Youth-onset type 2 diabetes mellitus—a distinct entity?

S. V. Madhu¹

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Diabetes mellitus is a chronic and lifelong disease that causes a huge burden to the healthcare system. Its prevalence is increasing worldwide. Global estimates suggest that 463 million individuals have diabetes as of 2019 and that this number will increase to 700 million by 2045, whereas in India 77 million individuals have diabetes as of 2019 and this will increase to 134 million by 2045 [1]. Over 90% of cases of diabetes are of type 2 diabetes mellitus. The increase in the prevalence of diabetes among older adults is well recognised but the rising number of young people with type 2 diabetes is a more recent development and is of particular concern. Type 2 diabetes mellitus in adolescents and young adults results in adverse societal effects because of the presence of a chronic disease throughout patients' working life and consequently greater propensity for long-term complications. Type 2 diabetes in young people could be more rapid and disruptive than in patients who have diabetes later in life, leading to early morbidity and poor quality of life [2].

There is a 31% increase in type 2 diabetes in age group 10–19 years in the USA between 2001 and 2009, resulting prevalence of 0.48 per 1000 in this age group [3]. Data from the SEARCH study [4] shows an annual increase of about 7% in the incidence of type 2 diabetes between 2002–2003 and 2011–2012 among people aged 10–19 years in the USA, with substantial relative increases in all ethnic minority groups compared with non-Hispanic White people.

The registry of youth-onset diabetes in India (YDR) reported that over 25% of youth-onset diabetes less than 25 years were type 2 diabetes mellitus [5] with an incidence of 0.5 cases/100,000 in those under 19 years [6]. In those less than 19 years of age, type 2 diabetes was equally common in both genders with the mean duration of diabetes at the presentation of 7 years. Most of these patients belonged to the high socioeconomic group, over 57% were

either overweight or obese and over 70% had HbA1C of more than 9% indicating poor control [7]. The prevalence of DKA among T2D in SEARCH and YDR was 5.5% and 6.6% respectively [8].

The development and progression of type 2 diabetes represent a complex interplay between genetic, epigenetic, lifestyle, demographic, socioeconomic, therapeutic and environmental factors. A majority of patients with type 2 diabetes have at least one parent with type 2 diabetes mellitus [9]. The mechanisms leading to the development of type 2 diabetes in young people are similar to those in older patients, but the speed of onset, severity and interplay of reduced insulin sensitivity and defective insulin secretion may be different in patients who develop type 2 diabetes at a younger age [10] and a better understanding of this would help in improvement in its management. Type 2 diabetes in young people was thought to be associated with chronic complications due to longer disease duration but now there is increasing evidence that the disease could have a faster rate of progression in young people.

As seen with late-onset type 2 diabetes, adolescents also have initial deterioration in β -cell function which is characterised by loss of the first phase of stimulated insulin secretion [4]. There is some evidence that the second phase of nutrient-induced insulin secretion might be compromised earlier in younger individuals with type 2 diabetes [10]. TODAY study showed a 20–35% annual decline in β -cell function in adolescents aged 10–19 years with type 2 as compared to a 7% decline in older individuals with type 2 diabetes [11]. The prevalence of obesity among children, adolescents and young adults with type 2 diabetes is much greater than in older adults with type 2 diabetes and there is an inverse relationship between BMI and age at diagnosis of type 2 diabetes [12]. Physical inactivity is associated with an increased risk of obesity. The CARDIA study [13] which was a multicentre cohort study in 5115 participants aged 18–30 years showed that physical inactivity was strongly associated with risk of type 2 diabetes, hypertension and metabolic syndrome. Intrauterine environment can affect the development of obesity and type 2 diabetes in adolescents

✉ S. V. Madhu
drsvmadhu@gmail.com

¹ Department of Endocrinology, Center for Diabetes, Endocrinology and Metabolism, University College of Medical Sciences, Delhi, India

and young adults. Maternal undernutrition and overnutrition are associated with an increased risk of obesity and type 2 diabetes in the adolescent period and early adulthood [14, 15]. Socioeconomic deprivation in affluent societies is a risk factor for obesity and type 2 diabetes because of consumption of energy dense foods and sedentary habits rather than because of absolute lack of availability or affordability of healthier options. Obesity is also common in affluent societies that are not deprived thus implicating individual lifestyle and behavioral choices as risk factors with the greatest effect on the pathogenesis of type 2 diabetes in young people [16, 17].

A family history of type 2 diabetes is inversely associated with the age of onset of type 2 diabetes [18]. Studies [19, 20] in Mexican and Asian populations have identified several mutations associated with type 2 diabetes in young people. The high prevalence of type 2 diabetes in the parents of young people diagnosed with type 2 diabetes reflects a stronger genetic predisposition. SEARCH study of US children and adolescents (aged 10–19 years) showed that incidence of type 2 diabetes in female individuals was nearly twice that of male individuals [4]. The risk of type 2 diabetes is increased in young women diagnosed with polycystic ovary syndrome [21] and is possibly due to insulin resistance in polycystic ovary syndrome [22, 23]. Non-alcoholic fatty liver disease (NAFLD) is a stronger risk factor for young-onset type 2 diabetes than for type 2 diabetes that develops in middle or later life. NAFLD is twice as more common in adolescents than in older patients with type 2 diabetes and is commonly associated with insulin resistance in adolescents and young adults with type 2 diabetes.

The clinical characteristics of type 2 diabetes in young people overlap substantially with those of type 1 diabetes, from which it needs to be differentiated, as well as with those of type 2 diabetes in older adults. The early loss of insulin secretory capacity in young patients of type 2 diabetes is similar to the demise of β -cell function in type 1 diabetes, whereas the high prevalence of obesity seen in young people with type 2 diabetes is more in keeping with type 2 diabetes in older adults. Adolescents who develop type 2 diabetes also show similar clinical features of insulin resistance, dyslipidemia, hypertension and polycystic ovary syndrome as seen in the late onset of disease, but the long-term consequences of the early-onset disease are only now becoming apparent [24, 25].

People diagnosed with type 2 diabetes at a younger age still have the potential to develop complications at an earlier stage of life, at a time when the complications are more likely to cause greater disability and loss of productivity compared with people diagnosed at an older age. To examine the effect of age of onset of disease on risks of complications, focusing on all-cause mortality, macrovascular events and microvascular events a comprehensive systematic review

and meta-analysis was done which compiled the results of 26 studies investigating the effects of age at diabetes diagnosis on mortality and subsequent complications in 1,325,493 participants with type 2 diabetes from diverse populations across the Asia Pacific, Europe and North America. In this review, an inverse relationship was reported between age at diabetes diagnosis and risk of major diabetes complications after adjustment for the current age. Each 1-year increase in age was associated with a 4%, 3% and 5% decreased risk of all-cause mortality, macrovascular disease and microvascular disease, respectively. These effects were consistent across the individual components of the composite outcomes (CHD, cerebrovascular disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy) and reversed when the models included diabetes duration rather than current age. In this review, it was seen that younger rather than older age at diabetes diagnosis was associated with a higher risk of mortality and vascular disease. Thus, early and sustained interventions to delay type 2 diabetes onset and improve blood glucose levels and cardiovascular risk profiles of those already diagnosed with the disease are essential to reduce morbidity and mortality [26]. An association of cardiometabolic multimorbidity and depression with cardiovascular events in early-onset adult type 2 diabetes has been seen from a multi-ethnic study from the USA [27].

The study by Ashraf et al. in the current issue compares clinical features, complication profile and achievement of guideline targets in early- and late-onset type 2 diabetes patients from North India. In a large study conducted in over 5000 patients, they report that nearly one-third of all type 2 diabetic patients had an early onset before 40 years of age. These patients were more obese, had a stronger family history of diabetes and displayed more severe dyslipidemia. Comorbid conditions and diabetes-related vascular complications were higher in late-onset patients. This observation is in contrast to earlier suggestions that youth-onset type 2 diabetes is likely to be more aggressive and as a consequence develop complications more often. However, in this study, as the groups were not matched for duration of diabetes and level of glycemic control, these findings have to be interpreted with caution. Long-term follow-up studies with incident rates of complications may be a better way to assess complications.

Recently, distinct clusters or subgroups of individuals with diabetes have been identified in a Scandinavian population in 8980 patients. Clusters were based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c and homoeostatic model assessment 2 estimates of β -cell function and insulin resistance). These subgroups were (1) severely autoimmune diabetes (SAID), (2) severely insulin-deficient diabetes (SIDD), (3) severely insulin-resistant diabetes (SIRD), (4) mild obesity-related diabetes (MOD) and (5) mild age-related diabetes (MARD).

These subgroups differed not only with respect to clinical characteristics at diagnosis, but also with pathophysiological mechanisms and susceptibility to complications. Cluster 1 comprised 6.4% of patients and this cluster was characterised by early-onset disease, relatively low BMI, poor metabolic control, insulin deficiency and presence of anti-GAD antibodies. Cluster 2 comprised 17.5% of patients who were GADA negative but otherwise similar to cluster 1 and had young age at onset, relatively low BMI, low insulin secretion (low HOMA2-B index) and poor metabolic control. Cluster 3 had 15.3% patients and was characterised by insulin resistance (high HOMA2-IR index) and higher BMI. Cluster 4 had 21.6% of patients which was also characterised by obesity but not by insulin resistance. Cluster 5 had 39.1% of patients and this cluster had older patients than in other clusters but had only modest metabolic derangements [28]. This study also compared the diabetic complications in different clusters. Ketoacidosis at diagnosis was common in cluster 1 (31%) and cluster 2 (25%) both of which had patients with younger age at onset and were less than 5% in other clusters. Similarly, the risk of retinopathy was highest in cluster 2. Cluster 3 had the highest prevalence of non-alcoholic fatty liver disease and the highest risk of developing chronic kidney disease. We can clearly observe that age is one of the important variables in identifying these clusters and younger patients could belong to distinct clusters and older ones to others with distinct phenotypic characteristics. The long-term follow-up of these patients will provide greater clarity on the incidence of complications in them. A similar study from India defined four clusters of patients with type 2 diabetes mellitus differing in phenotypic characteristics as well as disease outcomes [29]. However, clear age-related differences were not described.

Identification and quantification of the increased risk of mortality and vascular disease due to younger age at type 2 diabetes diagnosis may enable risk stratification of people early in the condition and provide greater opportunities for interventions to reduce the risk of complication associated morbidity and mortality for this increasing population of young type 2 diabetes patients. Younger people also pose a significant challenge for clinicians who should be aware of these compounding pathologies of natural ageing and premature vascular ageing associated with young age type 2 diabetes patients.

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