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Clinical Features and Microvascular Complications Risk Factors of Early-onset Type 2 Diabetes Mellitus

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Summary: The aim of this research was to study the clinical features and microvascular complications risk factors of early-onset type 2 diabetes mellitus (T2DM). We analyzed the clinical data from 1421 T2DM inpatients at Wuhan Union Hospital. Subjects were divided into early-onset T2DM group (diagnostic age ≤40 years) and late-onset T2DM group (diagnostic age >40 years). All subjects underwent a standardized assessment of microvascular complications. Data were compared with independent-samples *t* test or Chi-square test. Multiple logistic regression was used to determine the risk factors of microvascular complications. Patients with early-onset T2DM were more inclined to have a lower systolic blood pressure (SBP), a longer duration of diabetes and higher levels of body mass index (BMI), uric acid (UA), fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG) and glycosylated hemoglobin (HbA1c) than those with late-onset T2DM (P<0.05). The prevalence of diabetic retinopathy (DR) was significantly higher and that of diabetic peripheral neuropathy (DPN) was significantly lower in early-onset group than in late-onset group (P<0.05). For DN, UA was an independent risk factor in early-onset T2DM. SBP and TG were independent risk factors in late-onset T2DM. For DR, duration of diabetes and SBP were independent risk factors in early-onset T2DM. Duration of diabetes, SBP and HbA1c were independent risk factors in late-onset T2DM. This study demonstrated that the clinical characteristics of early-onset T2DM were metabolic disorders, including glucose metabolism, lipid metabolism and amino acid metabolism. Early-onset T2DM was more likely to be associated with DR. The potential pathogenesis of early and late-onset T2DM might be different. The management of metabolic risk factors especially HbA1c, SBP, TG and UA is advised to be performed in the early stage of diabetes.
Key words: early-onset type 2 diabetes mellitus; diabetic microvascular complication; diabetic nephropathy; diabetic retinopathy; diabetic peripheral neuropathy

With the change of modern lifestyle and diet structure, type 2 diabetes mellitus (T2DM) is gradually becoming popular among children and adolescents[1, 2]. Early-onset diabetes is defined as the diabetes diagnosed at a young age, with different age criteria for diagnosis (30–45 years old)[3–6]. Most of studies have used 40 years as the cut-off point of age for diagnosis[7–10]. Early-onset diabetes is an emerging public health problem especially in developing countries[11]. The number of early-onset diabetes cases increased almost 4-fold from 1997 to 2010 in China[3]. It was found that the degree of obesity was negatively correlated with age of diabetes diagnosis, which indicated that the increase in the prevalence of obesity in young people might be an important reason for young onset of diabetes[12].

Chinese with early-onset diabetes have a marked increased incidence of cardiovascular complications (odds ratio, OR=1.91; 95% confidence interval, CI: 1.81–2.02)[13]. So it is necessary for us to pay attention to early-onset diabetes and its complications. In order to study the clinical features and microvascular complications risk factors of early-onset T2DM, the following study was conducted.

1 MATERIALS AND METHODS

1.1 Study Population and Design

Totally, 1421 inpatients with T2DM between October 2012 and October 2016 in the Endocrinology Department of Wuhan Union Hospital were recruited. The research was approved by the Ethics Committee of

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Wuhan Union Hospital, Huazhong University of Science and Technology. All subjects voluntarily participated in this study and signed the informed consent.

Patients were included if they met the diabetes diagnostic criteria proposed by the World Health Organization Diabetes Experts Committee in 1999. Exclusion criteria were as follows: (1) type 1 diabetes (patients were classified as type 1 diabetes if they presented with diabetic ketoacidosis or required continuous insulin therapy within 1 year of diagnosis); (2) other types of diabetes, including secondary diabetes and gestational diabetes. Subjects were divided into early-onset T2DM group (diagnostic age ≤40 years old) and late-onset T2DM group (diagnostic age >40 years).

1.2 Data Collection

Information about smoking history and family history of diabetes were collected. The body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Blood pressure was measured twice using a mercurial sphygmomanometer. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded.

All subjects underwent a series of comprehensive tests after fasting for 8 h. Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), serum creatinine (SCr) and blood urea nitrogen (BUN) were measured by kinetic enzymatic method. Uric acid (UA) and microalbuminuria (MAU) were measured using immunoassay. Glycosylated hemoglobin (HbA1c) was evaluated using chromatography.

1.3 Definitions of Diabetes Microvascular Complications

According to the 2017 edition of the guidelines for the prevention and treatment of T2DM in China: (1) diabetic nephropathy (DN) was defined as the presence of proteinuria, namely MAU ≥30 mg/24 h after excluding other causes of kidney damage; (2) the diagnosis of diabetic retinopathy (DR) was based on typical changes on funduscopic examination, including microaneurysm, hemorrhage spot, neovascularization, vitreous hemorrhage, cotton-wool spot and macular lesion; (3) the diagnosis of diabetic peripheral neuropathy (DPN) was based on the symptoms, such as numbness, pain, hypersensitivity and hypoesthesia, etc., and the results of nerve quantitative sensory examination, while excluding neuropathy caused by other etiology.

1.4 Statistical Analysis

Data were analyzed with SPSS 22.0. Continuous data were represented as mean±standard deviations (SD) and compared with independent-samples *t* test or one factor analysis of variance. Categorical data were represented as percentages and compared with Chi-square test. Multiple logistic regression was used to determine the risk factors of microvascular complications. $P<0.05$ was considered statistically significant.

2 RESULTS

Among 1421 participants with T2DM (826 men and 595 women), there were 340 cases of early-onset T2DM (23.9%), and 1081 cases of late-onset T2DM (76.1%). The onset age of early-onset and late-onset T2DM was 33.3±6.3 and 53.2±8.5 years old, respectively. The duration of diabetes of two groups was 9.0±8.6 years and 7.4±6.4 years, respectively.

2.1 Clinical Features

Early-onset diabetes participants included a higher proportion of males, smoking and family history of diabetes mellitus than late-onset diabetes participants ($P<0.05$). Patients with early-onset T2DM were more inclined to have a lower SBP, a longer duration of diabetes and higher levels of BMI, UA, FPG, TC, TG and HbA1c than those with late-onset T2DM ($P<0.05$). There were no significant differences in DBP, WHR, SCr, BUN, HDL-C and LDL-C between the two groups ($P>0.05$) (table 1).

2.2 Prevalence of Microvascular Complications

Early-onset group had a higher prevalence of DR and a lower prevalence of DPN than late-onset group ($P<0.05$). However, there was no significant difference in DN between the two groups ($P>0.05$) (fig. 1).

2.3 Clinical Features and Prevalence of Microvascular Complications in Early-onset and Late-onset T2DM

To eliminate the impact of duration of diabetes, subjects were further divided into three groups: disease duration <5 years, 5–15 years and >15 years. It was

Table 1 Clinical features of early-onset and late-onset groups

Clinical index	Early-onset (340 cases)	Late-onset (1081 cases)	*P* value
Male (%)	73.8	53.2	0.000
Age (year)	42.2±11.3	60.6±9.7	0.000
Disease duration (year)	9.0±8.6	7.4±6.4	0.002
Smoking ratio (%)	37.1	26.7	0.000
Family history (%)	41.8	25.6	0.000
SBP (mmHg)	126.1±16.8	131.8±19.4	0.000
DBP (mmHg)	80.5±10.6	79.5±11.5	0.159
WHR	0.9±0.1	0.9±0.1	0.080
BMI (kg/m²)	25.5±4.3	24.9±3.7	0.018
SCr (μmol/L)	84.7±91.5	78.5±59.8	0.260
BUN (mmol/L)	5.7±3.2	6.1±2.7	0.073
UA (μmol/L)	330.0±107.8	314.7±94.5	0.014
FPG (mmol/L)	8.6±3.7	8.1±3.5	0.034
TC (mmol/L)	4.6±1.3	4.5±1.1	0.033
TG (mmol/L)	2.5±3.3	2.0±2.1	0.004
HDL-C (mmol/L)	1.2±0.3	1.3±0.3	0.121
LDL-C (mmol/L)	2.4±0.8	2.4±0.8	0.455
HbA1c (%)	9.2±2.2	8.6±2.2	0.000

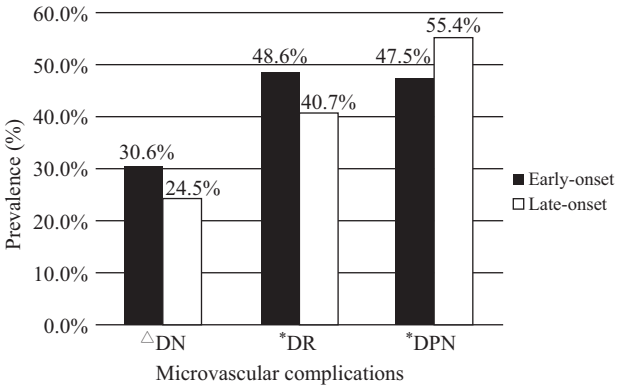

Fig. 1 Prevalence of microvascular complications in early-onset and late-onset groups
*P<0.05, △P>0.05

found that, the levels of SBP, SCr and BUN all increased with the prolongation of disease duration in early-onset and late-onset T2DM groups (P<0.05). SBP level was significantly lower and proportions of male patients were significantly higher in early-onset T2DM group than in later-onset T2DM (P<0.05) (table 2).

In late-onset T2DM group, the prevalence of DN increased with the prolongation of the disease duration (P<0.05). The prevalence of DR increased with the prolongation of the disease duration in both early-onset and late-onset T2DM groups (P<0.05). In the group of disease duration <5 years, the prevalence of DN was significantly higher in early-onset T2DM group (P<0.05) (table 3).

2.4 Risk Factors for Microvascular Complications

Logistic regression analysis was performed to calculate OR for microvascular complications in early-onset and late-onset T2DM groups. After adjusting for related parameters (duration of diabetes, SBP, BMI, UA, FPG, TC, TG and HbA1c), for DN, UA was an independent risk factor in early-onset T2DM. SBP and TG were independent risk factors in late-onset T2DM (P<0.05) (table 4).

After adjusting for related parameters (duration of diabetes, SBP, BMI, UA, FPG, TC, TG and HbA1c), for DR, duration of diabetes and SBP were independent risk factors in early-onset T2DM. Duration of diabetes, SBP and HbA1c were independent risk factors in late-onset T2DM (P<0.05) (table 5).

After adjusting for related parameters (duration of diabetes, SBP, BMI, UA, FPG, TC, TG and HbA1c), for DPN, no significant differences were observed in duration of diabetes, BMI, UA, FPG, TC, TG and HbA1c between the two groups (P>0.05) (table 6).

3 DISCUSSION

The prevalence of early-onset T2DM in China is significantly higher than International Diabetes Federation (IDF) predicted values in other countries[14].

Table 2 Clinical data grouped by disease duration

Parameters	Disease duration (year)					
	Early-onset			Late-onset		
	<5	5–15	>15	<5	5–15	>15
Male (%)	78.1	73.9	65.2	52.8	54.2	50.4
Age (years)	32.2	44.5	56.3	56.0	61.6	71.6
Smoking ratio (%)	28.9	43.0	40.6	26.6	28.7	17.9
Family history (%)	40.6	44.4	39.1	22.8	27.9	26.8
SBP (mmHg)	123.3	125.7	131.8	128.4	132.8	138.3
DBP (mmHg)	80.9	81.2	78.0	81.1	78.9	76.8
WHR	0.9	0.9	0.9	0.9	0.9	0.9
BMI (kg/m²)	26.3	25.0	24.8	24.8	24.9	24.9
SCr (μmol/L)	65.4	91.0	104.7	67.4	79.2	110.5
BUN (mmol/L)	4.6	6.3	6.7	5.5	6.1	7.6
UA (μmol/L)	345.0	321.3	324.2	302.1	322.6	320.1
FPG (mmol/L)	8.6	8.6	8.5	8.3	8.1	7.6
TC (mmol/L)	4.7	4.7	4.4	4.6	4.5	4.1
TG (mmol/L)	3.0	2.5	2.0	2.1	2.0	1.5
HDL (mmol/L)	1.2	1.3	1.3	1.3	1.3	1.2
LDL (mmol/L)	2.4	2.4	2.3	2.5	2.3	2.2
HbA1c (%)	9.8	9.0	8.5	9.0	8.4	8.3

Table 3 Prevalence of microvascular complications grouped by disease duration (%)

Groups (year)	DN		DR		DPN	
	Early-onset	Late-onset	Early-onset	Late-onset	Early-onset	Late-onset
<5	27.9	16.7	34.5	31.4	45.7	54.0
5–15	29.7	26.4	53.3	45.6	47.6	55.6
>15	37.8	42.3	68.0	60.0	50.0	57.5

Table 4 Multiple logistic regression analysis for DN

		OR (95%CI)	*P* value
Early-onset	Duration of diabetes	1.033 (0.987–1.081)	0.163
	SBP	1.027 (0.999–1.055)	0.056
	BMI	1.025 (0.927–1.132)	0.631
	UA	1.006 (1.001–1.010)	0.009
	FPG	0.881 (0.774–1.002)	0.053
	TC	1.379 (0.974–1.952)	0.070
	TG	1.010 (0.898–1.136)	0.863
	HbA1c	1.125 (0.936–1.354)	0.210
Late-onset	Duration of diabetes	1.024 (0.991–1.058)	0.156
	SBP	1.024 (1.012–1.037)	0.000
	BMI	1.027 (0.964–1.093)	0.411
	UA	1.002 (0.999–1.004)	0.143
	FPG	0.978 (0.904–1.058)	0.578
	TC	0.918 (0.739–1.141)	0.440
	TG	1.123 (1.009–1.251)	0.034
	HbA1c	1.120 (0.998–1.256)	0.054

Table 5 Multiple logistic regression analysis for DR

		OR (95%CI)	*P* value
Early-onset	Duration of diabetes	1.086 (1.039–1.136)	0.000
	SBP	1.025 (1.003–1.046)	0.024
	BMI	0.965 (0.887–1.050)	0.408
	UA	1.001 (0.998–1.004)	0.523
	FPG	0.984 (0.902–1.074)	0.720
	TC	1.094 (0.816–1.467)	0.547
	TG	0.972 (0.871–1.084)	0.609
	HbA1c	1.025 (0.878–1.195)	0.757
Late-onset	Duration of diabetes	1.077 (1.042–1.112)	0.000
	SBP	1.021 (1.011–1.032)	0.000
	BMI	0.998 (0.944–1.054)	0.929
	UA	0.997 (0.995–0.999)	0.011
	FPG	0.950 (0.885–1.019)	0.154
	TC	1.022 (0.859–1.215)	0.808
	TG	1.002 (0.911–1.104)	0.960
	HbA1c	1.134 (1.028–1.252)	0.012

Table 6 Multiple logistic regression analysis for DPN

		OR (95%CI)	*P* value
Early-onset	Duration of diabetes	1.010 (0.972–1.051)	0.602
	SBP	0.978 (0.957–1.000)	0.049
	BMI	1.050 (0.962–1.146)	0.272
	UA	1.002 (0.999–1.006)	0.176
	FPG	1.006 (0.925–1.094)	0.890
	TC	1.032 (0.768–1.387)	0.832
	TG	0.933 (0.842–1.035)	0.190
	HbA1c	0.980 (0.841–1.143)	0.800
Late-onset	Duration of diabetes	1.017 (0.987–1.049)	0.269
	SBP	1.000 (0.990–1.010)	0.965
	BMI	0.962 (0.912–1.016)	0.161
	UA	1.002 (1.000–1.004)	0.118
	FPG	0.962 (0.901–1.027)	0.246
	TC	0.994 (0.825–1.198)	0.951
	TG	1.000 (0.897–1.116)	0.996
	HbA1c	1.076 (0.976–1.186)	0.141

Thus, public health emergency is needed to prevent diabetes, especially in the young Chinese population. It is likely that early onset visceral obesity and related insulin resistance are the main risk factors for early progression of diabetes[15, 16].

In this study, patients with early-onset T2DM had a series of cardiovascular risk factors. For example, the levels of UA, FPG, TC, TG and HbA1c were higher in the early-onset group. Hyperglycemia, dyslipidemia and hyperuricemia are important components of metabolic syndrome and may be the early manifestations of insulin resistance[17]. The patients with early-onset T2DM were characterized by a higher level of BMI than late-onset T2DM. As an important indicator to reflect the obesity, BMI can effectively evaluate the severity of insulin resistance in obese T2DM patients. These results suggested that there were significant metabolic disorders and insulin resistance in patients with early-onset T2DM. Thus, patients with early-onset T2DM are advised to correct metabolic disorders and improve insulin resistance as soon as possible.

In terms of the prevalence of microvascular complications, the results were similar to other studies. A 7-year prospective study showed that patients with early-onset T2DM had higher risks for cardiovascular-renal complications at any given age[4]. And chronic ocular diseases were more common in patients with early-onset diabetes (6% *vs.* 2%)[18]. Our study also showed that early-onset group had a higher prevalence of DR than late-onset group, despite no significant difference was found in DN between the two groups. In recent years, "metabolic memory" has become a hot issue in the field of diabetes. The theory which supports our study suggests that the longer a patient is exposed to hyperglycemia, the more likely it is to suffer from microvascular disease[19–21]. Moreover, the damage of hyperglycemia to microvessels can be sustained for a long time after lowering blood glucose[22]. The study of the United States Diabetes Control and Complications Trial (DCCT) confirmed this view.

In this study, hyperuricemia was a prominent risk factor for DN in early-onset T2DM, while SBP and TG seemed to play a more important role in late-onset T2DM, which indicated that the potential pathogeneses of early and late-onset T2DM were different. Thus, in patients with early-onset T2DM, the level of UA should be strictly controlled. Meanwhile, patients with late-onset T2DM were advised to control the levels of SBP and TG to reduce the risk of DN. This study also indicated that HbA1c was an independent risk factor for DR in late-onset T2DM instead of early-onset T2DM. Therefore, patients with late-onset T2DM were advised to rationally control blood glucose.

Besides, this study found no significant relationship between the occurrence of DPN and general metabolic factors. A hospital based study also found that DN and DR were associated with dyslipidemia, while DPN was

not associated with blood lipids[23]. It is well known that current diagnostic criteria and clinical testing methods of DPN mainly rely on the subjective feelings of patients. On the other hand, the exact pathogenesis of DPN is not fully understood as yet. It is the result of multiple factors, including metabolic disorders, vascular damage, neurotrophic factor deficiency, cytokine abnormalities, oxidative stress and immune factors[24], which need further study.

To sum up, this study demonstrated that the clinical characteristics of early-onset T2DM were metabolic disorders, including glucose metabolism, lipid metabolism and amino acid metabolism. Early-onset T2DM was more likely to be associated with DR. The potential pathogenesis of early and late-onset T2DM might be different. The management of metabolic risk factors especially HbA1c, SBP, TG and UA is advised to be performed in the early stage of diabetes.

Conflict of Interest Statement

No conflict of interest exits in the submission of this manuscript, which is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All authors agree to authorize the global copyright of the thesis to Current Medical Science magazine.

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