Early-onset diabetes: an epidemic in China

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Abstract   **Although type 2 diabetes is a disease often associated with aging, the global prevalence of early-onset diabetes has been increasing due to man's sedentary lifestyle, low-physical activity, obesity, and some non-modifiable risk factors. Many studies have found that individuals with early-onset type 2 diabetes were at higher risk of developing vascular complications than those with late-onset diabetes. Individuals with early-onset diabetes are usually unwilling to visit hospital and have more confidence in their health, which results in poor glycemic control and the delayed detection of diabetes-related complications. Few studies have focused on the treatment and prevention of complications in specific population of individuals with early-onset type 2 diabetes. Therefore, focusing on this particular population is critical for the government and academic societies. Screening for T2DM is imminent for young adults with a family history of diabetes, obesity, markers of insulin resistance, or alcohol consumption. More data are definitely required to establish a reasonable risk model to screen for early-onset diabetes.**

Keywords   diabetes; early-onset; diabetes complications

Introduction

Diabetes is a metabolic disorder that has been increasing worldwide. Over 10% of Chinese adults were diagnosed with diabetes in 2010, suggesting the rapid growth of this disease in China [1]. Aging has been reported as an important element associated with type 2 diabetes mellitus (T2DM); however, the age at diagnosis has gradually decreased recently [2–4]. A huge increase in the incidence of early-onset T2DM has become a new trend all over the world. According to a large-scale survey in Chinese mainland, the percentages of adults reported with diabetes and prediabetes are 5.7% and 44%, respectively, among adults younger than 40 years old [5]. In this review, we describe the pathophysiology and characteristics of early-onset type 2 diabetes and its relationship with the risks for microvascular and macrovascular complications.

The epidemiology of early-onset diabetes

Most of the evidence for an epidemic of T2DM in younger people originate from western countries. Between 1990 and 2000, New York experienced a 10-fold increase in T2DM in children [6]. The UK has witnessed similar increases in early-onset T2DM, accounting for 5% of the diabetes population under < 30 years of age in 2003, increasing to 12% by 2006 [7], and extending to 24% of the diabetes population under < 40 years of age [8]. A higher proportion of early-onset diabetes has been observed to be highly prevalent in Asian countries [1,9]. In a study conducted in 2001 among 9243 patients from 194 primary care centers across Asia, the proportion of T2DM patients diagnosed before the age of 30 varied from 0.5% in Taiwan (China) and 1.5% in Korea to 5.4% in the Philippines [10]. From 1994 to 2000, China experienced an 88% increase in the prevalence of diabetes in a nationally represented population aged 35–44 years from an InterASIA study [11]. The updated prevalence of prediabetes in 2013 was significantly higher than that in 2010 (28.8% vs. 9.0%) among adults younger than 40 years old. The 3.2% prevalence of diabetes in 2010 increased to 5.8% by 2013 in a population with younger

than 40 years [5,12]. These reports further supported the hypothesis that early-onset diabetes is becoming one of the major health burdens in China.

Risk factors of early-onset diabetes

The development of early-onset T2DM represents a complex interaction between genetic and environmental factors. Table 1 summarizes the risk factors for developing early-onset T2DM. In general, the risk factors for early-onset T2DM are similar to those for late-onset T2DM, which includes rapid transitions from energy scarcity to energy abundance, physical activity to sedentary lifestyles, and a disease pattern dominated by infection to non-communicable disease, with the additional risks factors of male sex and puberty. These factors can lead to biological, psychological, and behavioral maladaptation, possibly with a genetic or epigenetic basis.

Table 1 Risk factors for early-onset type 2 diabetes

Modifiable	Non-modifiable
Obesity	Ethnicity (Han, Manchu)
Low physical activity	Family history of T2DM
High sedentary behavior	Puberty
Socioeconomic status	Low birth weight
	Male sex
	Intrauterine hyperglycemia
	Previous gestational diabetes

Obesity is the major risk factor of early onset diabetes. Surveys in the UK have shown that the major population with early onset T2DM are obese (80%–92%) compared with merely 56% of older adults [13,14], in addition to an adverse linear relationship between BMI and the age at diagnosis of T2DM [15]. With China having undergone shift in economic development over the last few decades, the prevalence of overweight and obese individuals has increased by 414% in China from 3.7% in 1982 to 19.0% in 2002 [16]. Consequently, metabolic syndrome has gotten increasingly prevalent at an alarming rate and is about to contribute to the annual 9 million deaths from cardiovascular diseases by 2030 [17]. The main factor driving the obesity epidemic is the rapid nutrition transition occurring in the last few decades, that is, the shift to higher fat and lower carbohydrate content in the diet, as well as increased intake of foods from animal sources, edible oils, and added sugars [18]. In China, the intake of dietary fat rose from 19.3% in 1989 to 27.3% in 1997 [19]. In conclusion, obesity has become common and contributed greatly to the prevalence of early-onset

diabetes in China.

Substantial differences are present in genes, culture, socioeconomic levels, climate, lifestyle, and geographical features of residential area among ethnic groups. Worldwide, Japanese, Hispanics, and Native Americans have the highest risks of developing T2DM in childhood [20–23]. China has 56 ethnic groups, in which Chinese Han is the majority. Compared with Han participants, most major minority ethnic groups, except for Manchu participants, had a significantly lower prevalence of both total diabetes and prediabetes [5]. Tibetan highlanders have been shown to have accelerated vulnerability to diabetes with lifestyle change or aging [24]. However, data for the ethnic variation in early-onset diabetes prevalence is difficult to determine from the cross-sectional survey. Further investigation is required.

In Chinese mainland, a population-based cross-sectional study has found that a higher proportion of males is included in newly diagnosed early-onset diabetes participants compared with those who had diabetes onset at 53 years or later [25]. A recent analysis of the "National Health Insurance database" from Taiwan noted that the prevalence of diagnosed diabetes among those aged 20–39 has increased by 15% (from 0.45 to 0.5) for women and 54% (from 0.52 to 0.78) for men during 2000–2008 [26]. A large population-based study reported that the prevalence of diabetes has become significantly higher among men than in women, but the prevalence of prediabetes does not differ significantly according to sex [12].

Intrauterine environment and gestational diabetes mellitus (GDM) play parts in the development of early-onset diabetes. A study has indicated that apart from genetic factors, intrauterine environment can play an important part in the evolution of β cell dysfunction and insulin resistance, which then increase the risk of obesity, T2DM, and cardiovascular disease later in life [27,28]. The mechanism is thought to be mediated by heritable alterations in gene expression rather than variation in DNA sequence, but involve epigenetic modifications, such as DNA methylation and histone modification [29]. Statistics approved of this conclusion. In a Chinese study, offspring whose mothers were exposed to famine had increased risk of diabetes or hyperglycemia in adulthood, especially when the offspring was brought up in a nutrient-rich urban environment [30]. An Indian survey showed that an offspring with experienced intrauterine hyperglycemia was found to be connected with increased risk of diabetes and obesity [31]. Chinese specialists reported that offspring (aged 8–10 years) of mothers with GDM tended to have higher blood pressure and more inverse cardio–metabolic profile than peers with normoglycemic mothers [32]. Women with a history of GDM were at a sevenfold increased risk of diabetes later in their lives [33]. Thus, a vicious cycle of diabetes begetting diabetes exists; this cycle calls for imminent concern in

China in driving the escalating epidemic of early-onset diabetes.

Etiology of early-onset diabetes

Early-onset diabetes usually refers to diabetes that develops in adults less than 40 years old. Although this population may include latent autoimmune diabetes in adults (LADA) and individuals with classic type 1 diabetes, these two conditions can be ignored because they are both rare conditions in China. Moreover, classic type 1 diabetes is characterized with a clinical feature of abrupt onset and classic symptoms such as polydipsia, polyuria, weight loss, and ketonuria or ketoacidosis.

The pathophysiology of early-onset type 2 diabetes is related to multiple factors, including genetic, socioeconomic, psychological, and behavioral factors. The consultation rate of individuals with early-onset diabetes is lower due to less free time and more assurance in their physical condition with the absence of typical symptoms. Ignoring the progression of diabetes would cause worse metabolic control and exacerbate the reduced β cell function. Clinical decision-making relies heavily on understanding the pathophysiology of early-onset diabetes. However, it is hard to compare the β cell function between individuals with newly diagnosed early-onset diabetes and those with late-onset diabetes for lack of population-based studies. Few studies were concerned about the pathophysiological and genetic factors that may be related to newly diagnosed early-onset diabetes.

Generally, common Maturity Onset Diabetes of the Young (MODY) gene mutations are not the etiology of early-onset type 2 diabetes. A Spanish study stated that the T130I variant in HNF4A is a major susceptibility genotype associated with early-onset type 2 diabetes in an individual from central Spain [34]. Six known MODY genes, namely, *HNF-4α*, *GCK*, *HNF-1α*, *IPF-1*, *HNF-1β*, and *NeuroD1* were screened, and a small percentage of Thai subjects with early-onset type 2 diabetes (10%) presented with changes in these six MODY genes [35]. However, a Mexican study also indicated that these variants would not necessarily cause early-onset diabetes under normal circumstances [36]. Therefore, many genes are still to be identified in most early-onset type 2 diabetes subjects. In diabetic Asian patients, family history of diabetes and low body mass index (BMI) have both been reported to be related to poor pancreatic function [3]. Genetic factors, together with the possible pathogenic role of epigenetics (which may affect β cell development in individuals with a family history of diabetes), might play a particularly important role in early-onset diabetes.

A Chinese study compared insulin resistance and β cell function in individuals with early- and late-onset diabetes. The early-onset diabetes group showed increased first-phase insulin release but similar late-phase insulin release compared with individuals with late-onset diabetes. The study also demonstrated that when age-matched healthy subjects were used as reference, the magnitude of β cell dysfunction was greater in those with early-onset diabetes than in those with middle-aged-onset and late-onset diabetes. The study also compared the characteristics of participants with early-onset diabetes with those of their healthy aged-matched peers in the appropriate context. In accordance with previous findings, a more rapid decline of β cell function is suggested in subjects with early-onset diabetes than in subjects with late-onset diabetes [37]. Accelerated switch from oral anti-diabetes medications to insulin injections may occur when β cell function declines rapidly in individuals with early-onset diabetes. The findings explained the reason for higher insulin injection rate in individuals with early-onset diabetes even after adjusting for the disease duration [25].

Type 1 diabetes mellitus (T1DM) is characterized by having a more progressive deterioration of β cell function compared with T2DM. Individuals with T2DM possibly have prolonged asymptomatic disease. The onset is usually abrupt in T1DM; however, it is insidious, asymptomatic and can go undiagnosed for several years in T2DM. Compared with T1DM patients, one factor that contributed to the higher risk of microvascular complications in T2DM patients is their less intensive glycemic control in a durable period. According to the Diabetes Control and Complications Trial (DCCT), UK Prospective Diabetes Study (UKPDS), and Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) [38–40] studies, the risk of microvascular complications can be reduced when patients achieve more intensive glycemic control. T2DM patients having higher complication rates despite better lipid control and similar blood pressure suggests a more aggressive feature in early-onset T2DM than T1DM [41].

Socioeconomic, psychological, and behavioral factors (including less physical work and dietary changes) contribute to the pathophysiology of early-onset type 2 diabetes. From a behavioral perspective, a young adult with diabetes is more likely to have increased stress, depressive symptoms, and poor self-management [42]. Young patients usually have higher default rates and poorer medication compliance than older patients, which may be due to competing priorities such as accumulation of wealth and raising a family [43]. Although individuals with early-onset diabetes are more likely to receive formal diabetes education than those with late-onset diabetes, they are less likely to have a healthy lifestyle and aggressively manage their disease [44]. Additionally, physicians might feel hesitant to prescribe multiple lifelong drugs to young patients due to the uncertainty of the long-term side-effects, especially in women of childbearing age [45].

Characteristics of early-onset diabetes

Since the early 21st century, some national clinical studies have examined the increasing prevalence of early-onset diabetes as well as the characteristics associated with early-onset diabetes and compared the results with those of classic type 1 diabetes or late-onset diabetes.

A cross-sectional, retrospective study in Korea compared the clinical characteristics of early- and late-onset diabetes. In comparison with late-onset diabetic patients, individuals with early-onset diabetes are characterized with higher glycated hemoglobin (HbA1c), fasting glucose, postprandial glucose levels, and more reports of a family history, typical symptoms, microalbuminuria, as well as implementation of insulin therapy as the initial treatment [46].

Two studies in hospital settings in Western and Asian countries indicated that early-onset diabetes patients had a more extensive family history of diabetes, as well as a higher BMI and elevated HbA1c and low-density lipoprotein cholesterol (LDL-C) level [44,47]. A large-scale hospital-based study in Chinese mainland suggested that individuals with early-onset diabetes had lower systolic blood pressure (SBP), lower LDL-C, higher HbA1c, and similar BMI and triglyceride levels than individuals with late-onset diabetes [5]. The two results differed among the hospital-based studies, which may be attributed to inevitable selection bias, especially when electing control subjects among healthy participants in the hospital system.

A national cross-sectional study investigated the characteristics of Chinese individuals newly diagnosed with early-onset diabetes; 2801 subjects newly diagnosed with diabetes and without known diabetes or pre-diabetes were enrolled. This large, multi-center, cross-sectional, population-based study revealed that the incidence of early-onset diabetes among newly diagnosed patients was 23.3%. This result is consistent with the China Non-Communicable Disease Surveillance Survey, another large population-based study conducted in 2010, concluding that the percentage of participants aged 18–40 years was 15.7% among all newly diagnosed diabetes cases, as determined by the oral glucose tolerance test (OGTT) [1]. This result is much higher than the International Diabetes Federation (IDF)-predicted values in Australia, the UK, and Japan [41]. The 2010 study also found that the early-onset diabetes group had lower SBP (levels of total cholesterol, low-density lipoprotein cholesterol, and 2-hour post-prandial blood glucose) and urinary albumin creatinine ratio. No difference was found in the BMI and family history of diabetes between the early-onset diabetes subjects and any other age groups. Homeostasis model assessment of insulin resistance (HOMA-IR) is one of the most extensively used methods for evaluating insulin resistance in epidemiological studies, and insulin resis-

tance assessed by HOMA-IR was independently positively associated with age in newly diagnosed diabetes. The early-onset diabetes group had an increased HOMA-IR and disposition index 30 minutes after glucose load. The decline in β cell function was more pronounced in individuals with early-onset diabetes. An increased insulin resistance and more severe β cell failure can be found in diabetic individuals at a younger age [37].

Patients with early-onset diabetes were less likely to meet treatment goals. In an American study, patients younger than 40 years with type 2 diabetes and an HbA1c concentration greater than 6.5% had a 3.8-fold increased risk of death before the age of 55 years compared with individuals with an HbA1c concentration below 5.7% after adjusting for sex and ethnic origin [48]. The Joint Asia Diabetes Evaluation (JADE) program also found that young age at the time of diagnosis remained independently associated with poor glycemic control even after adjusting for major confounders. This conclusion was consistent across all countries despite the wide variability of clinical practices, health-care systems, and coverage for insurance and medication and also suggested that other mechanisms such as genetic, socioeconomic, psychological, or behavioral factors were involved [44].

Early-onset diabetes and microvascular disease

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and results from retinal vascular damage due to poor glycemic control and prolonged duration of unregulated diabetes. DR is more aggressive and accelerated in T1DM. The onset of T1DM is usually abrupt, whereas in T2DM, it is asymptomatic and can go undiagnosed for several years. Many researchers and scholars have focused on the microvascular complications associated with early-onset diabetes and provided us more incontrovertible data.

The JADE cohort compared clinical characteristics, metabolic risk factors, and the prevalence of complications between participants with early- and late-onset diabetes in subjects with type 2 diabetes selected from 245 outpatient clinics in nine Asian countries or regions. In this clinic-based setting across Asia, one in five adult patients had early-onset diabetes, and patients with early-onset diabetes had higher mean concentrations of HbA1c and a higher prevalence of retinopathy than those with late-onset diabetes. In comparison with patients with late-onset diabetes, patients with early-onset diabetes had poorer metabolic control, and few received organ-protective drugs [44].

With 29 442 patients of T2DM from 77 tertiary hospitals enrolled, a Chinese mainland cross-sectional survey analyzed the prevalence and risk factors of diabetic

retinopathy in China. According to the result, a total of 3192 (11.2%) individuals less than 40 years old were diagnosed with diabetes. The occurrence of microvascular complications in early-onset diabetes is substantially higher than late-onset diabetes (nephropathy: 5.1% vs. 1.5%; retinopathy: 7.1% vs. 2.7%). Age and sex were adjusted to evaluate the risk of developing microvascular diseases in T2DM, which showed a 1.69-fold higher risk in patients with early-onset T2DM than those with late-onset T2DM [49].

A cross-sectional study in Sri Lanka evaluated the rate of DR and its risk factors among young adult patients with diabetes. The study found out that the percentage of patients with early-onset diabetes diagnosed with retinopathy reaches nearly 20%. Factors including age, duration of diabetes, HbA1c, and urinary albumin levels play an important role in the presence of retinopathy, and among them, HbA1c was remarkably related to its severity [50].

The study by Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) was the first prospective study to assess the complications and comorbidities of T2DM in an adolescent population. This study reported that the presence of hypertension was increased from 11.6% to 33.8% as time went from the baseline to the end of the study. During this period, the risk for elevated LDL-C levels rose from 4.5% to 10.7%. Microalbuminuria was found in 6.3% of the cohort at baseline but grew up to 16.6% at the end of the study. Retinopathy was present in 13.9% of individuals in the TODAY cohort by the end of the study [51].

A cross-sectional study in India also screened the vascular complications in individuals newly diagnosed with early-onset type 2 diabetes and found that DR, neuropathy, and nephropathy were observed in 5.1%, 13.2%, and 0.9%, respectively, of the individuals [52] (Table 2). This study reiterated that screening for complications of newly diagnosed diabetes even in young population is important, as recognizing and aggressively treating complications and their associated risk factors can decelerate the development of these complications. Another clinical study in India also compared the prevalence and risk factors for DR in Indians with early-onset type 1 and type 2 diabetes. The results showed that the prevalence of DR was 53.3% among individuals with T1DM and 52.7% among those with T2DM. The study performed the multivariable logistic regression analysis and found that diabetes duration (OR = 1.99), waist circumference (OR = 1.28), and microalbuminuria (OR = 2.39) were associated with DR in early-onset T1DM. Diabetes duration (OR = 2.21), diastolic blood pressure (OR = 1.54), glycated hemoglobin (OR = 1.37), and lower stimulated c-peptide (OR = 1.54) were associated with DR in early-onset T2DM [53].

Only a few prospective studies that compare the incidence of DR among individuals with early-onset and late-onset type 1 or type 2 diabetes have been carried out. A prospective Indian study with median follow-up of 5 years was carried out to compare the incidence of complications among individuals with type 1 or type 2 early-onset diabetes. In total, 108 subjects with T1DM and 90 subjects with T2DM were enrolled. The incidence of micro- and macro-complications reported in numbers/1000 person-years of follow-up of T1DM and T2DM were as follows: retinopathy, 77.4 versus 78.0/1000 person-years; nephropathy, 62.0 versus 58.8; neuropathy 7.8 versus 13.9 and ischemic heart disease, 1.2 versus 5.4. In the Cox regression analysis with the adjustment for age, HbA1c, SBP, and serum cholesterol, T2DM subjects had a 2.11-fold higher risk of developing any diabetes-related vascular complication than T1DM subjects [40]. Notably, T2DM with early onset would have more adverse consequence, especially macro-vascular complications than T1DM.

The leading cause of end-stage renal disease in China is diabetic nephropathy, and the prevalence of diabetic nephropathy is continuously increasing with the increasing prevalence of diabetes. Albuminuria is a marker known to be used in the assessment of the early period of diabetic nephropathy. The JADE clinical study demonstrated that early-onset T2DM had a much higher incidence of renal complications than late-onset T2DM; this incidence was even higher than that among patients with T1DM [44]. Some small-sample cross-sectional data from individuals with early-onset T2DM suggested that the percentage of patients developed with microalbuminuria within 10 years of diagnosis ranged from 18% to 72%, and the progression rates of incidence and development of nephropathy were similar between T1DM and T2DM [54]. In an Australian cohort of adolescents with early-onset T2DM, around 45% of subjects had abnormally elevated urinary albumin levels [55]. In another group of 68 Australian adolescents with T2DM, the percentage of the group with microalbuminuria is 7%, which increased to 28% over an approximately 2-year period [56]. In a cohort of 105 early-onset T2DM in New Zealand, the percentage of individuals developing microalbuminuria added up to 72% in 3 years' time [57]. From the SEARCH study, 22% of T2DM subjects with an average age of 16.2 years and diabetes duration of 1.9 years had abnormal albumin-to-creatinine ratios [58]. However, very few studies have assessed the longitudinal progression of renal disease in early-onset T2DM despite these alarming cross-sectional data.

Early-onset diabetes and macrovascular diseases

Cardiovascular disease is a leading killer in most developed countries, as well as in many developing countries. Unlike patients with late-onset diabetes,

individuals with early-onset type 2 diabetes seem to be at higher risk of cardiovascular complications and more aggressive progression of vascular complications. Although cardiovascular risk factors are similar between early-onset and late-onset diabetes, individuals with early-onset diabetes would be exposed to these risk factors much longer than those with late-onset diabetes due to longer life expectancies. In fact, the progression of atherosclerosis is affected by the same multiple factors, including smoking, hypertension, obesity, and dyslipidemia in young and older individuals [59]. Prolonged duration of diabetes might result in decreased β cell function, elevated oxidative stress, and activation of the renin-angiotensin system, which then could cause the rise of LDL-C and SBP levels. Thus, the risk of cardiovascular disease was raised a lot owing to the long-lasting duration of diabetes and exacerbated metabolic factors.

An Australian prospective study compared long-term clinical outcomes and survival between early-onset type 2 and type 1 diabetes and found that early-onset T2DM had a significant increase in mortality with an increased hazard for death (HR = 2.0). More individuals with early-onset T2DM died due to cardiovascular-related events [60] (Table 2). A clinical study from Hong Kong also showed that early-onset T2DM had a remarkably increased incidence of cardiovascular complications compared with patients with late-onset diabetes. In an around 10 000 Chinese T2DM cohort, more than 20% had early-onset diabetes with a median follow-up period of 7.5 years. Patients with early- or late-onset diabetes shared similar risk factors despite a 20-year gap in age. For the same disease duration, patients with early-onset diabetes had lower incidence of cardiovascular disease but higher cumulative rates of clinical events at any given age. For patients with early-onset diabetes at any age, the increased risk for cardiovascular-renal complications is likely to be due to longer disease duration [61]. A cross-sectional study in Mexico evaluated the cardiovascular surrogate including carotid intima-media thickness, atherosclerotic plaques at the carotid level, and ankle-arm index between early- and late-onset type 2 diabetes. The number of early-onset T2DM with atheroma plaque almost doubled compared with the late-onset group (10.4% vs. 6.1%, respectively) [62].

A cross-sectional study also conducted in India determined the prevalence of macrovascular complications in patients newly diagnosed with early-onset diabetes. As a result, ischemic heart disease, peripheral vascular disease, and stroke were found to be presented in 0.7%, 2%, and 0.1%, respectively, of all enrolled subjects [63].

Another large-scale cross-sectional multi-center survey was conducted in 2012 using data from the China National HbA1c Surveillance System, which included more than 2 million Chinese T2DM patients. After adjusting for age, higher prevalence of non-fatal cardiovascular disease can be found in patients with early-onset diabetes than late-onset (11.1% vs. 4.9%; $P < 0.001$). Patients with early-onset type 2 diabetes were at higher risk of developing non-fatal cardiovascular disease than those with late-onset type 2 diabetes after the adjustment of age and sex (OR = 1.91). When the duration of diabetes was adjusted, the effect size for the risk of non-fatal cardiovascular diseases was significantly attenuated (OR = 1.13). Consequently, the longer duration of diabetes may contribute a lot to an increased risk of cardiovascular disease [4].

A longitudinal study of 4045 men aged 60 to 79 years old with a mean follow-up of 9 years was conducted to examine the influence of age at onset and diabetes duration on the risk of cardiovascular disease and all-cause mortality. Early- and late-onset diabetes were concluded to increase the risk of major coronary heart disease (CHD) events and mortality, but early-onset diabetes appeared to be a CHD equivalent factor when the disease duration exceeded 10 years [64].

Table 2 The prevalence of macrovascular and microvascular complications among individuals with early-onset diabetes

	CINDI 2[a]	MI Constantino[b]	JADE[c]
Diabetes duration	Newly diagnosed	11.6	10
Neuropathy	13.2		11
Retinopathy	5.06	37	20
Nephropathy	0.93		10
Microalbuminuria		47.4	
Ischemic heart disease	0.66	2.5	5
Peripheral vascular disease	2	14.4	7
Cerebrovascular disease	0.13	4.3	2

[a] Cardiovascular risk factors, micro- and macrovascular complications at diagnosis in patients with young onset type 2 diabetes in India: CINDI 2. Indian J Endocrinol Metab 2016; 20(1): 114–118.
[b] Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013; 36(12): 3863–3869.
[c] Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE program): a cross-sectional study of a prospective cohort. Lancet Diabetes Endocrinol 2014; 2(12): 935–943.

Treatment and prevention

Few studies have focused on the treatment of specific population of individuals with early-onset type 2 diabetes. Regardless of the elevated prevalence of T2DM among the young adult population, data for appropriate treatment guideline is rare. The TODAY study is the first and only large-scale randomized trial to assess the impact of intensive therapy on individuals with early-onset T2DM. This study was a multi-center, randomized clinical trial with volunteers observed for about 3.86 years on the average. The results showed that metformin monotherapy was related to long-lasting control of glucose in approximately 50% of children and adolescents with T2DM. The additional supplement of rosiglitazone, instead of an active lifestyle intervention, was superior to metformin alone. These results indicated that the bulk of young people with T2DM may need combined treatments or insulin injection no longer than 5 years after diagnosis [64]. Metformin and insulin are the only drugs approved for use in pediatric patients with T2DM. Moreover, a randomized double-blinded study revealed the safety of using metformin in 82 individuals aged 10–16 years for up to 16 weeks, with a reduction in HbA1c compared with the placebo group [65]. Another randomized single-blinded study reported a reduction in HbA1c in 263 young people with T2DM (mean age 13.8 years) using metformin (–0.54%) and glimepiride (–0.71%), both of which were safe to use within the 26-week follow-up period [66].

Though implementing diabetes-prevention programs among young population is highly important, limited progression has been worked out due to difficulty in distinguishing young adults at risk for T2DM. Considering themselves as sound and healthy, young adults tend to ignore their own vulnerabilities to prediabetes or diabetes and rarely receive diabetes screenings. One study characterized risk factors concerned with type 2 diabetes in Indian–American youth to determine a non-invasive risk model. The risk prediction model finally showed that a direct family history of diabetes, obesity, alcohol consumption, and high fasting glucose level were significantly associated with the onset of prediabetes or diabetes within 5 years. Although this novel non-invasive screening model has the potential to assess the risk of young adults in developing diabetes, it is still needed to be verified in other racial young adults [67].

Studies that focus on the prevention of early onset diabetes are rare. Adjusting obesity and impaired glucose regulation with diet and exercise interventions or pharmacological therapy such as metformin and thiazolidinediones can prevent T2DM [68,69]. A study of US Diabetes Prevention Program operated among 3234 non-diabetic individuals with elevated plasma glucose concentrations showed that lifestyle intervention, including physical activity and weight loss, reduced the risk of type 2 diabetes, where relative risk reduction (RRR) is 58%, which was more effective than metformin (RRR 31%) or placebo. This benefit could be found in all participant populations including individuals aged 25–44 years [70].

For the sake of preventing micro- and macrovascular complications of diabetes, treatments of hyperglycemia, blood pressure, and lipids were needed in this process [71]. An angiotensin-converting enzyme inhibitor or statin should be taken when hypertension or hyperlipidemia developed [72]. However, we could not find any pharmacotherapeutic outcome studies of such agents in early-onset T2DM.

Conclusions

China bears the heaviest burden from diabetes and its complications worldwide. Academic societies have implemented actions in diverse aspects and coordinated multi-level activities in China. An elevation in the prevalence of diabetes in China was observed, with much more young population developing diabetes. Plenty of large-scale epidemiological studies have confirmed that early-onset diabetes rapidly raised the incidence of macrovascular and microvascular complications. This increase is mainly due to longer duration of diabetes and unoptimized glycemic control at the beginning of diagnosis. All these findings imply the urgency of taking actions to prevent diabetes, especially in young Chinese adults. This review highlights the steps necessary for the government's establishment of policies aimed at young people to cut down the vascular complications of this disease.

With the high prevalence of macrovascular and microvascular complications of early-onset diabetes, screening cardiovascular risk factors and diabetes-related complications in early-onset diabetes at the time of diagnosis is crucial.

In conclusion, the majority of early-onset diabetes stay asymptomatic for a long period. Thus, screening for T2DM is imminent for young adults with a family history of diabetes, obesity, markers of insulin resistance, or alcohol consumption. More data are definitely required to establish a reasonable risk model to screen for early-onset diabetes.

Compliance with ethics guidelines

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