

## RESEARCH

# Factors associated with resistance to complications in long-standing type 1 diabetes in China

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## Abstract

**Objective:** Type 1 diabetes (T1DM) is associated with a higher risk of premature death, but there are factors in certain patients with T1DM that protect them from complications and premature death. These factors had not been identified in non-Caucasian populations, so we aimed to identify factors that protect against the development of diabetic nephropathy (DN) and diabetic retinopathy (DR) in long-standing T1DM in China.

**Methods:** Ninety-five T1DM patients with >30 years' duration of diabetes were enrolled in this nationwide study. Differences between groups of patients with and without complications were compared, and multivariable regression analysis was used to evaluate the relationships between candidate protective factors and the development of DN or DR.

**Results:** Thirty of the participants did not have DN and the same amount did not have DR. 6/52 of participants without DN were from a rural area, whereas 11/28 of participants with DN had been born in a rural area ( $P = 0.005$ ). Systolic blood pressure (SBP) was higher in participants with DN ( $135 \pm 26$  mmHg vs  $121 \pm 13$  mmHg;  $P = 0.002$ ). In participants without DR, 27/30 were married or cohabitating, and only 3/30 were single, never married, or widowed, but for those with proliferative DR (PDR), 13/26 had been married ( $P = 0.003$ ). A rural or urban origin and SBP were associated with DN in the multivariable analysis.

**Conclusion:** we have shown that higher socioeconomic status, indicated by birth in an urban area, and being married or cohabitating, are accompanied by better blood pressure control and a lower risk of microvascular complications in Chinese patients with long-standing T1DM. These findings illustrate the importance of improving care for patients with T1DM in China.

## Key Words

- ▶ diabetic retinopathy
- ▶ diabetic nephropathy
- ▶ type 1 diabetes
- ▶ longevity

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## Introduction

Chronic complications cause the largest proportion of deaths and increase in prevalence with the duration of the disease in long-standing type 1 diabetes (T1DM). (1) Indeed, the duration of diabetes and severity of hyperglycemia are the conventionally used predictors of diabetic retinopathy (DR) and diabetic nephropathy (DN). (2, 3) Previous studies have shown that almost all

T1DM patients are likely to develop some degree of DN within 20 years of diagnosis. (4, 5) In addition, DN affects nearly 30% of T1DM patients and is associated with poor prognosis, being the most common reason for end-stage renal disease (ESRD) to develop in the US. (6) However, a study by Keenan *et al.* (7) of the Joslin Medalist group of T1DM patients identified individuals with diabetes for

$\geq 50$  years who appeared to be protected against DR and DN. Similar results have also been identified in other long-standing T1DM cohorts, such as the Golden Years study in UK and the Canadian study of the longevity of T1DM patients. (8, 9) These findings suggest that individuals with an extremely long duration of T1DM are either protected from or show slower progression of diabetic microvascular complications. This survival bias inherent in studying patients with a long duration of T1DM permits the evaluation of protective factors. However, all these studies of long-standing T1DM have been conducted in Caucasians; there have been no studies to date of the factors associated with DR and DN in equivalent non-Caucasian cohorts.

The prevalence of T1DM in China is extremely low compared with that in some European countries and North America, (10) and little is known about the features of long-term T1DM in patients in China. In the 3C Study of coverage, cost, and care for type 1 diabetes in China, there were only a few participants who had had diabetes for  $>30$  years, (11) implying that few patients can live with the disease for more than 30 years, likely because of an overall deficit in care. Therefore, we aimed to characterize the prevalence of microvascular complications and risk factors associated with long-standing T1DM in China by studying a nationwide cohort of patients who had had diabetes for at least 30 years. (12)

## Materials and methods

### Study overview

To encourage people with T1DM to manage the disease more effectively, the Chinese Diabetes Society (CDS) pursued a 'Care for Life, Hand in Hand' program between December 2012 and December 2013, which aimed to identify people across China who had survived  $\geq 30$  years with T1DM. The diagnosis was confirmed by clinical endocrinologists, on the basis of hospital medical records. During the 1-year enrollment period, 105 individuals living across China were identified. As an incentive, they were provided with free insulin detemir, insulin aspart, and glucose monitoring strips for 3 years. The study was a cross-sectional, observational study of the participants that enrolled in the program. The Peking University People's Hospital Institutional Review Board approved the study, and all the participants provided their written informed consent.

### Participants

Between December 2015 and December 2016, all of the registered participants were contacted, and 95 of them had completed their study visit. The reasons for non-participation were death ( $n=4$ ), moving to the countryside ( $n=3$ ), and lack of interest ( $n=3$ ). The participants were from 21 provinces (Supplementary Fig. 1, see section on [supplementary materials](#) given at the end of this article), of which the most common were Beijing (17.5%), Jiangsu (16.5%), and Shanxi (10.3%).

### Clinical and anthropometric assessments

Demographic and socioeconomic data, body mass, height, and blood pressure were assessed by study physicians and researchers. Blood and urine samples were also collected locally and shipped using a biosecure transportation system at  $-80^{\circ}\text{C}$  to Peking University People's Hospital within 24 h.

HbA1c was measured using an automated HPLC system (Primus Ultra 2, Trinity Biotech, Bray, Ireland). Serum lipids, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations, were measured using an automated Hitachi-008 system (Hitachi). Urine albumin/creatinine ratio (UACR) was measured using a Roche-c311 system (Roche).

The patients' renal status was assessed using the mean UACR obtained from two fasting and one post-meal urine samples. Participants without albuminuria (UACR  $< 30$  mg/g) were compared with those with albuminuria (UACR  $\geq 30$  mg/g). DR was diagnosed by an ophthalmologist, using a slit lamp and an ophthalmoscope, and the severity of DR was classified as (1) no DR; (2) non-proliferative DR (NPDR); or (3) proliferative DR (PDR).

### Statistical analysis

The data are expressed as means (s.d,s) for continuous variables, and percentages for categorical variables. Parameters were compared between groups using ANOVA for numeric data and the chi-square test for categorical data.  $P < 0.05$  was considered to represent statistical significance. Multivariable logistic regression analysis was used to determine the odds ratios (ORs) for factors potentially associated with DN and the severity of DR. All parameters with  $P < 0.10$  in the chi-square or ANOVA analyses were included in the multivariable regression model. Statistical analysis was performed using SPSS software (version 23.0, IBM).

## Results

### DN in patients with long-standing T1DM

Of the 95 participants enrolled in the study, 30 did not have albuminuria and the remainder did. 14 of the 30 with, and 28 of the 60 without DN were male. The age and the age at diagnosis were similar between participants with and without DN (56.0±9.5 years vs 59.4±12.6 years, and 16.3±6.7 years vs 19.2±11.6 years, respectively). The duration of diabetes was also similar between the two groups (39.7±6.9 years vs 39.9±6.1 years).

Of the participants who did not have DN, 6/52 had been born in a rural area, whereas 11/28 of participants with DN had been born in a rural area ( $P=0.005$ ). Systolic blood pressure (SBP) was higher in the DN group (135±26 mmHg vs 121±13 mmHg,  $P=0.002$ ) and HbA1c was slightly higher in individuals with DN (7.4±1.3% vs 6.9±1.2%), but this difference failed to reach statistical significance ( $P=0.075$ ). A comparison of the lipid profiles of the two groups showed no significant differences ( $P=0.118$ , 0.822, 0.079, and 0.130 for TC, HDL-C, LDL-C, and TG, respectively). (Table 1)

### DR in participants with long-standing T1DM

Thirty participants did not have DR, and the number of participants with NPDR and PDR were both 26.

Of the participants without DR, or with NPDR or PDR, 15/30, 11/26, and 10/26, respectively, were male ( $P=0.673$ ). Participants with NPDR were the oldest (59.7±10.8 years), those with PDR the youngest (52.1±8.5 years), and those without DR intermediate in age (58.2±10.9 years) ( $P=0.035$ ).

We also analyzed marital status, and found that in participants without DR, 27/30 were married or cohabitating, and only 3/30 were single, never married, or widowed. However, among those with PDR, only 13/26 were married or cohabiting ( $P=0.003$ ).

Lipid profile analysis showed that the TC concentrations was highest in participants with PDR, lowest in those without DR, and intermediate for those with NPDR (5.7±1.3 mmol/L, 4.8±1.1 mmol/L, and 5.7±1.2 mmol/L, respectively;  $P=0.018$ ). There were similar trends for HDL-C and LDL-C concentrations, but these did not reach statistical significance ( $P=0.052$  and  $P=0.067$ , respectively). (Table 2)

### Factors associated with DN

In the multivariable regression analysis, which was adjusted for HbA1c and LDL-C, urban/rural background, and SBP maintained their associations with DN. The OR (95% CI) for birth in a rural location was 4.76 (1.82, 8.81),

**Table 1** Demographic, biochemical and clinical differences between participants with and without DN.

	Without albuminuria ( $n=30$ ) <sup>a</sup>	With albuminuria ( $n=60$ ) <sup>a</sup>	P value <sup>b</sup>
Male, $n$	14/30	28/60	0.588
Mean (s.d.) age, years	56.0 (9.5)	59.4 (12.6)	0.234
Mean (s.d.) age at diagnosis, years	16.3 (6.7)	19.2 (11.6)	0.197
Mean (s.d.) diabetes duration, years	39.7 (6.9)	39.9 (6.1)	0.920
Family resources, $n^a$			
Rural area	11/28	6/52	0.005
Urban area	17/28	46/52	
Highest level of education, $n^a$			0.359
< University	24/28	41/52	
≥ University	4/28	11/52	
Marital status, $n^a$			0.389
Married/cohabitating	20/28	40/52	
Single/never married/widowed	8/28	12/52	
Mean (s.d.) BMI (kg/m <sup>2</sup> )	22.3 (2.9)	22.6 (2.7)	0.623
Mean (s.d.) SBP, mmHg	121 (13)	135 (26)	0.002
Mean (s.d.) DBP, mmHg	72 (8)	74 (13)	0.317
Mean (s.d.) HbA1c, %	6.9 (1.2)	7.4 (1.3)	0.075
Mean (s.d.) total cholesterol, mmol/L	4.9 (1.2)	5.4 (1.3)	0.118
Mean (s.d.) HDL-C, mmol/L	1.6 (0.3)	1.6 (0.4)	0.822
Mean (s.d.) LDL-C, mmol/L	2.6 (1.0)	3.1 (1.1)	0.079
Mean (s.d.) triglyceride, mmol/L	1.0 (0.5)	1.2 (0.5)	0.130

<sup>a</sup>4 were missing for diabetes nephropathy status; 10 were missing for family resources, highest level of education, and marital status; <sup>b</sup>P value < 0.05 from chi-squared test and ANOVA test comparing participants with and without DN.

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

compared with an urban location, and the equivalent statistics for SBP were 1.05 (1.01, 1.08). However, HbA1c and LDL-C were not associated with DN (the ORs (95% CIs) were 1.12 (0.61, 2.08) for HbA1c and 1.59 (0.83, 3.02) for LDL-C). (Table 3)

### Factors associated with DR

The association of marital status with DR remained after adjustment for age, age at diagnosis, TC, HDL-C, and LDL-C. The OR (95% CI) was 3.63 (1.49, 6.61) for non-proliferative DR *versus* no DR in patients who were married or cohabitating, and the OR (95% CI) was 8.09 (2.21, 14.11) for patients with PDR compared with noDR (Table 4).

## Discussion

People who have lived with T1DM for a long time are likely to have characteristics that protect them against morbidity and mortality due to complications. This survival bias in the population enabled us to evaluate which factors might be protective in the present study. Our findings suggest that patients with T1DM who do not develop microvascular complications are more likely to have higher socio-economic status, illustrated by a

higher likelihood of having been born in urban area, to be married or cohabitating, and in the case of DN, to have lower blood pressure.

The presence of renal disease is the major predictor of mortality for patients with T1DM, and those without renal disease have been shown to show mortality comparable to the general population. (13) In the present study, only 28/60 of the participants were normoalbuminuric, which is a lower percentage than that previously published for Caucasians. In the Joslin 50-Year Medalist Study of patients who had had diabetes for more than 50 years, 70.3% were normoalbuminuric, (7) and in the UK Golden Years Cohort, a group of 400 patients with T1DM of >50 years' duration, 64% were normoalbuminuric. (14, 15) Efficient long-term self-management aimed at improving blood glucose, blood pressure, and cholesterol control, are crucial for the prevention of microvascular complications in diabetes. Given fact that China was underdeveloped and had limited health care resources 30 years ago, it is reasonable to infer that the higher prevalence of DN in the present study was largely due to poor diabetes care in the past.

We found that birth location was associated with the development of DN in the present study. This is an important sociodemographic characteristic in China, which is representative of the kind of social environment

**Table 2** Demographic, biochemical and clinical differences among participants without DR, NPDR and PDR.

	Without DR (n = 30) <sup>a</sup>	NPDR (n = 26) <sup>a</sup>	PDR (n = 26) <sup>a</sup>	P value <sup>b</sup>
Male, n	15/30	11/26	10/26	0.673
Mean (s.d.) age, years	58.2 (10.9)	59.7 (10.8)	52.1 (8.5)	0.035
Mean (s.d.) age at diagnosis, years	18.7 (8.5)	19.6 (8.9)	12.7 (6.5)	0.011
Mean (s.d.) diabetes duration, years	39.6 (7.2)	39.9 (6.9)	39.4 (5.7)	0.967
Family resources, n <sup>a</sup>				0.510
Rural area	5/30	4/26	7/26	
Urban area	25/30	22/26	19/26	
Highest level of education, n <sup>a</sup>				0.342
< University	24/30	21/26	21/26	
≥ University	6/30	5/26	5/26	
Marital status, n <sup>a</sup>				0.003
Married/cohabitating	27/30	20/26	13/26	
Single/never married/widowed	3/30	6/26	13/26	
Mean (s.d.) BMI (kg/m <sup>2</sup> )	21.9 (2.4)	23.2 (3.7)	22.0 (1.7)	0.235
Mean (s.d.) SBP, mmHg	124 (14)	126 (21)	128 (23)	0.778
Mean (s.d.) DBP, mmHg	72 (8)	72 (14)	74 (9)	0.657
Mean (s.d.) HbA1c, %	6.8 (1.3)	7.3 (1.4)	6.8 (0.9)	0.233
Mean (s.d.) total cholesterol, mmol/L	4.8 (1.1)	4.9 (1.3)	5.7 (1.2)	0.018
Mean (s.d.) HDL-C, mmol/L	1.5 (0.3)	1.5 (0.3)	1.7 (0.4)	0.052
Mean (s.d.) LDL-C, mmol/L	2.5 (0.7)	2.8 (1.1)	3.2 (1.1)	0.067
Mean (s.d.) triglyceride, mmol/L	1.1 (0.6)	1.1 (0.4)	1.0 (0.5)	0.972

<sup>a</sup>12 were missing for diabetes nephropathy status; 8 were missing for family resources, highest level of education, and marital status; <sup>b</sup>P value < 0.05 from chi-squared test and ANOVA test comparing participants without DR, with NPDR and with PDR.

BMI, body mass index; DBP, diastolic blood pressure; DR, diabetes retinopathy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPDR, non-proliferative diabetes retinopathy; PDR, proliferative diabetes retinopathy; SBP, systolic blood pressure.

**Table 3** Factors associated with albuminuria according to multivariable logistic regression.

	OR	95% CI
Family resources		
Rural area	4.76	1.82, 8.81
SBP, mmHg	1.05	1.01, 1.08
HbA1c, %	1.12	0.61, 2.08
LDL-C, mmol/L	1.59	0.83, 3.02

Multivariable logistic regression including all variables with  $P < 0.10$  in bivariate analysis.

DN, diabetes nephropathy; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

in which an individual is born and brought up. China was underdeveloped three decades ago, especially in rural areas. It is likely that individuals who did not have DN had better glucose control, particularly during the early phase of their diabetes, than those who had developed DN. In the T1D Exchange Clinic Registry cohort, indicators of higher socio-economic status, such as income, health insurance, educational level, and marital status were also associated with better glycemic control. (16) Socioeconomic status correlates with the level of self-management skills, such as the frequency of self-monitoring of blood glucose (SMBG) measurements, the timing of the meal bolus, and the frequency with which an insulin dose is missed, all of which are important for good glycemic control and better long-term outcomes. In the Finnish Diabetic Nephropathy (FinnDiane) study, which had a median 7-year follow-up period, chronic kidney disease was shown to predict all-cause mortality in T1DM patients. (17) Furthermore, an analysis of data from the Swedish National Diabetes Register of 24,947 T1DM patients showed that lower socioeconomic status increases the risk of mortality by a factor of two-to-three. (18) Deficiencies in diabetes care and resources, particularly soon after diagnosis, may account for the high prevalence of DN in the present cohort, and might

also explain the overall higher mortality risk for people with T1DM living in China.

As shown in previous studies, SBP was also associated with the development of DN in the present cohort. In the UK Golden Years Cohort, hypertension was also significantly associated with DN. (8) In addition, similar results were obtained in the study of Swedish National Diabetes Register data, which suggested that better SBP control is protective against DN in patients who have had T1DM for >50 years. (19) Given the fact that careful blood pressure control is crucial for the prevention of DN in T1DM, our study highlights the importance of screening for and the treatment of hypertension in T1DM patients to prevent DN.

One interesting finding of the present study is that marital status was associated with DR in the multivariable analysis, an association that has not been identified in other studies of long-standing T1DM. However, individuals who are married or cohabitating are also more likely to have higher socioeconomic status, and the cross-sectional design of the present study means that a causal relationship between marital status and diabetic complications cannot be inferred. However, a previous study of T1DM patients showed that married or cohabitating individuals were more likely to show better glycemic control and self-care (20). These findings remind us of the importance of considering the well-being of patients with this chronic disease in clinical practice.

Although there was a trend for lower HbA1c to be associated with the absence of DN, HbA1c was not associated with DN or DR in the multivariable analyses. This might be because we provided free insulin and glucose strips for the participants, which better enabled them to achieve appropriate glycemic control. Indeed, the mean HbA1c of nearly 7.0% in the present cohort is indicative of good glucose control in many of the participants. Future studies follow the current and other

**Table 4** Factors associated with NPDR and PDR according to multivariable logistic regression.

	OR	95% CI	OR	95% CI
Marital status				
Married/cohabitating	Referent		Referent	
Single/never married/widowed	3.63	1.49, 6.61	8.09	2.21, 14.11
Age, years	1.06	0.96, 1.17	0.94	0.82, 1.07
Age at diagnosis, years	0.99	0.87, 1.11	0.98	0.85, 1.14
Total cholesterol, mmol/L	0.83	0.61, 2.12	2.54	1.35, 8.47
HDL-C, mmol/L	1.25	0.15, 8.24	1.72	0.23, 8.54
LDL-C, mmol/L	1.85	0.51, 5.59	1.90	0.81, 7.37

Multivariable logistic regression including all variables with  $P < 0.10$  in bivariate analysis.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPDR, non-proliferative diabetes retinopathy; PDR, proliferative diabetes retinopathy.



cohorts longitudinally to more accurately determine the relationships between HbA1c and the development of microvascular complications.

Relative youth, a shorter duration of diabetes, and lower HbA1c, BMI, and triglyceride concentration have been shown to be protective against microvascular complications in other similar studies. (8, 15) Although we were able to see beneficial trends for lower HbA1c and better lipid control in the present study, multivariable analysis showed no significant associations between these factors and the development of microvascular complications. One possible reason for this may be the relatively small number of participants in the present study. However, given that this was a nationwide program initiated by the CDS, which provided diabetic care supplies as an incentive, the care of patients with T1DM in China is a cause for concern.

There were several limitations to the present study. First, it is important to emphasize that due to the cross-sectional design of the study, selection bias may represent a major confounder, because patients with advanced microvascular complications may not have survived long enough to be enrolled in the study. Second, we studied a relatively small cohort, which reduces the statistical power of the analyses and generates less precise estimates.

In conclusion, our study has shown that higher socioeconomic status, represented by birth in an urban area, being married or cohabitating, and better blood pressure control are associated with a lower risk of diabetic microvascular complications in patients with long-standing T1DM living in China. These findings emphasize the importance of improving medical care for this group, and future studies should be conducted regarding the most appropriate targets and most effective approaches to the prevention of such complications.

#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-19-0521>.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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