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ORIGINAL RESEARCH

Association Between Abnormal Glycemic Phenotypes and Microvascular Complications of Type 2 Diabetes Mellitus Outpatients in China

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Purpose: The objective of this study was to investigate the association of abnormal glycemic phenotypes with microvascular complications in type 2 diabetes patients.

Participants and Methods: A total of 24,266 participants who were from the multicenter cross-sectional survey of China National HbA1c Surveillance System across China were included in the present study. Diabetes patients with abnormal glucose were divided into three groups according to phenotype: isolated fasting hyperglycemia (IFH), isolated post-prandial hyperglycemia (IPH), or combined hyperglycemia (CH). The main outcomes were isolated diabetic retinopathy, isolated diabetic nephropathy, and combined diabetic retinopathy with nephropathy. Multivariate logistic regression was used to assess the association of abnormal glycemic phenotypes with microvascular complications.

Results: The CH phenotype had the highest prevalence of isolated diabetic retinopathy, isolated diabetic nephropathy and combined diabetic retinopathy with nephropathy, followed by IPH. Multivariate analysis showed that the CH phenotype was associated with the highest risk of isolated diabetic retinopathy (OR: 1.20, 95% CI: 1.02–1.41), isolated diabetic nephropathy (OR: 1.59, 95% CI: 1.27–2.01) and combined diabetic retinopathy with nephropathy (OR: 1.93, 95% CI: 1.44–2.59). More importantly, participants with IPH phenotype also showed significantly higher risks of isolated diabetic retinopathy (OR: 1.16, 95% CI: 1.05–1.28), isolated diabetic nephropathy (OR: 1.37, 95% CI: 1.09–1.37) and combined diabetic retinopathy with nephropathy (OR:1.64, 95% CI: 1.21–2.21) compared to the IFH phenotype. After stratifying by age, sex, diabetes duration and BMI, the higher risks of isolated diabetic retinopathy, isolated diabetic nephropathy and combined diabetic retinopathy with nephropathy were confirmed in IPH phenotype group, compared to the IFH phenotype group.

Conclusion: Diabetic patients with IPH phenotype had higher risks of isolated diabetic retinopathy, isolated diabetic nephropathy and combined diabetic retinopathy with nephropathy compared with the participants phenotype of IFH, but lower than the phenotype of CH.

Keywords: abnormal glycemic phenotype, diabetic nephropathy, diabetic retinopathy, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) has become a substantial threat to human health in the past decades. According to the estimation from World Health Organization (WHO), the worldwide number of diabetic people would exceed 366 million by 2030.[1] In China, the prevalence of diabetes has also risen from 0.67% in 1980 to 10.9% in 2013[2] and the number is expected to exceed 129.7 million by the year

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2030.[3] T2DM could lead to microvascular complications which include diabetic nephropathy and diabetic retinopathy. More than 40% of T2DM patients have diabetic nephropathy[4] and 18% ~ 43% patients have diabetic retinopathy.[5] Furthermore, nephropathy or retinopathy is a major risk factor for end-stage renal disease[4] and vision loss[6] for the diabetic population, which makes diabetes mellitus a most alarming public health problem.

T2DM is characterized by chronic abnormal glucose metabolism which includes abnormal fasting plasma glucose (FPG) and/or abnormal postprandial plasma glucose (PPG). Many previous studies focused on the association between glucose metabolism and risk of microvascular disease. Some findings showed that elevated FPG or PPG were related to the onset risk of retinopathy and nephropathy.[7–9] However, it is inconsistent regarding which type of abnormal glucose metabolism is associated with higher risk of nephropathy and retinopathy. A clinical trial of 151 Japanese T2DM patients showed that only PPG was significantly correlated with the progression of retinopathy and is a stronger predictive factor than FPG,[10] whereas another study showed that there was no difference in the predictive value of retinopathy between FPG and PPG.[11] For nephropathy, a cross-sectional study showed that FPG was a factor related to positive proteinuria and impaired glomerular filtration rate,[12] but one study based on the Systolic Blood Pressure Intervention Trial (SPRINT) found that FPG was not associated with the development of kidney disease.[13] The data from a cohort study demonstrated that PPG was a more important determinant of onset and development of nephropathy in T2DM patients.[14] Nevertheless, McCance et al reported PPG was equally predictive of nephropathy in T2DM.[11] The existing evidence indicates a certain association between the elevation of fasting or postprandial glucose and increasing risk of microvascular disease, however, the type of hyperglycemia that has a larger effect on microvascular complications has not been uniformly addressed. The inconsistency may be explained by the difference in sample size and ethnic group in different studies. To our knowledge, few studies were performed to investigate the contribution of FPG and PPG to the risk of retinopathy and nephropathy in a Chinese population.

To clarify these issues, we extracted a T2DM population to assess the association between abnormal glycemic phenotypes and the risk of microvascular diseases in a Chinese population. This population was collected from a nationwide multicenter study of China National HbA1c Surveillance System (CNHSS).

Participants and Methods

Study Population

The CNHSS project was a cross-sectional large population survey conducted from April to June in 2013 in Mainland China, which was launched by the Chinses Diabetes Society. The CNHSS was established to monitor glycemic control among adult patients with T2DM. The survey recruited a total of 238,639 participants with T2DM from 602 hospitals located in all provincial administrative regions (except Guangxi Zhuang Autonomous Region and Tibet) in China mainland. The inclusion and exclusion criteria have been described previously.[15] Briefly, the inclusion criteria were: 1) T2DM outpatients who were 18 years or more; 2) diagnosed by 1999 WHO's criteria;[16] 3) treated with antidiabetic agents, diet or lifestyle therapy. The exclusion criteria included: 1) diabetes secondary to other diseases; 2) retinopathy or nephropathy diagnosed prior to diabetes diagnosis; 3) being treated with Chinese herbal medicine only; 4) being pregnant or breast-feeding; and 5) unconsciousness or being unable to communicate. In each workday during the survey period, the first consecutive 7 participants who entered each hospital's endocrinology outpatient department and had medical records and met the eligibility criteria, were invited to participate in involved hospitals, until 400 participants were recruited in each involved hospital during the whole recruitment period unless the recruitment period had ended. In order to select a representative population whose key features were similar to those of the national T2DM population,[2] we randomly selected the sample using a three-stage stratification-random clustering sampling method, based on the distribution proportion of T2DM participants in geographic distribution, economic status and age. Furthermore, the T2DM participants whose date of diagnosis was later than the date of occurrence of microvascular disease were excluded. Finally, 24,266 participants were included in this analysis. All the T2DM participants provided written informed consent before entering the study. Ethics approval was obtained from the Ethics Committee for Clinical Research of the People's Liberation Army General Hospital, and also accepted by all the participating hospitals.

Data Collection

Information such as age, sex, height, weight, and blood pressure, was collected using a structured form through

face-to-face interview by trained fieldworkers or measured through physical examination in the involved hospitals. Clinical characteristics were obtained by checking the medical records, which included glucose level at diagnosis of diabetes, the history of disease, as well as diagnosis date. Participants were required to confirm again whether they were diagnosed with any concomitant diseases or diabetes complications, including hypertension, coronary heart disease, cerebrovascular disease, dyslipidemia, diabetic retinopathy, and diabetic nephropathy, and diagnosis date, and this was checked via medical records of local hospital or diagnosis certificate by secondary or tertiary hospital. They were also required to report treatment information of management of T2DM, including the use of oral antidiabetic drugs (OADs), and different types of insulin, as well as diet or lifestyle therapy. Heights and weights were measured, in light clothing, with the use of standardized stadiometers and scales, respectively. Blood pressure was measured on the right arm using a standard mercury sphygmomanometer or an electronic sphygmomanometer with the subjects resting for at least 5 minutes in a sitting position. All laboratory examinations for FPG, 2-hour PPG (2hPPG), HbA1c and lipids such as triglyceride, total cholesterol and low-density lipoprotein, were performed in local hospital during the survey period. Blood sample was collected in local hospital after overnight 10h fasting for biochemical analyses. The 2hPPG was measured after the participants had completed the 75 g oral glucose tolerance test. All designated researchers were trained on basics of T2DM, procedures of data collection and entry, and details of the face-to-face interview. In addition, quality supervisors checked the reliability of the data by randomly re-interviewing some participants. All the data were entered and uploaded to the central database of CNHSS by experienced fieldworkers.

Definitions of Key Variables

According to FPG and 2hPPG level at diagnosis of diabetes, the abnormal glycemic phenotype included isolated fasting hyperglycemia (IFH) defined as FPG≥7.0 mmol/L and 2hPPG<11.1 mmol/L, isolated postprandial hyperglycemia (IPH) defined as 2hPPG≥11.1 mmol/L and FPG<7.0 mmol/L and combined hyperglycemia (CH) defined as FPG≥7.0 mmol/L and 2hPPG≥11.1 mmol/L. The economic development level was defined as undeveloped region, intermediately developed and developed region based on the Gross Domestic Product (GDP) of each province in 2013. The blood pressure control target was defined as systolic blood pressure<140 mmHg and diastolic blood pressure <90 mmHg. HbA1c control target was defined as <7.0% (53 mmol/mol). The diagnosis of microvascular diseases was confirmed by the medical recordings. Diabetic retinopathy was diagnosed by ophthalmologist based on typical changes of retinopathy on funduscopic examination due to diabetes, including background, pre-proliferative, proliferative or maculopathy. Diabetic nephropathy was defined as having persistent proteinuria, such as urinary albumin excretion rate ≥20 μg/min or urinary albumin ≥30 mg/24h after excluding other causes of kidney damage, urinary system infection, and blood in urine. In this study, the outcomes mainly included isolated diabetic retinopathy (IDR) defined as only diabetic retinopathy not diabetic nephropathy, isolated diabetic nephropathy (IDN) defined as only diabetic nephropathy not diabetic retinopathy and combined diabetic retinopathy and nephropathy (CRN) defined as both of them.

Statistical Analysis

Continuous variables of clinical characteristics were presented as mean with standard deviation or median with interquartile range (IQR). Categorical variables were described as frequency with proportion. Analysis of variance (ANOVA) test or Kruskal–Wallis rank test was applied to compare continuous variables among T2DM participants with different phenotypes. The Bonferroni or Nemenyi test was used for pairwise comparison among three groups. Chi-squared test and Fisher's exact test were used to compare categorical variables.

Unconditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the association between abnormal glycemic phenotypes (IFH group as reference) and microvascular complications, which were adjusted for potential confounding factors by four step forward multivariable-adjusted models. Model 1 was no adjustment of covariates. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, and diabetes duration. Model 4 was adjusted for age, sex, diabetes duration, BMI, self-monitoring of blood glucose, diabetes treatment, the target of blood pressure control, the target of lipid control, HbA1c and economic development level. Kaplan-Meier analysis was used to plot cumulative incidence of microvascular disease of different abnormal glycemic phenotypes. Then the Log rank test was used to compare the difference of cumulative

incidence among abnormal glycemic phenotypes. When we compared the cumulative incidence of microvascular diseases among abnormal glycemic phenotypes, the cross-sectional survey was transformed into a retrospective cohort. The follow-up time was calculated as time in years from the date of diagnosis of diabetes to the date of occurrence of the disease or the date of the survey, whichever came first.

All statistical analyses were performed by the statistical analysis system (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided value of P <0.05 was considered statistically significant. Kaplan-Meier plot and forest plot

Table 1 Characteristics of T2DM Participants with Different Abnormal Glycemic Phenotypes

Characteristics	Overall (n=24,266)	IFH (n=4493)	IPH (n=10,453)	CH (n=9320)	P	P_1	P_2	P_3
Age, years	58.9±11.3	58.0±11.1	58.6±11.6	59.7±11.2	<0.001	<0.001	0.001	<0.001
Sex, male	13,156 (54.2)	2390 (53.2)	5579 (53.4)	5187 (55.7)	<0.001	0.841	0.007	0.001
Diabetes duration, years Median (IQR)	4.2 (2.0–8.4)	3.9 (1.8–7.4)	4.2 (1.6–9.0)	4.4 (2.3–8.4)	<0.001	<0.001	<0.001	<0.001
BMI, Kg/m^2	24.2±3.0	23.9±3.0	24.1±3.0	24.5±3.0	<0.001	0.010	<0.0.01	<0.01
FPG at diagnosis, mmol/L	8.2±2.6	8.5±1.4	6.3±0.8	10.3±2.6	<0.001	<0.001	<0.001	<0.001
2h-PPG at diagnosis, mmol/L	13.8±3.5	9.7±1.3	14.0±2.5	15.5±3.6	<0.001	<0.001	<0.001	<0.001
HbA1c, %	7.4±1.5	7.3±1.3	7.4±1.5	7.8±1.6	<0.001	<0.001	<0.001	<0.001
HbA1c control target	6715 (27.7)	1474 (32.8)	3042 (29.1)	2199 (23.6)	<0.001	<0.001	<0.001	<0.001
SBP, mmHg	132.2±15.0	131.1±14.6	132.4±15.0	132.5±15.2	<0.001	<0.001	<0.001	0.593
DBP, mmHg	81.9±10.9	81.7±10.6	81.8±11.0	82.1±10.9	0.129	0.484	0.063	0.135
Blood pressure control target	14,121 (58.9)	2755 (61.3)	5848 (55.9)	5518 (59.2)	<0.001	<0.001	0.018	<0.001
Self-monitoring of blood glucose	9972 (41.1)	1631 (36.3)	4344(41.6)	3997 (42.9)	<0.001	<0.001	<0.001	0.059
Triglycerides, mmol/L, mmol/L	2.0±1.1	2.1±1.4	1.9±1.0	2.5±1.1	<0.001	<0.001	<0.001	<0.001
Low density lipoprotein cholesterol, mmol/L	2.8±1.0	2.7±1.0	2.8±0.9	2.8±1.0	<0.001	<0.001	<0.001	0.918
Total cholesterol, mmol/L	4.8±1.4	4.9±1.7	4.7±1.4	4.9±1.3	<0.001	<0.001	0.620	<0.001
Lipid target	5942 (24.5)	1177 (26.2)	2498 (23.9)	2267 (24.3)	<0.001	0.003	0.017	0.484
Diabetes treatment								
OAD only	13,580(56.0)	2674(59.5)	6462(61.8)	4444(47.7)	<0.001	<0.001	<0.001	<0.001
OAD plus insulin	5185 (21.4)	780(17.4)	1976(18.9)	2429(26.1)	<0.001	<0.001	<0.001	<0.001
OAD plus GLP-1	35 (0.1)	8(0.2)	9(0.1)	18(0.2)	0.113	0.126	0.848	0.042
Insulin only	5054 (20.8)	954(21.2)	1772(17.0)	2328(25.0)	<0.001	<0.001	<0.001	<0.001
GLP-1 only	31 (0.1)	9(0.2)	10(0.1)	12(0.1)	0.259	0.100	0.312	0.486
Lifestyle only	381 (1.6)	68(1.5)	224(2.1)	89(0.9)	<0.001	<0.001	<0.001	<0.001
Economic development level								
Underdeveloped	3516 (14.5)	482(10.7)	1444(13.8)	1590(17.1)	<0.001	<0.001	<0.001	<0.001
Intermediately developed	1997(16.5)	749(16.7)	1566(15.0)	1682(18.0)	<0.001	0.009	0.047	<0.001
Developed	16,753(69.0)	3262(72.6)	7443(71.2)	6048(64.9)	<0.001	0.082	<0.001	<0.001
Macrovascular complications								
Isolated coronary heart disease	2226(9.2)	332(7.4)	1073(10.3)	821(8.8)	<0.001	<0.001	0.005	0.001
Isolated cerebrovascular disease	758(3.1)	100(2.2)	322(3.1)	336(3.6)	<0.001	0.004	<0.001	0.040
Combined cardiovascular and cerebrovascular disease	478(2.0)	58(1.3)	231(2.2)	189(2.0)	0.001	<0.001	0.002	0.376
Microvascular complications								
IDR	1435(5.9)	230 (5.1)	580 (5.6)	625 (6.7)	<0.001	0.288	<0.001	0.001
IDN	781(3.2)	99 (2.2)	322 (3.1)	360 (3.9)	<0.001	0.003	<0.001	0.003
CRN	533(2.2)	58 (1.3)	207 (2.0)	268 (2.9)	<0.001	0.003	<0.001	<0.001

Notes: Data were expressed as mean ± standard deviation or n (%), unless otherwise indicated. Blood pressure target was defined as <140/90 mmHg. Lipid target was defined as TG < 1.7 mmol/L and LDL-C < 2.6 mmo/L. P value was derived from ANOVA, χ^2 test, Fisher's exact test or Kruskal–Wallis rank test among three groups. P_1 value was for pairwise comparison between IFH and IPH. P_2 value was for pairwise comparison between IFH and CH. P_3 value was for pairwise comparison between IPH and CH.

Abbreviations: IQR, interquartile range; IFH, isolated fasting hyperglycemia; IPH, isolated postprandial hyperglycemia; CH, combined hyperglycemia; OAD, oral antidiabetic drugs. GLP-1, glucagon-like peptide-1; IDR, isolated diabetic retinopathy; IDN, isolated diabetic nephropathy; CRN, combined diabetic retinopathy and nephropathy.

were drawn by Graphpad Prism 7 (Graphpad Software Company, CA, USA).

Results

Clinical Characteristics of T2DM Participants

Among the 24,266 participants included in this study, the mean age was 58.9 years (SD 11.3 years). About 54% of participants were male. The number of IFH participants, IPH participants, CH participants was 4493 (18.5%), 10,453 (43.1%) and 9320 (38.4%), respectively. The participants in CH group were more likely to be older; had slightly higher BMI, triglyceride, glucose indices and longer duration of diabetes; had higher proportion of treatment with OADs plus insulin and treatment with insulin only; and had a lower proportion of participants in economically developed region, blood pressure control target and HbA1c control target (Table 1).

Cumulative Incidence of Microvascular Diseases Among T2DM Participants with Different Abnormal Glycemic Phenotypes

In different phenotype groups of IFH, IPH and CH, the cumulative incidences of IDR were 5.1%, 5.5% and 6.7%, the cumulative incidences of IDN were 2.2%, 3.1% and 3.9%, and the cumulative incidences of CRN were 1.3%, 2.0% and 2.9% (Table 1). Kaplan-Meier curves in three phenotype groups appeared slightly different within diabetes duration of 5 years and started to separate and continued to diverge with increasing diabetes duration (Figure 1). Participants with CH phenotype showed the highest cumulative incidences of IDR, IDN and CRN, followed by IPH phenotype (Log rank test P<0.001). Through pairwise comparison, the phenotype of IPH showed a significantly higher cumulative incidence of IDR, IDN and CRN than IFH phenotype group, but lower cumulative incidence compared to those in the CH phenotype group (All P for pairwise comparison <0.001).

Association Between Abnormal Glycemic Phenotypes and Microvascular Diseases in T2DM Participants

In the multivariable-adjusted model, after step forward adjustment for age, sex, diabetes duration, BMI, self-monitoring of blood glucose, diabetes treatment, the target of blood pressure control, the target of lipid control, HbA1c and economic development level, the results were similar across different models. The full adjusted covariate model, using the phenotype of IFH as reference, showed

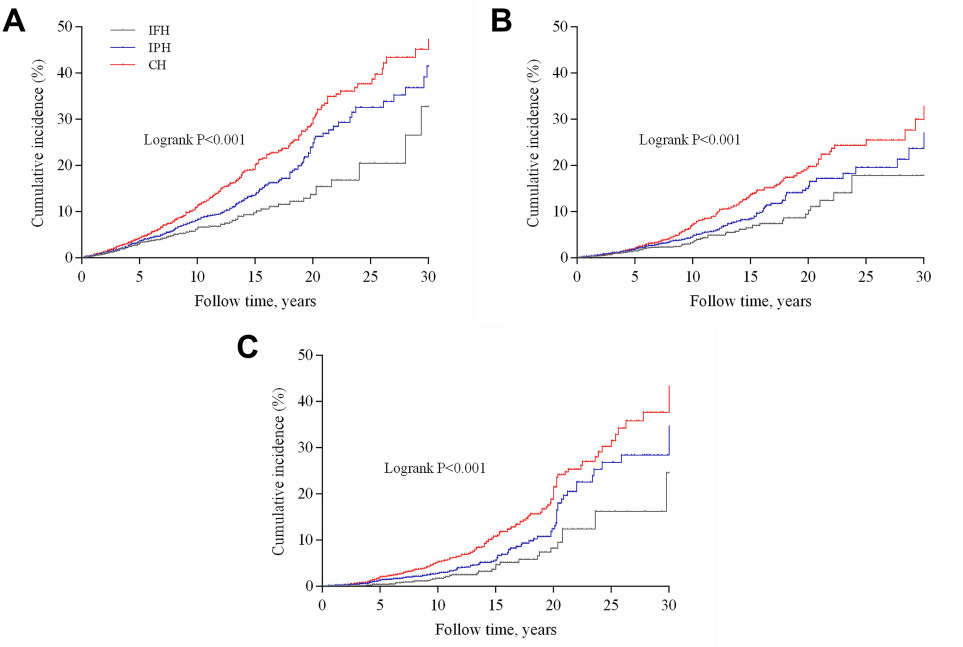

Figure 1 Cumulative incidence of microvascular diseases stratified by abnormal glycemic phenotype for T2DM participants: (**A**) isolated diabetic retinopathy (IDR), (**B**) isolated diabetic nephropathy (IDN), (**C**) combined diabetic retinopathy and nephropathy (CRN). Log rank test for microvascular diseases of T2DM participants with different abnormal glycemic phenotype (all P<0.05 in pairwise comparison among three phenotypes: IDR, IDN and CRN).

that participants with IPH phenotype presented a significantly higher risk of IDR (OR: 1.16, 95% CI: 1.05–1.28), IDN (OR: 1.37, 95% CI: 1.09–1.37) and CRN (OR:1.64, 95% CI: 1.21–2.21). Understandably, the phenotype of CH was associated with the highest risk of IDR (OR: 1.20; 95% CI: 1.02–1.41), IDN (OR: 1.59; 95% CI: 1.27–2.01) and CRN (OR: 1.93, 95% CI: 1.44–2.59) (Table 2). After stratifying the participants by age, sex, duration of diabetes, and BMI, the subgroup analysis still indicated similar results of the higher risks of IDR, IDN and CRN in IPH compared with the phenotype of IFH (Figure 2).

Discussion

In the present study, we demonstrated that participants with IPH phenotype had higher cumulative occurrence and onset risks of IDR, IDN and CRN compared with the participants with IFH phenotype, but lower cumulative onset risks and onset risks of IDR, IDN and CRN compared with the CH phenotype group. These results further occurred in the subgroup analysis stratified by age, sex, duration of diabetes and BMI. To the best of our knowledge, this is the first population-based study to demonstrate the association between abnormal glycemic phenotypes and the onset risk of diabetic microvascular complications in Chinese T2DM population.

Several reasons might account for the higher risk of microvascular complications in IPH phenotype group in our study. Firstly, HbA1c elevation has been accepted as an independent risk factor for diabetic microvascular disease. Several clinical trials previously demonstrated that intensive glucose control (mostly HbA1c target < 7%) can prevent the development or

Table 2 Association Between Abnormal Glycemic Phenotypes and Microvascular Disease in Type 2 Diabetes Mellitus Participants

	IDR	IDN	CRN
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Model 1			
IFH	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
IPH	1.23 (1.07–1.40)	1.43 (1.14–1.80)	1.57 (1.17–2.10)
CH	1.38 (1.18–2.62)	1.85 (1.48–2.32)	2.35 (1.77–2.13)
Model fit (C)	0.541	0.555	0.577z
Model 2			
IFH	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
IPH	1.14 (1.05–1.25)	1.35 (1.08–1.70)	1.46 (1.08–1.95)
CH	1.37 (1.17–1.60)	1.82 (1.45–2.28)	2.30 (1.73–3.06)
Age, years	1.03 (1.02–1.03)	1.04 (1.03–1.04)	1.04 (1.04–1.04)
Model fit (C)	0.596	0.620	0.640
Model 3			
IFH	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
IPH	1.11 (1.03–1.21)	1.31 (1.04–1.65)	1.41 (1.05–1.90)
CH	1.33 (1.14–1.56)	1.77 (1.41–2.22)	2.24 (1.67–2.30)
Age, years	1.01 (1.00–1.02)	1.02 (1.01–1.03)	1.02 (1.01–1.03)
Duration of diabetes, years	1.09 (1.08–1.10)	1.09 (1.07–1.10)	1.12 (1.11–1.14)
Model fit (C)	0.663	0.682	0.744
Model 4			
IFH	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
IPH	1.16 (1.05–1.28)	1.37 (1.09–1.73)	1.64 (1.21–2.21)
CH	1.20 (1.02–1.41)	1.59 (1.27–2.01)	1.93 (1.44–2.59)
Age, years	1.01 (1.01–1.02)	1.02 (1.01–1.03)	1.02 (1.01–1.03)
Duration of diabetes, years	1.08 (1.07–1.09)	1.08 (1.07–1.09)	1.11 (1.10–1.13)
Model fit (C)	0.711	0.717	0.792

Notes: Data are odds ratio (95% CI) from logistic regression model. Model 1 has no adjustment of covariable. Model 2 was adjusted for age, sex. Model 3 was adjusted for age, sex. Model 4 was adjusted for age, sex, BMI, self-monitoring of blood glucose, diabetes treatment, the target of blood pressure control, the target of lipid control, HbA1c and economic development level.

Abbreviations: IFH, isolated fasting hyperglycemia; IPH, isolated postprandial hyperglycemia; CH, combined hyperglycemia; IDR, isolated diabetic retinopathy; IDN, isolated diabetic nephropathy; CRN, combined diabetic retinopathy and nephropathy; CI, confidence interval.

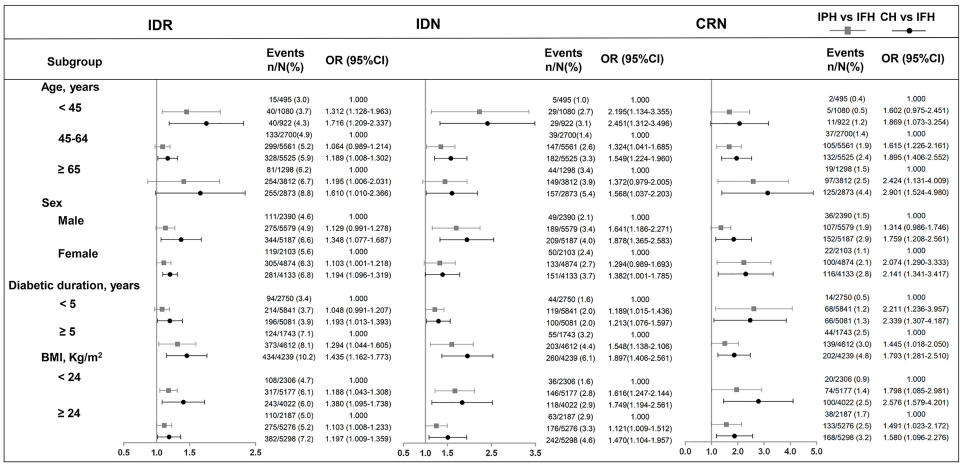

Figure 2 Subgroup analysis of association between abnormal glycemic phenotypes and microvascular complication for type 2 diabetes mellitus participants.
Abbreviations: IDR, isolated diabetic retinopathy; IDN, isolated diabetic nephropathy; CRN, combined diabetic retinopathy and nephropathy; IFH, isolated fasting hyperglycemia; IPH, isolated postprandial hyperglycemia; CH, combined hyperglycemia; BMI, body mass index; OR, odds ratio; CI, confidence interval.

slow down the progress of microvascular complications.[17–19] It was reported that postprandial glucose exceeded 50% or fasting glucose for the contribution of HbA1c when HbA1c < 8.4% or 5.1%-7.4%, respectively.[20] Furthermore, compared with Caucasians, postprandial blood glucose has a more prominent contribution to HbA1c for Chinese or Asian people.[21] A national diabetes epidemiology survey showed nearly half of newly diagnosed diabetes patients had IPH phenotype in China.[22] A meta-analysis also reported that PPG had a closer association with HbA1c than FPG, and had a better predictive performance in predicting overall glycemic control.[23] As a result, we speculated that intensive HbA1c control caused by decreasing postprandial glucose would obtain more benefit in preventing microvascular disease. Additionally, the mean level of HbA1c was 7.4% in our study, and the participants with IPH phenotype had a worse HbA1c, so the IPH phenotype group presented a greater risk of microvascular complications in this study. In addition, postprandial hyperglycemia is characterized by a rapid and large increase in blood glucose concentrations, which produce an increase in glomerular filtration rate in diabetic patients.[24] The hyperperfusion results in a greater stimulus for hyperproduction of collagen which was considered as an important event for pathogenesis of diabetic nephropathy.[25] Simultaneously, blood flow was also closely parallel with plasma glucose concentrations,[26] which are both pathogenetic factors that are important in the occurrence and progression of retinopathy in diabetic patients.[27] For CH phenotype, T2DM patients presented the characteristic of combined fasting and postprandial hyperglycemia, so it had the worst HbA1c control and the highest risks of IDR, IDN or CRN.

The strength of our study is the relatively large sample size, and the participants were recruited from almost all the provinces of China, representing people with T2DM throughout China to some extent. Moreover, the targeted study population was proportionally randomly selected using a three-stage stratification-random clustering sampling method, resulting in the utmost reduction of selection bias. However, there were several limitations in this study. Firstly, diabetes complication cases were ascertained by reviewing medical records, not by systematical screening. Some medical records were not exactly available and therefore some microvascular disease cases might have been missed, especially for T2DM participants in economically disadvantaged regions. As a result, the true prevalence of diabetes complication might have been underestimated. Secondly, lifestyle information such as smoking, drinking, physical exercise and dietary intake, which are associated with vascular disease, was not collected. Thirdly, the study design was cross-sectional, so competing risks could not be considered, and the causal association between phenotypes and complication was not investigated. Fourth, considering the feasibility of the study, the sampling approach of including the first 7 consecutive patients was not completely random, which may have led to bias.

Conclusion

In summary, our data suggest that T2DM participants with IPH phenotype have higher risk of microvascular disease than T2DM patients with IFH phenotype. Through analyzing the differences in the risks of microvascular diseases including IDR, IDN, and CRN, in participants with abnormal glycemic

phenotypes, this study could help endocrinologists better identify the high-risk population. Special focus should be directed on T2DM patients with IPH phenotype for the prevention of microvascular diseases in the early stage of diabetes.

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Disclosure

The authors report no conflicts of interest in this work.

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