Original Article

Clinical Determinants of Diabetes Progression in Multiethnic Asians with Type 2 Diabetes – A 3-Year Prospective Cohort Study

Sylvia Liu, [1]*BSc*, Jian Jun Liu, [1]*MBBS, PhD,* Resham L Gurung, [1]*PhD,* Clara Chan, [1]*BSc*, Darren Yeo, [1]*BSc*, Keven Ang, [1]*PhD*, Wern Ee Tang, [2]*MBBS*, Subramaniam Tavintharan, [3]*MBBS, MRCP*, Chee Fang Sum, [3]*MBBS, MRCP*, Su Chi Lim, [1,3,4]*MBBS, PhD*

Abstract

Introduction: The risk for diabetes progression varies greatly in individuals with type 2 diabetes mellitus (T2DM). We aimed to study the clinical determinants of diabetes progression in multiethnic Asians with T2DM. Materials and Methods: A total of 2057 outpatients with T2DM from a secondary-level Singapore hospital were recruited for the study. Diabetes progression was defined as transition from non-insulin use to requiring sustained insulin treatment or glycated haemoglobin (HbA1c) ≥8.5% when treated with 2 or more oral hypoglycaemic medications. Multivariable logistic regression (LR) was used to study the clinical and biochemical variables that were independently associated with diabetes progression. Forward LR was then used to select variables for a parsimonious model. Results: A total of 940 participants with no insulin use or indication for insulin treatment were analysed. In 3.2 ± 0.4 (mean ± SD) years' follow-up, 163 (17%) participants experienced diabetes progression. Multivariable LR revealed that age at T2DM diagnosis (odds ratio [95% confidence interval], 0.96 [0.94-0.98]), Malay ethnicity (1.94 [1.19-3.19]), baseline HbA1c (2.22 [1.80-2.72]), body mass index (0.96 [0.92-1.00]) and number of oral glucose-lowering medications (1.87 [1.39-2.51]) were independently associated with diabetes progression. Area under receiver operating characteristic curve of the parsimonious model selected by forward LR (age at T2DM diagnosis, Malay ethnicity, HbA1c and number of glucose-lowering medication) was 0.76 (95% CI, 0.72-0.80). Conclusion: Young age at T2DM diagnosis, high baseline HbA1c and Malay ethnicity are independent determinants of diabetes progression in Asians with T2DM. Further mechanistic studies are needed to elucidate the pathophysiology underpinning progressive loss of glycaemic control in patients with T2DM.

Ann Acad Med Singapore 2019;48:217-23

Key words: Glucose-lowering medications, Glycaemic control, High-density lipoprotein

Introduction

In patients with type 2 diabetes mellitus (T2DM), good glycaemic control leads to a substantial fall in microvascular complications and a potential decline in macrovascular complications.[1,2] However, as T2DM is a progressive disease, a large number of patients will need multiple therapies to achieve glycaemic control for a few years following the onset of diabetes.[3,4] It is for this reason that clinical guidelines recommend metformin as the preferred option for initiating medication (above lifestyle measures), followed by stepwise addition of other glucose-lowering medications that are based on a patient-centred approach.[2,5] However, about one-third of patients with T2DM eventually require exogenous insulin replacement due to progressive and uncontrolled hyperglycaemia.[6,7]

The progressive loss of beta cell function is central to diabetes progression, with insulin resistance playing a minor role in the process.[2,3,8,9] Significantly, diabetes progression rate in patients with T2DM varies greatly among individuals. Some patients may experience a rapid loss of glycaemic control necessitating early exogenous insulin replacement while others may have better controlled glycaemia needing only oral medication treatment for several years.[5,10] Thus, a study on the determinants of diabetes progression may

[1]Clinical Research Unit, Khoo Teck Puat Hospital, Singapore
[2]Clinical Research Unit, National Healthcare Group Polyclinics, Singapore
[3]Diabetes Centre, Admiralty Medical Centre, Singapore
[4]Saw Swee Hock School of Public Heath, National University of Singapore, Singapore
Address for Correspondence: A/Prof Lim Su Chi, Clinical Research Unit, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828.
Email: lim.su.chi@ktph.com.sg

guide stratified management of T2DM and potentially identify risk factors associated with progressive beta cell function loss. Early studies have identified clinical factors such as a younger age at T2DM diagnosis, dyslipidaemia and poor glycaemic control with accelerated diabetes progression.[7,10,11] However, to our knowledge, the majority of these studies were conducted on Caucasians. Data on clinical determinants of diabetes progression in multiethnic Asians with T2DM is scarce.

Singapore is a developed city-state in Southeast Asia, whose population consists of Chinese, Malays and Indians as major ethnic groups.[1] In the current work, we aimed to prospectively identify the clinical and biochemical factors associated with progression of diabetes to a clinical requirement for insulin replacement therapy in a multiethnic T2DM cohort in Singapore.

Materials and Methods

Singapore Study of Macro-Angiopathy and Microvascular Reactivity in Type 2 Diabetes (SMART2D) Cohort

A total of 2057 outpatients with T2DM were enrolled in the Singapore Study of Macro-Angiopathy and Microvascular Reactivity in Type 2 Diabetes (SMART2D) cohort from a regional hospital and a primary care medical facility in Singapore between 2011 and 2014. The inclusion and exclusion criteria for the cohort assembly have been described previously.[12] The determination of T2DM was based on exclusion of type 1 diabetes and diabetes attributed to other specific causes. Type 1 diabetes was diagnosed as requiring sustained insulin treatment 1 year after the onset of diabetes. Three years after enrolment, participants were invited by phone calls and written mails to the planned follow-up. By August 2017, 1478 participants had completed the follow-up study.

Definition of Diabetes Progression and Participant Selection

To our knowledge, there is no consensus or "gold standard" in defining T2DM progression.[5,7] We defined it as requiring sustained insulin treatment for more than 6 months.[10] To account for inertia in insulin treatment initiation, those with glycated haemoglobin (HbA1c) ≥8.5% (when taking ≥2 non-insulin glucose-lowering medications) were also considered as having diabetes progression.[10] Participants with existing insulin use and those taking ≥2 oral glucose-lowering medications but having HbA1c ≥8.5% at-baseline were excluded from the study. Of the 1478 participants with 3-year follow-up data, 940 met the criteria for study inclusion (Fig. 1).

The study was approved by the Singapore National Healthcare Group Ethics Review Board. All participants had provided written informed consent.

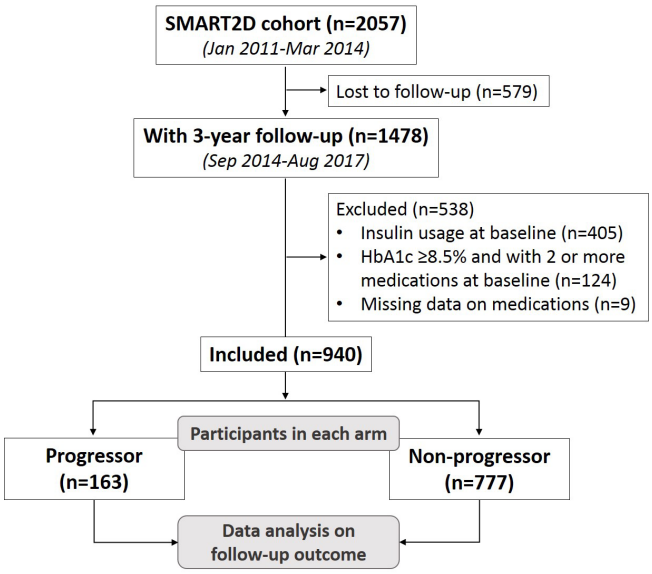

Fig. 1. Flowchart of the participants' selection.

Clinical and Biochemical Variables

Ethnicity and smoking status were self-reported. While duration of diabetes and age at T2DM diagnosis were also self-reported, these were further validated by medical records. Blood pressure was measured 3 times in a sitting position with a semi-automatic sphygmomanometer. An average of 3 readings was used. HbA1c was quantified by a point-of-care instrument (DCA VantageTM Analyzer, Siemens, Germany). High-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triacylglycerol were measured by enzymatic assays (Roche Cobas Integra 700, Roche Diagnostics, Switzerland). Creatinine was measured by an enzymatic method which was traceable to isotope dilution mass spectrometry reference. Glomerular filtration rate (GFR) was estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Urinary albumin level was measured by a solid phase competitive chemiluminescent immunoassay (DPC Immulite, Gwynedd, United Kingdom) and presented as albumin-to-creatinine ratio (ACR, mg/g).

Data on medication use were retrieved from medical records by trained research nurses. Metformin, sulfonylurea, dipeptidyl peptidase-4 (DPP4) inhibitors and thiazolidinediones were oral glucose-lowering medication used at-baseline. No participant used sodium-glucose co-transporter-2 (SGLT2) inhibitors at-baseline while 23 (2.4%) participants were on SGLT2 inhibitor treatment at 3 years' follow-up. Only 1 participant was on glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide treatment at-baseline and in the follow-up study, respectively.

Statistical Analysis

Descriptive data were presented as mean ± standard deviation (SD), median (interquartile range, IQR) or proportions. Between-group and across-group differences were compared by Student's t-test, Mann-Whitney U test, one-way analysis of variance (ANOVA), Kruskal-Wallis test or χ^2 test, where appropriate.

We used multivariable logistic regression (LR) to study which variables were independently associated with diabetes progression. Inclusion of the independent variables was based on biological plausibility. Age at T2DM diagnosis, sex, ethnicity, current smoking, body mass index (BMI), duration of diabetes, HbA1c, systolic blood pressure, HDL cholesterol, triacylglycerol, eGFR and number of oral glucose-lowering medications at-baseline were included as independent variables in the model. Given that: 1) age at T2DM diagnosis has been associated with diabetes progression[7,10] and 2) age at T2DM diagnosis and chronological age were highly correlated (Pearson, r = 0.73), we only included the former in the multivariable model. In the posthoc power estimation based on the work by Peduzzi et al (n = 10 k/p, where p is the smallest of the proportions of negative or positive subjects and k is the number of covariates),[13] our study had the power to include up to 16 independent variables in the multivariable LR model, given the sample size of 940 and number of diabetes progressors of 17.3%.

Additionally, we employed forward LR to select determinants of diabetes progression to build a parsimonious model. Variables with P <0.05 were included whereas those with P >0.1 were excluded in the iteration. C statistics (area under receiver operating characteristics curve, AUC) were applied to assess goodness-of-fit of the model with selected determinants included.

In sensitivity analyses, we included only participants with transition-to-sustained insulin treatment (n = 72) as diabetes progressors to assess the robustness of selected clinical determinants. Separately, we excluded participants with normal or below-normal BMI (≤23 kg/m^2) from the analysis to partially mitigate the potential confounding by latent autoimmune diabetes of the adult (LADA).

Statistical analyses were performed using SPSS (version 22) and MedCalc (version 18.2.1). A 2-sided P <0.05 was considered statistically significant.

Results

Participant Baseline Characteristics

At 3 years' (3.2 ± 0.4) follow-up, 163 participants (17%) experienced diabetes progression (72 on sustained insulin treatment and 91 had indication for insulin treatment). As shown in Table 1, participants with diabetes progression were younger at cohort enrolment and at T2DM diagnosis compared to non-progressors. They had a higher level of HbA1c, a lower level of HDL cholesterol and a higher level of triacylglycerol. In addition, they were more likely to be on sulfonylurea and DPP4 inhibitor treatments and were more likely to be ethnic minorities. There were no statistical differences in BMI, blood pressure and LDL cholesterol levels between progressors and non-progressors. The number of participants with normal or below-normal BMI (≤23 kg/m^2) did not significantly differ between the 2 groups (17.2% in progressors vs 22.5% in non-progressors, P = 0.14).

Stratification of participants by ethnicity showed that Malays and Indians had younger chronological age and shorter diabetes duration at-baseline as compared to their Chinese counterparts. They also had higher BMIs and lower HDL cholesterol levels. In addition, Malay participants had a higher proportion of current smokers and higher levels of LDL cholesterol and triacylglycerol as compared to the other 2 ethnic groups. There were no statistical differences in age at T2DM diagnosis, blood pressure, HbA1c and use of oral glucose-lowering medications at-baseline across the 3 ethnic groups (Table 2).

Clinical and Biochemical Determinants of Diabetes Progression

Multivariable LR showed that age at T2DM diagnosis, Malay ethnicity, BMI, baseline HbA1c and number of oral glucose-lowering medications were significantly associated with diabetes progression, independent of other clinical and biochemical covariates (Table 3).

Forward LR suggested that 4 variables—age at T2DM diagnosis, Malay ethnicity, HbA1c and number of oral glucose-lowering medications—were independent determinants for diabetes progression (Table 4). AUC derived from the model of these 4 variables was 0.76 (95% confidence interval, 0.72-0.80).

A similar outcome was obtained when only participants with transition-to-sustained insulin use (n = 72) were considered as diabetes progressors in the multivariable analysis (Table 5). Excluding participants with normal BMIs from data analysis did not materially change the outcomes either (data not shown).

Discussion

In this 3-year follow-up study, we found that a younger age at T2DM diagnosis, poorer glycaemic control at-baseline and Malay ethnicity were independent determinants for progression to requirement of sustained insulin treatment in patients with T2DM. To our knowledge, this may be the first study on clinical determinants of diabetes progression in multiethnic Asians with T2DM.

The association between a higher HbA1c level and an increased risk of T2DM progression has been reported elsewhere.[4,10] A growing body of in vitro and in vivo data

Table 1. Clinical and Biochemical Characteristics of Participants with Type 2 Diabetes Stratified by Status of Diabetes Progression

	Total n = 940	**Non-Progressor n = 777**	**Progressor n = 163**	***P* Value***
Chronological age (years)	**57.6 ± 10.3**	**58.4 ± 9.9**	**54.1 ± 11.2**	**<0.001**
Age at T2DM diagnosis (years)	**48.8 ± 10.4**	**49.7 ± 10.3**	**44.6 ± 10.0**	**<0.001**
Male sex (%)	52.7	52.1	55.2	0.49
Ethnicity (%)				**0.04**
Chinese	**56.5**	**58.4**	**47.2**	
Malay	**18.3**	**16.9**	**25.2**	
Indian	**25.2**	**24.7**	**27.6**	
Diabetes duration (years)	7.0 (3.0 – 12.0)	6.0 (3.0 – 12.0)	8.0 (4.0 – 12.3)	0.27
Current smoker (%)	9.0	8.1	13.0	0.07
HbA1c (%)	**7.2 ± 0.9**	**7.1 ± 0.8**	**7.8 ± 1.0**	**<0.001**
mmol/mol	**55 ± 7**	**54 ± 6**	**62 ± 8**	
Body mass index (kg/m^2)	27.3 ± 5.0	27.3 ± 5.1	27.4 ± 4.7	0.72
Blood pressure (mmHg)				
Systolic	139 ± 18	139 ± 18	138 ± 17	0.63
Diastolic	79 ± 9	79 ± 9	79 ± 10	0.61
Lipids profile (mmol/L)				
HDL cholesterol	**1.31 ± 0.37**	**1.33 ± 0.37**	**1.22 ± 0.35**	**0.001**
LDL cholesterol	2.72 ± 0.81	2.71 ± 0.80	2.80 ± 0.85	0.19
Triacylglycerol	**1.33 (1.01 – 1.85)**	**1.29 (0.99 – 1.80)**	**1.48 (1.05 – 2.18)**	**0.002**
Renal function				
eGFR (ml/min/1.73 m^2)	**88.6 ± 22.4**	**87.9 ± 21.5**	**91.7 ± 26.2**	**0.05**
uACR (μg/mg)	**16.0 (5.0 – 58.0)**	**15.0 (4.0 – 50.5)**	**22.0 (7.0 – 89.5)**	**0.03**
Hypoglycaemic medications (%)				
Metformin	82.6	81.6	87.7	0.07
Sulfonylurea	**47.6**	**45.0**	**59.5**	**0.001**
DPP4 inhibitors	**6.1**	**5.0**	**11.1**	**0.01**
Thiazolidinediones	0.5	0.5	0.6	0.87

DPP4: Dipeptidyl peptidase-4; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; T2DM: Type 2 diabetes mellitus; uACR: Urinary albumin-to-creatinine ratio

Data are presented as proportion (%) for categorical variables, mean ± SD or median (IQR) for continuous variables.

*Differences between progressors and non-progressors were compared by Student's t-test, Mann-Whitney U test or χ^2 test, where appropriate. All tests had a power of >80%. Variables which differed significantly between groups are in bold.

have supported the important role of glucotoxicity in diabetes progression.[9] It has been known for decades that resolving hyperglycaemia itself may improve insulin secretion.[8] The mechanistic linkages between poor glycaemic control and diabetes progression may involve endoplasmic reticulum and oxidative stress which are closely related with beta cell dysfunction.[8,10,14] Data from our study reinforces the importance of better glycaemic control in slowing down diabetes progression (at least in patients with low risk of hypoglycaemia).

The association of young age at T2DM onset with diabetes progression has been reported in non-Asian populations.[4,10,15,16] Data from our study of Southeast Asians with T2DM are agreeable with the early literature. The pathophysiologic linkage between early age of T2DM onset and diabetes progression may be multifactorial. Age at T2DM diagnosis can be a determinant of the ability to cope with diabetes. Indeed, T2DM patients with young diabetes onset age in our SMART2D cohort are characterised by poorer glycaemic control.[17] Therefore, the resultant glucotoxicity in this group of patients may contribute to accelerated decline of beta cell function. On the other hand, behavioural and lifestyle risk factors may also be parts of the pathologic network which directly or indirectly affect the rate of diabetes progression. In corollary, patients with early-onset T2DM had a higher proportion of

Table 2. Clinical and Biochemical Characteristics of Participants with Type 2 Diabetes Stratified by Ethnicity

	Chinese n = 531	Malay n = 172	Indian n = 237	*P* Value*
Chronological age (years)	**58.8 ± 10.3**	**55.5 ± 9.1**	**56.2 ± 9.8**	**<0.001**
Age at T2DM diagnosis (years)	49.4 ± 10.4	48.0 ± 10.2	48.1 ± 10.0	0.15
Male sex (%)	54.0	52.9	49.4	0.49
Diabetes duration (years)	**8.0 (3.0 – 14.0)**	**5.0 (3.0 – 10.0)**	**7.0 (3.0 – 10)**	**0.01**
Current smoker (%)	**8.5**	**14.4**	**6.3**	**0.03**
HbA1c (%)	7.2 ± 0.9	7.1 ± 0.9	7.2 ± 0.9	0.63
mmol/mol	55 ± 7	54 ± 7	55 ± 7	
Body mass index (kg/m^2)	**26.2 ± 4.4**	**29.7 ± 5.6**	**28.1 ± 5.1**	**<0.001**
Blood pressure (mmHg)				
Systolic	139 ± 18	138 ± 17	137 ± 17	0.07
Diastolic	78 ± 9	80 ± 9	80 ± 10	0.12
Lipids profile (mmol/L)				
HDL cholesterol	**1.34 ± 0.35**	**1.26 ± 0.32**	**1.28 ± 0.42**	**0.01**
LDL cholesterol	**2.70 ± 0.80**	**2.86 ± 0.96**	**2.68 ± 0.71**	**0.05**
Triacylglycerol	**1.32 (1.01 – 1.85)**	**1.46 (1.10 – 2.14)**	**1.21 (0.94 – 1.64)**	**<0.001**
Renal function				
eGFR (ml/min/1.73 m^2)	**87.7 ± 22.6**	**85.9 ± 25.0**	**92.5 ± 19.6**	**0.01**
uACR (μg/mg)	**16.0 (5.0 – 66)**	**26.0 (8.0 – 89)**	**11.0 (3.0 – 35)**	**<0.001**
Hypoglycaemic medications (%)				
Metformin	82.1	83.7	83.1	0.87
Sulfonylurea	45.6	50.6	49.8	0.38
DPP4 inhibitors	6.8	6.4	4.2	0.38
Thiazolidinediones	0.2	0.6	1.3	0.17

DPP4: Dipeptidyl peptidase-4; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; T2DM: Type 2 diabetes mellitus; uACR: Urinary albumin-to-creatinine ratio
Data are presented as proportion (%) for categorical variables, mean ± SD or median (interquartile range) for continuous variables.
*Differences across ethnic groups were compared by one-way analysis of variance, Kruskal- Wallis test or χ^2 test, where appropriate. Variables which differed significantly across the 3 ethnic groups are in bold.

Table 3. Clinical and Biochemical Variables Associated with Diabetes Progression in Multivariable Analysis

	Odds Ratio (95% CI)	*P* Value
Age at T2DM diagnosis (years)	**0.96 (0.94 – 0.98)**	**0.001**
Female sex*	1.07 (0.71 – 1.63)	0.74
Malay ethnicity*	**1.94 (1.19 – 3.19)**	**0.009**
Indian ethnicity*	1.31 (0.83 – 2.06)	0.25
Current smoker*	1.13 (0.60 – 2.14)	0.70
Diabetes duration (years)	0.98 (0.95 – 1.01)	0.21
HbA1c (%)	**2.22 (1.80 – 2.72)**	**<0.0001**
Body mass index (kg/m^2)	**0.96 (0.92 – 1.00)**	**0.04**
Systolic blood pressure (mmHg)	1.00 (0.99 – 1.02)	0.49
HDL cholesterol (mmol/L)	0.60 (0.30 – 1.17)	0.13
Triacylglycerol (mmol/L)	1.12 (0.90 – 1.38)	0.30
eGFR (ml/min/1.73m^2)	1.00 (1.00 – 1.02)	0.38
No. of glucose-lowering medications	**1.87 (1.39 – 2.51)**	**<0.0001**

CI: Confidence interval; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; T2DM: Type 2 diabetes mellitus; uACR: Urinary albumin-to-creatinine ratio
Multivariable logistic regression: dependent variable – diabetes progression (binary).
All variables were entered as independent variables. Variables which were significantly associated with diabetes progression are in bold.
*Male sex, Chinese ethnicity and non-current smoker were taken as reference, respectively.

Table 4. Determinants of Diabetes Progression and Their Odds Ratios in the Parsimonious Model Selected by Forward Logistic Regression

	Odds Ratio (95% CI)	*P* Value
Age at T2DM diagnosis (years)	0.97 (0.95 – 0.98)	<0.001
Malay ethnicity*	1.86 (1.17 – 2.94)	0.009
HbA1c (%)	2.23 (1.83 – 2.72)	<0.0001
No. of glucose-lowering medications	1.80 (1.36 – 2.38)	<0.0001

CI: Confidence interval; HbA1c: Glycated haemoglobin; T2DM: Type 2 diabetes mellitus

Multivariable logistic regression: dependent variable – diabetes progression (binary). Independent variables: age at T2DM diagnosis, Malay ethnicity, HbA1c and number of glucose-lowing medications at-baseline as selected by the forward logistic regression.

*Chinese ethnicity was taken as reference.

Table 5. Clinical and Biochemical Variables Associated with Transition-to-Sustained Insulin Use in Multivariable Logistic Regression

	Odds Ratio (95% CI)	*P* Value
Age at T2DM diagnosis (years)	**0.95 (0.92 – 0.98)**	**<0.001**
Female sex*	1.62 (0.90 – 2.90)	0.11
Malay ethnicity*	**2.22 (1.16 – 4.24)**	**0.02**
Indian ethnicity*	0.92 (0.47 – 1.82)	0.82
Current smoker*	1.28 (0.53 – 3.08)	0.58
Diabetes duration (years)	0.98 (0.95 – 1.02)	0.42
HbA1c (%)	**2.20 (1.65 – 2.94)**	**<0.0001**
Body mass index (kg/m^2)	0.95 (0.90 – 1.01)	0.10
Systolic blood pressure (mmHg)	1.01 (1.00 – 1.03)	0.18
HDL cholesterol (mmol/L)	0.59 (0.23 – 1.53)	0.28
Triacylglycerol (mmol/L)	0.96 (0.66 – 1.38)	0.81
eGFR (ml/min/1.73m^2)	1.00 (0.99 – 1.01)	0.73
No. of glucose-lowering medications	**2.10 (1.39 – 3.19)**	**<0.001**

CI: Confidence interval; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; T2DM: Type 2 diabetes mellitus

Multivariable logistic regression: dependent variable – diabetes progression (binary). All variables in the table were entered as independent variables in the model.

*Male sex, Chinese ethnicity and non-current smoker were taken as reference, respectively. Variables which were significantly associated with diabetes progression are in bold.

current smokers.[17] Additionally, we postulate that genetic risk factors may play a role in risk of diabetes progression. Several genetic mutations related with beta cell function have been reported in patients with young-onset T2DM.[18] Given the rapid and increased prevalence of early-onset T2DM worldwide,[18,19] novel approaches are urgently needed to prevent or slow down the fast deterioration of diabetes control in this group of patients.

The independent association of Malay ethnicity with a higher risk of diabetes progression is novel. Malay participants in our cohort have a higher proportion of current smokers and higher levels of BMI and triacylglycerol at-baseline (Table 2). It is reasonable to postulate that these traditional risk factors may at least partly contribute to the accelerated diabetes progression in Malays with T2DM. Although several studies have examined ethnic differences in insulin resistance among the 3 ethnic groups in Singapore,[20,21] studies comparing beta cell function across ethnic groups are relatively scarce. One early study showed that healthy and lean Malay males exhibited a lower insulin secretory capacity that was accompanied by a higher glucose excursion in response to mixed-meal tolerance test as compared to their Chinese and Indian counterparts.[22] To our knowledge, no study has systematically compared beta cell function and its temporal change across Malay, Indian and Chinese patients with T2DM.

Strengths and Limitations

Our study has strengths and weaknesses. It is prospective in design with a planned follow-up. The cohort comprised multiethnic participants which may represent major subpopulations living in Southeast Asia. Nevertheless, several weaknesses should be mentioned. First, there is no consensus or "gold standard" to define diabetes progression. We took the requirement for sustained insulin treatment as a surrogate marker of diabetes progression. The decision for initiation of insulin treatment is sometimes arbitrary and determined by several patient- and clinician-related factors. Second, given the nature of the study, we were unable to elucidate the mechanistic linkage between identified clinical determinants and diabetes progression. Future studies on temporal changes in beta cell function and its related risk factors are needed. Third, it is possible that some participants with accelerated diabetes progression may have LADA, especially for those with rapid diabetes progression and normal BMI.[23] However, the number of participants with normal or below-normal BMI (≤23 kg/m^2) did not significantly differ between those with rapid diabetes progression and their counterparts. Also, excluding those with normal BMI from data analysis did not materially change the outcome. These analyses may partially mitigate the concern on confounding by LADA. Having said so, we did not have data on the islet-specific autoantibodies or C-peptide. Future studies are needed to further address this important question. Fourth, some risk factors such as socioeconomic status and medication adherence were not available in the study. These are also potential important determinants of diabetes progression. Finally, our participants were recruited from a regional hospital and a primary care facility. Hence, further studies are needed to assess the generalisability of the findings in our study.

Conclusion

In this 3-year follow-up study of multiethnic Asians with T2DM, 1 year younger at T2DM diagnosis and 1% increment of HbA1c at-baseline are associated with a 1.03-fold and a 2.23-fold increased odds for diabetes progression, respectively. Malay ethnicity is associated with a 1.86-fold increased odds for diabetes progression, independent of traditional risk factors, as compared to their Chinese counterparts. Further mechanistic studies are needed to shed light on novel strategies to slow down T2DM progression in multiethnic Asians with T2DM.

Acknowledgement

This study was partly supported by the National Medical Research Council (Grant no. CIRG/1395/2014). The funder had no roles in the study design, data collection, analysis, interpretation, writing of the report and the decision to submit the article for publication.

REFERENCES

1. Thai AC, Yeo PP, Lun KC, Hughes K, Ng WY, Lui KF, et al. Diabetes mellitus and its chronic complications in Singapore: an increasing healthcare problem. Ann Acad Med Singapore 1990;19:517-23.
2. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61:2461-98.
3. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. UK Prospective Diabetes Study Group. Diabetes 1995;44:1249-58.
4. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281:2005-12.
5. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. Diabetes Care 2017;40:S64-74.
6. Fitipaldi H, McCarthy MI, Florez JC, Franks PW. A global overview of precision medicine in type 2 diabetes. Diabetes 2018;67:1911-22.
7. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009;32:S151-6.
8. Halban PA, Polonsky KS, Bowden DW, Hawkins MA, Ling C, Mather KJ, et al. Beta-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. Diabetes Care 2014;37:1751-8.
9. White MG, Shaw JA, Taylor R. Type 2 diabetes: the pathologic basis of reversible beta-cell dysfunction. Diabetes Care 2016;39:2080-8.
10. Zhou K, Donnelly LA, Morris AD, Franks PW, Jennison C, Palmer CN, et al. Clinical and genetic determinants of progression of type 2 diabetes: a DIRECT study. Diabetes Care 2014;37:718-24.
11. Bagust A, Beale S. Deteriorating beta-cell function in type 2 diabetes: a long-term model. QJM 2003;96:281-8.
12. Liu JJ, Tavintharan S, Yeoh LY, Sum CF, Ng XW, Pek SL, et al. High normal albuminuria is independently associated with aortic stiffness in patients with type 2 diabetes. Diabet Med 2014;31:1199-204.
13. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-9.
14. Robertson RP. Beta-cell deterioration during diabetes: what's in the gun? Trends Endocrinol Metab 2009;20:388-93.
15. Donnan PT, Steinke DT, Newton RW, Morris AD, Collaboration DM. Changes in treatment after the start of oral hypoglycaemic therapy in type 2 diabetes: a population-based study. Diabet Med 2002;19:606-10.
16. Ringborg A, Lindgren P, Yin DD, Martinell M, Stalhammar J. Time to insulin treatment and factors associated with insulin prescription in Swedish patients with type 2 diabetes. Diabetes Metab 2010;36:198-203.
17. Liu JJ, Liu S, Gurung RL, Ang K, Tang WE, Sum CF, et al. Risk of progressive chronic kidney disease in individuals with early-onset type 2 diabetes: a prospective cohort study. Nephrol Dial Transplant 2018 Jul 10.
18. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol 2018;6:69-80.
19. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes Care 2018;41:2648-68.
20. Gao H, Salim A, Lee J, Tai ES, van Dam RM. Can body fat distribution, adiponectin levels and inflammation explain differences in insulin resistance between ethnic Chinese, Malays and Asian Indians? Int J Obes (Lond) 2012;36:1086-93.
21. Tan HC, Yew TW, Chacko S, Tai ES, Kovalik JP, Ching J, et al. Comprehensive assessment of insulin resistance in non-obese Asian Indian and Chinese men. J Diabetes Investig 2018;9:1296-303.
22. Tan VM, Lee YS, Venkataraman K, Khoo EY, Tai ES, Chong YS, et al. Ethnic differences in insulin sensitivity and beta-cell function among Asian men. Nutr Diabetes 2015;5:e173.
23. Salem SD, Saif-Ali R, Muniandy S, Al-Hamodi Z, Ismail IS. Comparison of adults with insulin resistance (IR) in latent autoimmune diabetes versus IR in glutamic acid decarboxylase antibody-negative diabetes. Ann Acad Med Singapore 2014;43:107-12.