Relationship between onset age of type 2 diabetes mellitus and vascular complications based on propensity score matching analysis

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INTRODUCTION
The quality of life of patients with type 2 diabetes mellitus is adversely affected by both macrovascular and microvascular complications. Atherosclerosis is a macrovascular complication that mostly develops in diabetes patients, and the life expectancy of diabetes patients is severely impaired¹⁻³. The risk of myocardial infarction and stroke increases greatly in these patients as well⁴⁻⁵. Diabetic nephropathy and retinopathy (DR) are the leading causes of end-stage renal disease and blindness¹⁻³. In previous decades, type 2 diabetes mellitus was a condition that usually developed in older people⁶. Currently, the incidence of early-onset type 2 diabetes mellitus (age ≤40 years) has increased globally as a result of the following factors: high-energy diets, reduced physical activity, and poor metabolic control of blood sugar, lipids and blood pressure⁷. Previous studies have reported that the risk of macrovascular events and mortality is higher in patients with type 2 diabetes...
mellitus. These complications mostly develop in the following cases: old age, prolonged duration of diabetes and diagnosis at a younger age. The risk of death is higher in patients with early-onset type 2 diabetes mellitus, and early cardiovascular disease (CVD) mortality is quite common in these patients. The risk factors for diabetic microvascular complications and CVD are as follows: hyperglycemia, diabetes duration, dyslipidemia, hypertension and insulin resistance. Compared with patients with late-onset diabetes (>40 years of age), metabolic control is poorer in patients with early-onset type 2 diabetes mellitus. In patients with early-onset type 2 diabetes mellitus, the protective effect of drugs is lesser and these patients have a higher risk of developing vascular complications. Furthermore, this effect is also closely related to diabetes duration. Previous studies only focused on single vascular complication events; the age- and sex-matching method of analysis was not used in these studies. In China, people aged ≥60 years are defined as the elderly. It is unknown whether the incidence of diabetes after the age of 60 years also brings a difference in complications. So, the aim of the present study was to determine if a clear difference between clinical features and vascular complications existed between EOD and LOD patients in two different age groups according to an onset age of 40 or 60 years.

MATERIALS AND METHODS

Study population and cohort

From March 2010 to July 2017, a total of 3,568 patients with type 2 diabetes mellitus were recruited at the Endocrinology Department of the First Affiliated Hospital of Fujian Medical University. The patients were divided into two groups according to an onset age of 40 or 60 years (EOD40 and LOD40 refer to the onset age before 40 years old and after 40 years, respectively; EOD60 and LOD60 refer to the onset age before 60 years and after 60 years, respectively). Propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex, yielding a total of 780 participants in the 40 years group: 520 participants in the LOD40 group and 260 participants in the EOD40 group. A total of 537 participants in the 60 years group: 358 participants in the LOD60 group and 179 participants in the EOD60 group (SAS Institute Inc., Cary, NC). The diagnostic criteria for type 2 diabetes mellitus were based on the 1999 World Health Organization’s criteria. The exclusion criteria were as follows: (i) type 1 diabetes, gestational diabetes or any other special types of diabetes, as such patients are prone to developing acute complications, such as diabetic ketoacidosis and heavy ketonuria; (ii) renal disease: this includes all kinds of acute or chronic glomerulonephritis, nephrotic syndrome, and acute and chronic renal failure; and (iii) neuropathy: this includes all kinds of neurotoxic effects: familial, alcoholic, nutritional, uremic, toxic and drug-induced. This study was approved by the Ethics Committee of Biomedical Research of the First Affiliated Hospital of Fujian Medical University, and all the participants provided signed informed consent.

Clinical measurements

By carrying out a detailed inquiry of patient history, the following information was obtained: sex, age, duration of diabetes, medical history, hypertensive and Toronto Clinical Scoring System neurological symptoms (numbness in lower extremities, pain in lower extremities, pricking, fatigue, difficulty in walking and upper limb symptoms). Physical examination parameters were as follows: height, weight, waist circumference, hip circumference, blood pressure, neurological examination and ophthalmic examination. Body mass index (BMI; kg/m²) = bodyweight (kg) / height² (m²). Body surface area (BSA; m²) = (men: 0.0067 × height [m] + 0.0127 × bodyweight [kg] − 0.0698; women: 0.00586 × height [m] + 0.0126 × bodyweight [kg] − 0.0461). Measurement of standardized systolic blood pressure and diastolic blood pressure was carried out after a rest of 15 min. Acupuncture was used to detect the severity of pain; 10 g of nylon silk was used for tactile sensation; a temperature sensation tester was used to determine temperature sensation; a standard 128-kHz tuning fork test was used for vibration sensation; and a tendon hammer was used to check iliac reflexes.

After the dilation of the pupils, the fundi of the eyes were examined by a professional ophthalmologist.

Biochemical measurements

Fasting blood glucose, serum creatinine, total cholesterol, triglycerides, low-density lipoprotein cholesterol and glycated hemoglobin (HbA1c) were analyzed. The HbA1c assay was determined by high-performance liquid chromatography (Variant TM II; Bio-Rad, Hercules, CA, USA). Urinary albumin-to-creatinine ratio was calculated by dividing the urine albumin by urine creatinine during mid-morning urine collection (mg/g). The estimated glomerular filtration rate (eGFR) was calculated by the dietary modification formula for kidney disease: eGFR = 186 × (creatinine [μmol/L] / 88.41) – 1.154 × age – 0.203 (×0.742, female).

Ultrasonic measurements

Carotid intima-media thickness, bilateral common carotid arteries, the bifurcation between both the common carotid arteries and bilateral subclavian intima-media thickness were measured with a Prosound z-10 color Doppler ultrasound system (ALOKA). To determine whether there is plaque adhesion between the bilateral common carotid artery, internal carotid artery, external carotid artery and subclavian artery, the transverse and longitudinal sections of ALOKA were scanned. The frequency of the probe was 5–13 MHz. The ankle-brachial index (ABI) was carried out using Vista AVS, which is a peripheral vascular diagnostic system (U.S. summit company, White Plains, NY, USA). To measure systolic pressure of the bilateral brachial and radial artery, the patient was asked to lie down for 15 min and then exercise, respectively. The frequency of the probe was 8 MHz. These steps follow the AHA statement. The formula for determining the ABI is as follows: ABI = ankle artery systolic pressure (mmHg) / brachial artery systolic pressure (mmHg). Echocardiographic measurements were as follows: left ventricular diastolic diameter (LVDd),
interventricular septal thickness (IVST) and left ventricular posterior wall end-diastolic thickness (LVPWT) were measured with two-dimensional Doppler echocardiography with Vivid 7 digital ultrasound system (GE-Vingmed Ultrasound, Horten, Norway). Early diastolic velocity (E), early diastolic annual velocities (e) and lateral e were determined in the apical four chamber view of these systems. The average "e" is the average of septal e and lateral e. Left ventricular mass (LVM) was calculated using the Devereux formula: \( \text{LVM (g)} = 0.8 \times \left[ 1.04 \times (\text{LVDd} + \text{IVST} + \text{LVPWT}) - 3 \right] + 0.6 \times \text{LVM (g/m}^2) \) = LVM / BSA. The relative thickness of left ventricular wall = (LVPWT + IVST)/LVDd.

**Metabolic index**

Hypertension: systolic blood pressure \( \geq 140\) mmHg and/or diastolic blood pressure \( \geq 90\) mmHg or taking antihypertensive drugs22. Proteinuria: albumin : creatinine ratio (ACR) \( \geq 30 \) mg/g. Targets of metabolic control: HbA1c concentration \( < 7\%\), low-density lipoprotein cholesterol \( < 2.6\) mmol/L and BMI \( < 24 \) kg/m\(^2\).

**Microvascular complications**

In the year 2014, the American Diabetes Association and the National Kidney Foundation defined the criteria for chronic kidney disease (CKD) for patients with type 2 diabetes mellitus and albuminuria (ACR \( > 30 \) mg/g at least twice in 3-6 months and/or eGFR < 60 mL/min/1.73 m\(^2\)); they excluded the possibility of another injured kidney24,25. To determine DR, physicians examined the fundus of the eye after the dilation of the pupil; some of the typical retinal changes are as follows: microaneurysma, hemorrhaging, exudate and vitreomma25,26. The diagnostic criteria for diabetic peripheral neuropathy (DPN) are as follows27: (i) clear history of diabetes; (ii) diagnosis of peripheral neuropathy during or after diabetes; (iii) clinical symptoms and signs that coincide with the performance of DPN; and (iv) patients with clinical symptoms, such as pain, numbness and paresthesia. These patients were examined by any one of the following five processes: acupuncture analgesia, touch–pressure sensation, temperature sensation, vibration sensation or tendon reflexes. There were patients that did not show any clinical symptoms (other causes of diabetic neuropathy were excluded).

**Macrovascular complications**

Carotid atherosclerosis (CAS), while carrying out vascular longitudinal and cross-sectional scans, was defined as follows: an echogenic structure that protrudes into the lumen, a blood flow defect that protrudes into the lumen and a local intima-media thickness \( \geq 1.3 \) mm29. Lower extremity atherosclerosis was defined as follows: resting ABI \( \leq 0.9 \) or ABI after exercise \( \geq 1.5\% \) in either side of the lower extremities29. Cardiovascular structural lesions: left ventricular remodeling: left ventricular mass index \( > 115 \) g/m\(^2\) (in men), 95 g/m\(^2\) (in women) or relative thickness of the left ventricular wall \( > 0.42 \). Left ventricular diastolic dysfunction: \( E/e > 15 \) or the average e \( < 0.09 \) m/s (when \( E/e = 8-15 \)). The 10-year risk score for coronary heart disease (Framingham risk score) was derived from the Framingham Heart Study, which calculated the risk of developing a coronary heart attack in the next 10 years based on the following factors: age, total cholesterol, history of smoking, high-density lipoprotein cholesterol and systolic blood pressure.

**Statistical analysis**

All statistical analyses were carried out using Statistical Analysis System (SAS; SAS Institute, Cary, NC, USA) and SPSS version 18 software (SPSS, Chicago, IL, USA). The median (interquartile range) was used to describe non-normal distribution data; the mean \pm standard deviation (SD) was used to describe the data of normal distribution, and count variables data were described by percentages. Normal distribution of continuous variables was tested with a Student’s t-test. Non-normal distribution of continuous variables was determined by analysis of a rank-sum test. The Pearson \( \chi^2 \)-test was used for classifying variables. To determine the correlation between EOD and LOD patients, diabetic vascular complications were analyzed by a two-classification logistic regression model. Statistical significance was determined by \( P < 0.05 \).

**RESULTS**

**Population characteristics**

*Baseline characteristics after propensity score matching*

A total of 3,568 patients with type 2 diabetes mellitus were recruited (Table 1). Propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex, yielding a total of 780 participants in the 40 years group: 520 participants in the LOD\(_{40}\) group and 260 participants in the EOD\(_{40}\) group. A total of 537 participants in the 60 years group: 358 participants in the LOD\(_{40}\) group and 179 participants in the EOD\(_{60}\) group. The results are shown in Table 1. In addition, compared with LOD\(_{40}\) patients, EOD\(_{40}\) patients had higher Toronto Clinical Scoring System and ACR scores. However, eGFR values of EOD\(_{40}\) patients were lower than those of LOD\(_{40}\) patients. Meanwhile, the prevalence of DR, CKD and DPN was higher in EOD\(_{40}\) patients (\( P < 0.05 \)). The same trend was seen in EOD\(_{60}\) patients.

Furthermore, compared with LOD\(_{40}\) patients, EOD\(_{40}\) patients had higher systolic blood pressure; therefore, EOD\(_{40}\) patients were more likely to use antihypertensive drugs and used a lipid-lowering strategy. Moreover, the prevalence of CAS was higher in EOD\(_{40}\) patients.

*Comparison in the prevalence of vascular complications for EOD and LOD groups after matching*

Compared with LOD patients, EOD patients had a significantly higher prevalence of microvascular complications (DR, CKD and DPN; EOD\(_{40}\) vs LOD\(_{40}\): 39.2% vs 26%, \( P < 0.001 \); 57.3% vs 38.5%, \( P < 0.001\); 34.2% vs 21.5%, \( P < 0.001 \)); EOD\(_{60}\) vs LOD\(_{40}\): 26.8% vs 16.5%, \( P = 0.005 \); 42.9% vs 27.9%, \( P = 0.001 \); 40.8% vs 26%, \( P < 0.001 \)). However, no statistical difference
### Table 1 | Patient characteristics after propensity score matching

|                        | Diabetes onset age by 40 years group |                      | Diabetes onset age 60 years group |                      |
|------------------------|--------------------------------------|----------------------|-----------------------------------|----------------------|
|                        | All (n = 780)                        | LOD40 group (n = 520) | EOD40 group (n = 260)             | All (n = 537)        |
| Male, n (%)            | 372 (47.7%)                          | 247 (47.5%)          | 125 (48.1%)                       | 268 (49.9%)          |
| Age (years)            | 53.32 ± 6.18                         | 53.44 ± 6.08         | 53.08 ± 6.37                      | 75.26 ± 3.83         |
| DM duration (years)    | 8 (3.1)                              | 5 (1.8)              | 15 (10.2)*                        | 10 (4.18)            |
| HT history, n (%)      | 339 (43.5%)                          | 206 (39.6%)          | 133 (51.2%)*                      | 382 (71.1%)          |
| Biguanides, n (%)      | 433 (55.5%)                          | 269 (51.7%)          | 164 (63.1%)*                      | 280 (52.1%)          |
| Insulin secretogogue, n (%) | 436 (55.9%)     | 285 (54.8%)          | 151 (58.1%)                       | 328 (61.1%)          |
| Other oral hypoglycemic drugs, n (%) | 139 (17.8%)     | 79 (15.2%)           | 60 (23.1%)*                       | 258 (48%)            |
| Insulin, n (%)         | 329 (42.2%)                          | 164 (31.5%)          | 165 (63.5%)*                      | 202 (37.6%)          |
| Antihypertensive drugs, n (%) | 215 (27.6%)     | 128 (24.6%)          | 87 (33.5%)*                       | 231 (43%)            |
| Lipid-lowering, n (%)  | 56 (7.2%)                            | 28 (5.4%)            | 28 (10.8%)                        | 55 (10.2%)           |
| SBP (mmHg)             | 135.01 ± 19.88                       | 132.85 ± 18.3        | 139.32 ± 22.11*                   | 142.88 ± 21.25       |
| DBP (mmHg)             | 79.89 ± 10.69                        | 79.77 ± 10.49        | 80.13 ± 11.13                     | 75.28 ± 11.75        |
| BMI (kg/m²)            | 24.25 ± 3.76                         | 24.14 ± 3.67         | 24.46 ± 3.94                      | 24.95 ± 3.63         |
| HbA1c (%)              | 945 ± 256                            | 949 ± 268            | 936.2 ± 23.3                      | 915.2 ± 243          |
| TCH (mmol/L)           | 485 ± 131                            | 487 ± 126            | 482.1 ± 141                       | 446.6 ± 125          |
| LDL (mmol/L)           | 302 ± 111                            | 303 ± 106            | 3 ± 11.9                          | 2.74 ± 1.06          |
| TG (mmol/L)            | 14.0 (2.1)                           | 14.4 (105.2)         | 13.2 (0.89225)                    | 1.58 ± 1.26          |
| <140/90 mmHg, n (%)    | 466 (59.7%)                          | 333 (64%)            | 133 (51.2%)*                      | 215 (40.3%)          |
| <24 kg/m², n (%)       | 375 (50.3%)                          | 262 (52.3%)          | 113 (46.3%)                       | 199 (41.4%)          |
| <16% n (%)             | 128 (16.8%)                          | 90 (17.7%)           | 38 (15.1%)                        | 108 (21.1%)          |
| LDL <2.6 mmol/L, n (%) | 291 (38.1%)                          | 190 (37.5%)          | 101 (39.5%)                       | 253 (48.7%)          |
| Left ABI (at rest)     | 108 ± 0.1                            | 109 ± 0.09           | 107 ± 0.12                        | 1.03 ± 0.19          |
| Right ABI (at rest)    | 109 ± 0.12                           | 109 ± 0.12           | 109 ± 0.11                        | 1.05 ± 0.24          |
| Left ABI (after exercise) | 106 ± 0.12  | 107 ± 0.13           | 103 ± 0.11                        | 1.08 ± 0.13          |
| Right ABI (after exercise) | 107 ± 0.14   | 109 ± 0.14           | 1.04 ± 0.11*                      | 1.06 ± 0.12          |
| RWT                    | 0.04 ± 0.06                           | 0.039 ± 0.05         | 0.04 ± 0.06*                      | 0.042 ± 0.06         |
| LVM (g)                | 140 ± 38.23                          | 138.59 ± 38.8        | 142.68 ± 37.07                    | 157.08 ± 49.49       |
| PVE/e                  | 958 ± 355                            | 92.2 ± 294           | 10.38 ± 4.47*                     | 11.8 ± 4.4           |
| Average e (m/s)        | 008 ± 002                            | 008 ± 002            | 007 ± 002                         | 11.8 ± 4.4           |
| Average (m/s)          | 008 ± 002                            | 008 ± 002            | 007 ± 002                         | 11.8 ± 4.4           |
| Framingham score (%)   | 662 ± 704                            | 644 ± 694            | 698.6 ± 724                       | 905.3 ± 275          |
| CAS, n (%)             | 134 (24.6%)                          | 82 (22.1%)           | 52 (29.9%)*                       | 916.5 ± 801          |
| LEA, n (%)             | 107 (18.1%)                          | 70 (17.9%)           | 37 (18.5%)                        | 141 (40.6%)          |
| LVDD, n (%)            | 201 (51.8%)                          | 133 (50.6%)          | 68 (54.4%)                        | 83 (21.9%)           |
| LVR, n (%)             | 402 (67.2%)                          | 263 (68.8%)          | 139 (68.1%)                       | 220 (90.5%)          |
| Cr (mmol/L)            | 58 (46.4702)                         | 56.5 (46.6785)       | 60.15 (48.7618)*                  | 66.55 (53.87)        |
| ACR (mg/g)             | 14.23 (66.9131)                      | 11.82 (63.3117)      | 27.82 (76.3185)*                  | 20.99 (62.81123)     |
| eGFR (mL/min/1.73 m²)  | 11803 (94.6814308)                   | 1199 (97.521439)     | 11289 (60.143791)                 | 92.23 (71.381198)    |
| Albuminuria, n (%)     | 162 (33.1%)                          | 82 (25.1%)           | 80 (49.4%)*                       | 129 (40.3%)          |
| TCSS score             | 316 ± 372                            | 273 ± 357            | 4 ± 404*                          | 3.67 ± 3.9           |
was observed in the prevalence of macrovascular complications, except for CAS. The prevalence of CAS was higher in EOD<sub>40</sub> patients (EOD<sub>40</sub> vs LOD<sub>40</sub>: 29.9% vs 22.1%, \(P = 0.049\); Table 1; Figure 1).

**Correlation between onset age and vascular complications in diabetes patients**

Binary regression analysis was carried out to determine the association between onset age and vascular complications in patients with diabetes (Figure 2). Propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex. Furthermore, adjustments for differences in the following parameters were made: HbA1c%, insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of hypertension. Compared with LOD<sub>40</sub> patients, the odds ratio for the prevalence of microvascular complications for DR, CKD and SN in EOD<sub>40</sub> patients was 2.906 (95% confidence interval [CI] 1.972–4.282), 1.967 (95% CI 1.387–2.791) and 1.672 (95% CI 1.152–2.429), respectively. Meanwhile, the odds ratio for the prevalence of DR and DPN in EOD<sub>60</sub> patients was 1.763 (95% CI 1.092–2.847) and 1.675 (95% CI 1.106–2.537), respectively. However, there were no statistically significant differences in macrovascular complications of EOD and LOD patients (Figure 2). A significant association between onset age and microvascular complications was found regardless of blood pressure, BMI or HbA1c value. The risks of vascular complications with onset age in different subgroups of patients with type 2 diabetes mellitus are shown (Figure 3).

**DISCUSSION**

The results of the present study show that early-onset age of type 2 diabetes mellitus increases the risk of microvascular complications later in life. Compared with late-onset type 2 diabetes mellitus, people with early-onset type 2 diabetes mellitus have a significantly higher risk of developing microvascular complications.

It was found in previous studies that patients with early-onset of type 2 diabetes mellitus had a higher risk of developing cardiovascular disease and a higher cardiac 10-year expected risk than patients with late-onset type 2 diabetes mellitus. Neither study was age or sex matched, nor were any other confounding variables considered\(^7,14-16\). Propensity score matching was carried out in the present study to adjust for differences in age and sex. It was found that there was no independent correlation between the onset age of type 2 diabetes mellitus and the following macrovascular complications: organic cardiopathy, carotid atherosclerosis or lower extremity atherosclerosis. This relationship can still be maintained after adjusting various related confounding factors.

Several epidemiological studies have reported that the risk of developing cardiovascular complications is higher in EOD patients. The occurrence and progression of vascular complications is also greater in EOD patients\(^7,14-16\). In EOD patients,
the risk of developing macrovascular events and death increases proportionally with decreases in age of diagnosis or duration of diabetes. For example, a study carried out on white individuals presented the following results. Compared with LOD patients, the risk of developing myocardial infarction was 14-fold greater in EOD patients (≥45 years onset age). A data registry from Hong Kong also showed that EOD patients have a higher risk of developing CVD in all age groups.

An Australian study showed that the increased death risk of early-onset type 2 diabetes mellitus is closely related with CVD. Hyperglycemia, diabetes duration, dyslipidemia, hypertension and insulin resistance were risk factors for developing diabetic CVD. Gunathilake et al. found that EOD patients (average age of diagnosis was 34 years) already have a higher risk of developing cardiovascular complications (obesity, hyperlipidemia and hypertension). These complications are similar to those observed in older patients with type 2 diabetes mellitus (the average age of diagnosis is 67 years).

Several studies have reported that obesity, dyslipidemia, hypertension and microalbuminuria are common in young type 2 diabetes mellitus patients. These complications can worsen over a certain period of time. The risk of developing macrovascular complications increases in EOD patients because of prolonged duration of diabetes and the fact that metabolic profiles of EOD patients worsen over time.

In the aforementioned studies, the effects of age and sex were reduced by the method of adjustment. For example, a large cross-sectional study was carried out by CNHSS (National

Figure 1 | Distribution of vascular complications in type 2 diabetes mellitus between the onset years of 40 and 60 years in the early-onset diabetes (EOD) group and late-onset diabetes (LOD) group.
HbA1c% Surveillance System in China). The results showed that compared with EOD patients, the risk of developing cardiovascular complications was higher in LOD patients. Compared with LOD patients, EOD patients have a significantly higher risk of developing non-fatal cardiovascular events in all age groups; this is because EOD patients have to manage diabetes over a longer period of time and their body is exposed to damaging high-glucose conditions over a longer period of time. Subsequently, the metabolic conditions of EOD patients deteriorate over a period of time. Various factors that influence the condition of EOD patients have been taken into consideration.

In the present study, propensity score matching was used to eliminate the effects of age and sex. Patients who were categorized in the both age EOD groups had a significantly higher risk of developing macro- and microvascular complications before PSM. After PSM, it was found that the risk of developing macrovascular complications does not increase in EOD patients. Both young and elderly patients are at an equal risk of developing cardiovascular complications. In patients with type 2 diabetes mellitus, the risk of developing macrovascular complications is not related to onset age of diabetes or diabetes duration. However, it was found that left ABI (after exercise), relative thickness of the left ventricular wall WT, peak mitral velocity E (PVE/e) and other macrovascular indicators were higher in EOD patients. Compared with EOD patients, LOD patients have a greater risk of developing macrovascular diseases. Blood vessels tend to harden with age, so the probability of vascular events also increases with age. Therefore, it is suggested that there is a close relationship between the risk of diabetic macrovascular complications and age.

Several previous studies have shown that compared with LOD patients, EOD patients have a higher risk of developing microvascular complications, including diabetic nephropathy, DR and diabetic neuropathy. Previous studies have reported that EOD patients suffer from this disease for a longer duration of time, because they develop severe metabolic disorders due to higher amounts of glucose and fat in their bloodstream. This causes oxidative stress, which activates the renin–angiotensin system. These events finally lead to the development of microvascular complications in EOD patients. In the present study, no significant difference was

|                | OR(95%CI) | P   |
|----------------|----------|-----|
| DR             | 2.906(1.972 - 4.282) | 0.000 |
| CKD            | 1.967(1.387 - 2.791) | 0.000 |
| DPN            | 1.672(1.152 - 2.429) | 0.007 |
| CAS            | 1.434(0.913 - 2.254) | 0.118 |
| LEA            | 0.992(0.601 - 1.638) | 0.975 |
| LVDD           | 1.047(0.641 - 1.710) | 0.835 |
| LVR            | 0.868(0.578 - 1.304) | 0.497 |
| DR             | 1.763(1.092 - 2.847) | 0.020 |
| CKD            | 1.448(0.948 - 2.211) | 0.087 |
| DPN            | 1.675(1.106 - 2.537) | 0.015 |
| CAS            | 1.046(0.623 - 1.758) | 0.864 |
| LEA            | 1.173(0.654 - 2.104) | 0.592 |
| LVDD           | 0.768(0.271 - 2.179) | 0.620 |
| LVR            | 1.174(0.559 - 2.466) | 0.672 |

Figure 2 | Forest plot of the risk of vascular complications of type 2 diabetes mellitus between early-onset diabetes and late-onset diabetes patients. A fully adjusted model including the following parameters: percentage glycated hemoglobin (HbA1c%), insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of hypertension. CAS, carotid atherosclerosis; CI, confidence interval; CKD, chronic kidney disease; DPN, diabetic peripheral neuropathy; DR, include diabetic retinopathy; EOD, early-onset diabetes; LEA, lower extremity atherosclerosis; LOD, late-onset diabetes; LVDD, left ventricular diastolic dysfunction; LVR, left ventricular remodeling; OR, odds ratio.
**ORIGINAL ARTICLE**

**T2DM onset and vascular complications**

| (a) BP>140mmHg | Divided by age 40 | OR(95% CI) | P  |
|-----------------|-------------------|------------|----|
| Micro DR       | 3.774(1.47 - 9.49) | 0.000      |    |
| CDFP           | 1.803(0.12 - 2.59) | 0.880      |    |
| Macro CAS      | 1.856(0.82 - 3.37) | 0.044      |    |
| LEA            | 5.858(1.94 - 17.70) | 0.000      |    |
| LVDD           | 6.457(1.72 - 23.82) | 0.000      |    |
| Divided by age 60 |                   |            |    |
| Micro DR       | 1.690(0.98 - 2.87) | 0.039      |    |
| CDFP           | 1.739(0.12 - 2.59) | 0.880      |    |
| Macro CAS      | 1.806(0.82 - 3.37) | 0.044      |    |
| LEA            | 5.858(1.94 - 17.70) | 0.000      |    |
| LVDD           | 6.457(1.72 - 23.82) | 0.000      |    |

| (b) BP<140mmHg | Divided by age 40 | OR(95% CI) | P  |
|-----------------|-------------------|------------|----|
| Micro DR       | 2.148(0.89 - 5.33) | 0.080      |    |
| CDFP           | 1.950(0.78 - 5.33) | 0.111      |    |
| Macro CAS      | 1.389(0.95 - 2.06) | 0.118      |    |
| LEA            | 0.657(0.30 - 1.52) | 0.374      |    |
| LVDD           | 1.949(0.78 - 5.33) | 0.111      |    |

| (c) BP>240mg/dl | Divided by age 40 | OR(95% CI) | P  |
|-----------------|-------------------|------------|----|
| Micro DR       | 3.774(1.47 - 9.49) | 0.000      |    |
| CDFP           | 1.803(0.12 - 2.59) | 0.880      |    |
| Macro CAS      | 1.856(0.82 - 3.37) | 0.044      |    |
| LEA            | 5.858(1.94 - 17.70) | 0.000      |    |
| LVDD           | 6.457(1.72 - 23.82) | 0.000      |    |

| (d) BMI>24kg/m² | Divided by age 40 | OR(95% CI) | P  |
|-----------------|-------------------|------------|----|
| Micro DR       | 2.148(0.89 - 5.33) | 0.080      |    |
| CDFP           | 1.950(0.78 - 5.33) | 0.111      |    |
| Macro CAS      | 1.389(0.95 - 2.06) | 0.118      |    |
| LEA            | 0.657(0.30 - 1.52) | 0.374      |    |
| LVDD           | 1.949(0.78 - 5.33) | 0.111      |    |

| (e) HbA1c>7.0% | Divided by age 40 | OR(95% CI) | P  |
|-----------------|-------------------|------------|----|
| Micro DR       | 3.774(1.47 - 9.49) | 0.000      |    |
| CDFP           | 1.803(0.12 - 2.59) | 0.880      |    |
| Macro CAS      | 1.856(0.82 - 3.37) | 0.044      |    |
| LEA            | 5.858(1.94 - 17.70) | 0.000      |    |
| LVDD           | 6.457(1.72 - 23.82) | 0.000      |    |

| (f) HbA1c>7.0% | Divided by age 40 | OR(95% CI) | P  |
|-----------------|-------------------|------------|----|
| Micro DR       | 2.148(0.89 - 5.33) | 0.080      |    |
| CDFP           | 1.950(0.78 - 5.33) | 0.111      |    |
| Macro CAS      | 1.389(0.95 - 2.06) | 0.118      |    |
| LEA            | 0.657(0.30 - 1.52) | 0.374      |    |
| LVDD           | 1.949(0.78 - 5.33) | 0.111      |    |

| (g) LDL<2.6mmol/L | Divided by age 40 | OR(95% CI) | P  |
|-------------------|-------------------|------------|----|
| Micro DR       | 3.774(1.47 - 9.49) | 0.000      |    |
| CDFP           | 1.803(0.12 - 2.59) | 0.880      |    |
| Macro CAS      | 1.856(0.82 - 3.37) | 0.044      |    |
| LEA            | 5.858(1.94 - 17.70) | 0.000      |    |
| LVDD           | 6.457(1.72 - 23.82) | 0.000      |    |

| (h) LDL<2.6mmol/L | Divided by age 40 | OR(95% CI) | P  |
|-------------------|-------------------|------------|----|
| Micro DR       | 2.148(0.89 - 5.33) | 0.080      |    |
| CDFP           | 1.950(0.78 - 5.33) | 0.111      |    |
| Macro CAS      | 1.389(0.95 - 2.06) | 0.118      |    |
| LEA            | 0.657(0.30 - 1.52) | 0.374      |    |
| LVDD           | 1.949(0.78 - 5.33) | 0.111      |    |

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observed in the HbA1c and lipid profiles of EOD and LOD patients. Compared with LOD patients, EOD patients required greater doses of insulin and lipid-lowering drugs. This was probably related to benefits from drug use. Furthermore, EOD patients have relatively poor metabolic control (BP ≥140/90 mmHg, BMI ≥24 kg/m², HbA1c% ≥7.0%, and low-density lipoprotein cholesterol ≥2.6 mmol/l). In the elderly population, there was no significant risk of developing microvascular complications in EOD patients compared with LOD patients. This is because the elderly population is more susceptible to developing hypertension and using antihypertensive drugs. There was no correlation between the incidence of macrovascular complications in EOD and LOD patients. This confirms that there is no correlation between the onset age of type 2 diabetes mellitus and macrovascular complications—it is not affected by metabolic factors, such as blood pressure, BMI, blood glucose or blood lipids.

In the present study, age and sex factors were matched from large, non-matched groups by segregating type 2 diabetes mellitus patients into smaller, matched groups. The participants were not matched according to their age and sex in previous studies. Thus, one can accurately assess the relationship between the onset age of type 2 diabetes mellitus and vascular complications. Chronic complications were evaluated with objective medical instruments. These findings are more accurate and objective than a self-reported analysis, which was carried out in previous large-scale studies.

Many studies focused on the clinical risk factors to prevent the chronic complications of diabetes. The development of diabetes complications is strictly related to many factors, such as age, sex, metabolic control, diabetes duration, hypertension and use of antihypertensive drugs/antidiabetic agents/lipid-lowering drugs and so on. In the present study, propensity score matching (EOD vs LOD = 1:2 match) was carried out to adjust for differences in age and sex. Furthermore, adjustments for differences in the following parameters were made: HbA1c%, insulin, oral hypoglycemic medications, hypotensive drugs, lipid-lowering drugs and history of HT. We adjusted the confounding factors to make the conclusion more credible. Of course, for patients with diabetes, the prevention of chronic complications, comprehensive management is very important.

Much emphasis has been laid on formulating a public health policy for the prevention of diabetes in China. In the past 30 years, the incidence of diabetes has been increasing steadily. Young people are being diagnosed with diabetes! In EOD patients, the risk of developing microvascular complications is higher than in LOD patients. Furthermore, EOD patients have a greater tendency of developing macrovascular complications. Therefore, it is proposed that adequate steps must be taken to prevent diabetes in young people. The diabetes duration has been thought to be an uncontrollable factor. The Da Qing Diabetes Prevention Study (DQDPS) showed that lifestyle intervention in people with IGT delayed the onset of type 2 diabetes, and reduced the incidence of cardiovascular events, microvascular complications, cardiovascular and all-cause mortality, and increased life expectancy.

The present study had some limitations. Maturity onset diabetes of the young or latent autoimmune diabetes in adults have been ruled out according to patient medical history and diabetes autoantibodies. It is a great pity that genetic testing has not been carried out. The age onset of type 2 diabetes mellitus was always underestimated due to a long asymptomatic stage. Patients were grouped according to their age at onset, but for asymptomatic patients, the age onset might be underestimated. This group failed to take the exact cardiovascular event as the end-point. The present study was carried out on non-severe hospitalized type 2 diabetes patients, so the hospital admission rate might also be biased. However, randomized, prospective, multicenter studies should be carried out to confirm this bias. Furthermore, this was a cross-sectional study that does not prove causality; it only suggests that there is a correlation between the two factors.

Compared with LOD patients, EOD patients have a greater tendency of developing microvascular complications; however, the risk of developing macrovascular complications is not significantly increased in EOD patients. It is suggested that there is a close relationship between the risk of diabetic macrovascular complications and age. Pre-emptive microvascular treatment or preventative measures in EOD patients who do not yet show symptoms might be beneficial.

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DISCLOSURE
The authors declare no conflict of interest.
Approval of the research protocol: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent: Obtained from all patients included in the study. This study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University, and the participants gave informed consent.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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