

# Similarities and differences in the natural history of youth-onset type 2 diabetes between the West and Asia

In the past, type 1 diabetes usually occurred in children or young adults. In recent decades, the West and the East have discovered that type 2 diabetes occurs in approximately 45% of adolescents with diabetes<sup>1</sup>. Now, type 2 diabetes with the age of onset before 20 years is defined as youth-onset type 2 diabetes, and it shows a gradually increasing incidence and prevalence worldwide<sup>1</sup>. As this disease is relatively new, relevant literature is scarce. Therefore, most of us are unfamiliar with the natural history, etiology, risk factors, comorbidities, treatment and complications of youth-onset type 2 diabetes.

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study group carried out a multicenter clinical trial from 2004 to 2011 to compare the glycemic control effects of metformin monotherapy, metformin plus rosiglitazone and metformin plus intensive lifestyle intervention in 677 patients with youth-onset type 2 diabetes. After completing the trial, 550 participants were transitioned to an observational follow-up study from 2011 to 2020<sup>2</sup>. Investigators annually examined the participants for diabetic kidney disease, hypertension, dyslipidemia and nerve disease; retinal disease was assessed twice (in 2010 or 2011 and 2017 or 2018); diabetes-related complications identified outside the study centers were confirmed and adjudicated by the

assessment committee. The baseline prevalence and cumulative incidence at the 15th year of follow up of comorbidities and complications were as follows (Table 1): overweight (baseline 78.9%), hypertension (19.2 and 67.5%), dyslipidemia (20.8 and 51.6%), chronic kidney disease (8.0 and 54.5%), nerve disease (1.0 and 32.4%) and incidence of retinopathy (13.7% in 2010 or 2011, 51.0% in 2017 or 2018). The cumulative incidence of microvascular complications was 50.0% by 9 years and 80.1% by 15 years. The adjudicated clinically identified complication rates were as follows: heart, vascular and cerebrovascular events (3.73 per 1,000 person-years, including 7 events with ischemic heart disease, 6 with congestive heart failures, 4 with stroke), renal events (0.44 per 1,000 person-years), ophthalmic events (12.17 per 1,000 person-years), neurological events (2.35 per 1,000 person-years) and liver, pancreas or gallbladder events (6.70 per 1,000 person-years); six deaths were reported (one each from myocardial infarction, renal failure, drug overdose and sepsis; two from sepsis plus multi-organ failure).

An Asian study on youth-onset type 2 diabetes in Taiwan showed that the baseline incidences of hypertension and dyslipidemia were 44.4 and 27.0%, respectively (Table 1)<sup>1</sup>. An assessment of 22 young Koreans with type 2 diabetes (age 8–28 years) showed an 18.2% prevalence of microalbuminuria and 4.5% prevalence of macroalbuminuria at follow up<sup>1</sup>. Three studies on early-onset type 2 diabetes (age <30 years) in Japan showed a 9.6% incidence of microalbuminuria at 6–8 years of diabetes duration, with an

incidence rate of 14.1 per 1,000 person-years; the incidence of background retinopathy was 9.3% at presentation, 18.3% at 4.4 years and 27% at 5.7 years, with an incidence rate of 48.1 per 1,000 person-years; the incidence of proliferative retinopathy was 12.7% at 7.1 years, with an incidence rate of 17.4 per 1,000 person-years<sup>1</sup>. A cohort study from a diabetes center in southern India investigated 368 patients with youth-onset type 2 diabetes, with obesity (52.5%), hypertension (23.7%), dyslipidemia (65.9%), retinopathy (4.2% [ $\leq 5$  years], 37.9% [ $>5$  to  $\leq 10$  years], 61.1% [ $>10$  to  $\leq 15$  years], 81.6% [ $>15$  years]), microalbuminuria (8.7% [ $\leq 5$  years], 16.4% [ $>5$  to  $\leq 10$  years], 28.6% [ $>10$  to  $\leq 15$  years], 29.6% [ $>15$  years]), nephropathy (0% [ $\leq 5$  years], 9.0% [ $>5$  to  $\leq 10$  years], 19.0% [ $>10$  to  $\leq 15$  years], 34.4% [ $>15$  years]) and neuropathy (3.0% [ $\leq 5$  years], 6.8% [ $>5$  to  $\leq 10$  years], 22.2% [ $>10$  to  $\leq 15$  years], 49.2% [ $>15$  years])<sup>3</sup>. Although the definition and methodology of comorbidities and complications showed some discrepancies between studies, all showed a high incidence of complications in patients with youth-onset type 2 diabetes.

The TODAY follow-up study also showed minority races, hyperglycemia, hypertension and dyslipidemia as risk factors for complications<sup>2</sup>. Suboptimal control of hyperglycemia, hypertension and dyslipidemia has also been reported in Asian studies<sup>4</sup>. Adolescents with type 2 diabetes are prone to treatment failure and rapid decline of insulin secretion, which might be due to genetic factors; however, environmental factors cannot be ignored. Most adolescents with

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**Table 1** | Presentation of comorbidities and complications in patients with youth-onset type 2 diabetes

Presentation	Site or population	Age at diagnosis of diabetes (years)	At diagnosis	Duration ≤5 years	Duration to ≤10 years	Duration >10 to ≤15 years	Duration >15 years	Incidence (per 1,000 person-years)
Hypertension	USA	10–17	19.2%	33.8%		67.5%		
	Taiwan	6–18	44.4%			51.6%		
Dyslipidemia	India	≤19	23.7%					
	United States	10–17	20.8%	12.7%				
Nephropathy	Taiwan	6–18	27.0%					
	India	≤19	65.9%					0.44
Microalbuminuria	United States	10–17	8.0%	0%	9.0%	54.8%	34.4%	
	India	≤19		18.2%		19.0%		
Macroalbuminuria	Korea	8–28			9.6%			14.1
	Japan	<30			16.4%	28.6%	29.6%	
Retinopathy	India	≤19		8.7%				
	Korea	8–28		4.5%				
Background retinopathy	United States	10–17		13.7%	37.9%	51.0%	81.5%	12.17
	India	≤19		4.2%		61.1%		
Proliferative retinopathy	Japan	<30	9.3%	18.3%	27%			48.1
	Japan	<30			12.7%			17.9
Neuropathy	Japan	<30				32.4%	49.2%	2.35
	USA	10–17	1.0%	3.0%	6.8%	22.2%		
	India	≤19						

type 2 diabetes are overweight or obese, with a preference for energy-dense foods and sweetened beverages, physical inactivity, excessive TV watching or prolonged use of electronic products, which might increase the risk of metabolic syndrome and insulin resistance<sup>5</sup>. Not many drugs can be used for adolescents with type 2 diabetes to provide glycemic control and organ protection. Some physicians might hesitate to prescribe cardiovascular medications for their young patients, and parents might be concerned about the side-effects of long-term drug use in children; furthermore, adolescents can often fail to have regular checkups and take medicines regularly<sup>1</sup>. The aforementioned reasons could result in suboptimal control of blood pressure, glucose and lipid levels, increasing the risk of future complications. More randomized trials and well-designed clinical studies in adolescents with type 2 diabetes might provide valuable information for a consensus on reliable recommendations to patients and care providers<sup>5</sup> to reduce concerns and improve treatment efficacy in adolescents with type 2 diabetes.

Approximately 80.4% of TODAY's adolescents with type 2 diabetes belonged to a minority population, 41.5% to economically disadvantaged families and 59.6% had a nuclear family history of diabetes. Approximately 44.8% of Indian adolescents with type 2 diabetes have a parental history of diabetes. However, the prevalence of young-onset type 2 diabetes and gestational diabetes in Asia is higher than in the West<sup>4</sup>. Mothers with diabetes are more likely to have siblings with diabetes, with a familial aggregation of diabetes in Asia showing a marked increase<sup>1,4</sup>. We must encourage pregnant women with diabetes to modify deeply entrenched living habits and develop a good lifestyle, with less consumption of sugar-containing drinks, a low-calorie diet, more high-fiber foods, reduced sedentary time and >150 min of moderate-intensity physical activity per week for better glycemic control and improved pregnancy outcomes. These mothers with diabetes can then transfer healthy habits to their offspring and

mitigate the future risk of youth-onset type 2 diabetes in children<sup>4,5</sup>.

In summary, the natural history of youth-onset type 2 diabetes between the West and the East seems similar, with a high proportion of comorbidities (obesity, hypertension and dyslipidemia), increased risk of microvascular complications and high treatment failure rates. However, the West might have to focus on children belonging to racial minorities or financially deprived families, and help them develop healthy lifestyle behaviors to reduce the risk of diabetes in the future. The East might need to focus on women with maternal diabetes and encourage healthy lifestyle behaviors to reduce the risk of future youth-onset type 2 diabetes in children.

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#### DISCLOSURE

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