08-2.21)	1.00	-	0.47
2nd quartile (2.22-3.84)	1.07	0.68-1.67	0.79
3rd quartile (3.85-6.27)	1.23	0.74-2.03	0.43
4th quartile (6.28-55.19)	1.51	0.87-2.61	0.14
HOMA β-cell			
1st quartile (2.11-39.71)	1.00	-	0.38
2nd quartile (39.72-69.03)	1.10	0.71-1.70	0.67
3rd quartile (69.04-115.83)	0.85	0.52-1.40	0.52
4th quartile (115.84-740.35)	0.71	0.40-1.26	0.25
BMI≥25 kg/m^2 (*n*=528)			
HOMA IR			
1st quartile (0.40-2.81)	1.00	-	0.06
2nd quartile (2.82-4.82)	1.34	0.72-2.48	0.36
3rd quartile (4.83-7.44)	2.19	1.12-4.26	0.022
4th quartile (7.45-28.42)	2.46	1.18-5.12	0.016
HOMA β-cell			
1st quartile (4.24-47.82)	1.00	-	0.08
2nd quartile (47.83-73.70)	0.92	0.52-1.64	0.77
3rd quartile (73.71-127.97)	0.61	0.31-1.21	0.16
4th quartile (127.98-626.36)	0.40	0.19-0.87	0.021
BMI<25 kg/m^2 (*n*=480)			
HOMA IR			
1st quartile (0.08-1.78)	1.00	-	1.00
2nd quartile (1.79-2.98)	0.98	0.49-1.94	0.95
3rd quartile (2.99-4.95)	1.06	0.51-2.24	0.87
4th quartile (4.96-55.19)	1.00	0.43-2.33	1.00
HOMA β-cell			
1st quartile (2.11-33.91)	1.00	-	0.21
2nd quartile (33.92-56.64)	1.24	0.63-2.44	0.53
3rd quartile (56.65-103.14)	0.69	0.31-1.53	0.36
4th quartile (103.15-740.35)	1.41	0.60-3.32	0.43

HOMA IR: Homeostasis model assessment of insulin resistance; HOMA β-cell: Homeostasis model assessment of β-cell function; DR: Diabetic retinopathy; DM: Diabetes mellitus; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein; TG: Triglycerides; HbA1c: Glycosylated hemoglobin A1c. OR: Odds ratio; CI: Confidence interval. Other confounding factors controlled included: sex, monthly income, education, DM duration, age when DM onset, current smoking, BMI, SBP, DBP, CRP, creatinine, TG, HbA1c, high albuminuria. $P<0.05$ was considered statistically significant.

possible covariates when all participants were polled together, whereas the onset of moderate NPDR or above (≥level 43) was associated with HOMA β-cell (OR 0.46, 95%CI: 0.23-0.90, *P*=0.025), but not with HOMA IR (OR 1.43, 95%CI: 0.77-2.67, *P*=0.26). The discrepancies between previous studies and the current study may be attributed to different methods for the assessment of IR/β-cell function and DR severity or racial differences.

The contribution of IR and β-cell dysfunction to T2DM may be different for obese and non-obese patients[15-16]. Elevated BMI has been shown to be an established risk factor for T2DM[31] and diabetic complications[32]. In the subgroup analysis after stratification by BMI, our data suggest that increased IR and decreased β-cell function were statistically significantly associated with the presence of any DR for the group of patients with BMI≥25 kg/m^2, but this association was not found for those with BMI<25 kg/m^2. For obese subjects, pro-inflammatory cytokines are highly expressed in adipose tissue, which contributes to a chronic low-grade inflammation and IR[33-34]. Coincidently, the level of CRP, the most extensively studied biomarker of systemic inflammation, is higher in obese subjects than non-obese subjects in the present study (median: 0.14 mg/dL *vs* 0.09 mg/dL, *P*<0.001). Moreover, adipose tissue exhibits a higher lipolysis rate, which leads to elevated levels of free fatty acids[34]. Higher levels of free fatty acids are known to be involved in the activation of inflammatory pathway, which may further cause IR and β-cell dysfunction[35-36]. We speculate that higher IR together with lower β-cell function may accelerate the development of DR under the low-grade inflammatory environment in diabetic patients with higher BMI. Although β-cell dysfunction was taken as the main etiological factor of T2DM in non-obese patients[16], we failed to show the association between lower β-cell function and DR for participants with lower BMI, suggesting that β-cell dysfunction may not have direct relationship with DR for diabetic patients with lower BMI.

Limitations of the study should be noted. Being a cross-sectional survey, the study explored only the association between IR/β-cell dysfunction and DR for T2DM patients, but a causal relationship cannot be established and needs to be verified in future longitudinal cohort studies. Moreover, the application condition of HOMA model requires exclusion of those participants treated with insulin, therefore only a small number of subjects with severe DR could be included into the study, making it nearly impossible to further analyze the relationship between IR/β-cell dysfunction and DR severity.

In conclusion, our data showed that IR and β-cell dysfunction may be related to the presence of DR for subjects with higher BMI in the studied Chinese patients with T2DM, whereas we failed to find the association in the subgroup of patients with lower BMI, implying that the clinical value of IR and β-cell dysfunction for the risk of DR may need to be evaluated differently for obese and non-obese patients, and hopefully provide personalized early interventions for diabetes with different individual characteristics. Further studies to confirm this observation would be warranted.

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