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Youth-onset type 2 diabetes mellitus: an urgent challenge

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Abstract

The incidence and prevalence of youth-onset type 2 diabetes mellitus (T2DM) and its complications is increasing worldwide. Youth-onset T2DM has been reported in all racial and ethnic groups but Indigenous peoples and people of colour are disproportionately affected. People with youth-onset T2DM often have a more aggressive clinical course than those with adult-onset T2DM and those with type 1 diabetes mellitus. Moreover, the available treatment options for children and adolescents with T2DM are more limited than for adult patients. Intermediate complications of youth-onset T2DM, such as increased albuminuria, often develop in late childhood or early adulthood, and end-stage complications, including kidney failure, develop in mid-life. The increasing frequency, earlier onset, and greater severity of childhood obesity in the past 50 years together with increasingly sedentary lifestyles and an increasing frequency of intrauterine exposure to diabetes are important drivers of the epidemic of youth-

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onset T2DM. The particularly high risk of the disease in historically disadvantaged populations suggests an important contribution of social and environmental factors, including limited access to high-quality healthcare, healthy food choices and opportunities for physical activity as well as exposure to stressors including systemic racism and environmental pollutants. Understanding the mechanisms that underlie the development and aggressive clinical course of youth-onset T2DM is key to identifying successful prevention and management strategies.

ToC

This Review describes the global epidemiology, clinical course and key complications of youth-onset type 2 diabetes mellitus. The authors also discuss the mechanisms that might underlie the aggressive clinical phenotype of this disease and current management strategies.

Introduction

Type 2 diabetes mellitus (T2DM) was traditionally considered to be a disease that arises in response to long-term insulin resistance and impaired insulin secretion, and therefore typically affects individuals aged ≥50 years. By contrast, type 1 diabetes mellitus (T1DM) is caused by an autoimmune reaction that destroys the insulin-producing β-cells of the pancreas and typically develops in children, adolescents and young adults. However, in the 1960s and 1970s, the first reports of asymptomatic hyperglycaemia and glucose intolerance in children and adults aged <45 years with obesity were published in the US and Europe[1–5]. These early studies were followed by reports of T2DM in children in populations across the Americas, Europe, Asia, Australasia, and the Middle East[6–15].

A review of T2DM among people aged <20 years in North America, where some of the highest prevalences of youth-onset T2DM have been reported, confirmed its presence in all racial and ethnic groups and noted a particularly high prevalence among American Indian and First Nations peoples[16]. In 2000, a consensus statement from the American Diabetes Association (ADA) concluded that up to 45% of new cases of diabetes among individuals aged <20 years in North America were not immune-mediated and the majority of these non-immune mediated cases were T2DM[17]. Since 2001, an increasing prevalence and incidence of youth-onset T2DM, particularly among minority racial and ethnic groups, has been reported in large multicenter studies in the US[18,19]. Importantly, youth-onset diabetes is a global problem and increasing prevalences have also been reported in studies from East Asia, Australasia and the Near and Middle East[14]. In Japan, for example, a study published in 2005 reported that 80% of new cases of youth-onset diabetes identified by diabetes screening in a large school health system were T2DM[14].

Youth-onset T2DM is associated with the development in midlife of major diabetes complications, including diabetic kidney disease (DKD), cardiovascular disease, retinopathy, and neuropathy[20,21]. The increasing frequency of youth-onset T2DM in populations worldwide together with its unexpectedly rapid and aggressive course compared with later-onset T2DM illustrates the urgent challenge of heightening our awareness of this rapidly evolving disease, establishing the mechanisms underlying its rapid progression, and finding effective therapeutic strategies to ameliorate its impact.

In this Review, we examine the emergence of youth-onset T2DM and its complicated course worldwide, emphasizing populations that are at considerable risk of this disease. We compare the clinical course of youth who develop T2DM with those who develop T1DM and with adults who develop T2DM. We also explore the impact of youth-onset T2DM on the key microvascular and macrovascular complications of diabetes, with a focus on the development and progression of DKD. Lastly, we examine the mechanisms that might explain the aggressive clinical phenotype observed in patients with youth-onset T2DM and discuss current management strategies and the challenges that are associated with their implementation in this population.

Epidemiology of youth-onset T2DM

Studies of adverse outcomes among patients with youth-onset T2DM are challenging because diagnosis of T2DM in youth, although increasing, remains uncommon compared with diagnosis in adulthood. Moreover, T2DM in children and adolescents is often not recognized because of its long subclinical stage and a lack of awareness among patients and providers of the increasing risk. Accordingly, data from national population-based disease registries might not adequately reflect the frequency and evolving trends of youth-onset T2DM.

United States and Canada

Although youth-onset T2DM has been reported in all racial and ethnic groups in the US, some populations are particularly notable for their increased risk. For example, Indigenous peoples in the Americas have an exceptionally high prevalence of T2DM and were among the first populations in which youth-onset T2DM was identified. The high risk of youth-onset T2DM in these historically disadvantaged populations suggests an important contribution of stress, historical trauma, and adverse socioeconomic factors to the development of this disease[22,23].

United States.—In the US, the National Health and Nutrition Examination Survey (NHANES) and the National Health Interview Survey (NHIS) monitor the prevalence and incidence of diabetes. Differentiation between T1DM and T2DM in these surveys is based on self-reported age at diabetes onset, insulin use and reported diabetes type. The prevalence of diabetes among people aged 12–19-years was estimated to be 0.41% in NHANES 1988-1994[24] and 0.84% in NHANES 1999-2010, which also reported a prevalence of T1DM of 0.48% and of T2DM of 0.36% in this age group[25]. In 2016, NHIS estimated that the prevalence of diabetes among people aged 18-29 years in the US was 0.45% for T1DM and 0.66% for T2DM[26]. None of the national surveys have a large enough sample size to accurately assess diabetes prevalence and incidence in youth at the state or national level or in race and ethnicity subgroups.

In the US, 574 American Indian and Alaska Native tribes and villages are federally recognized. Much of what is known about the long-term effects of youth-onset T2DM comes from population research conducted in Pima Indians from the Gila River Indian Community in Arizona. Diabetes among Pima Indian children and adolescents was first identified in the mid-1960s owing to the initiation of a longitudinal population study[27].

This youth-onset diabetes was entirely attributed to T2DM[12] as it was characterized by ongoing insulin secretion[28], lack of insulin dependence, absent or low levels of islet cell and glutamic acid decarboxylase antibodies[29,30], and absence of strong linkage or association with maturity-onset diabetes of youth (MODY) loci[31,32]. The prevalence of youth-onset T2DM among Pima Indian children increased between 1967 and 1996[33], due in part to an increasing prevalence and severity of obesity in childhood and adolescence[34–36] and to a growing incidence of exposure to intrauterine diabetes[33,34]. In boys, the prevalence of T2DM increased from 0% in 1967-1976 to 1.40% in 1987-1996 among those aged 10-14 years and from 2.43% to 3.78% among those aged 15-19 years. In the same period, the prevalence of T2DM in girls increased from 0.72% to 2.88% among those aged 10-14-years and from 2.73% to 5.31% among those aged 15-19 years[33].

Canada.—A national surveillance study that was conducted in Canada between April 2006 and March 2008 reported a minimum incidence of T2DM among children aged <18 years of 1.54 cases per 100,000 per year[37]. The study identified substantial regional variation, with the highest minimum incidence of 12.45 cases per 100,000 children per year in Manitoba and no cases reported in the Northwest Territories, Yukon and Nunavut. This regional variation could be explained predominantly by the distribution of race and ethnicity, as 44.1% of children with new-onset T2DM were Indigenous people and most of these children were from Manitoba.

Canada recognizes three distinct groups of Indigenous peoples, First Nations, Inuit, and Métis, of which First Nations peoples are the largest and most diverse group. Diabetes among these populations was increasingly recognized following the Second World War[38]. The incidence increased dramatically between the 1970s and 1990s, with studies consistently reporting a 2-5-fold increased risk of diabetes among First Nations peoples compared to other populations[39,40]. A 2016 study estimated that as many as 8 in 10 First Nations people aged 20 years will develop T2DM in their lifetime, compared with 5 in 10 non-First Nations people aged 20 years[41].

In the 1980s, the first cases of youth-onset T2DM in Canada were identified among Oji-Cree children in Manitoba, about two decades after cases were first observed in Pima Indian youth from Arizona[38]. Subsequent studies suggest that the majority of Canadian patients with youth-onset T2DM are located in the provinces of Manitoba and Ontario due to their large populations of First Nations people[7,42,43]. The prevalence of youth-onset diabetes in Canadian First Nations communities with active surveillance is as high as 1-3%[43,44]. Health disparities such as a lack of access to high quality health care, particularly for First Nations children living in rural areas, might contribute to the differences in prevalence between First Nations and non-First Nations individuals[45].

Europe

The prevalence of youth-onset T2DM is generally lower in Europe than in other developed countries[23,46]. This lower prevalence is partly due to the lower numbers of youths who belong to high risk racial and ethnic groups in many European countries[46]. The United Kingdom has the highest reported prevalence of childhood T2DM in Europe and a more

racially diverse population than many other European countries[47]. A study that estimated the incidence of youth-onset T2DM in 11,274,750 children aged <17 years in 2015 found that the incidence in the 1,096,304 Asian and 537,938 Black children (2.92 and 1.67 per 100,000, respectively) was much higher than the incidence in the 8,921,552 white children (0.44 per 100,000)[48].

South America

Data on youth-onset T2DM in South America are scarce. However, a Brazilian cross-sectional school-based study that collected data from 37,854 students aged 12-17 years in 2013 and 2014 reported a prevalence of T2DM among adolescents of 3.3%[15]. Brazil has the fourth largest population of people with T2DM worldwide[49]. These data show that T2DM is not only an important public health challenge for the adult population, but also for the adolescent population, which has a high prevalence of T2DM[15].

Africa

Few studies have examined the prevalence of diabetes in youth in Africa and most studies in sub-Saharan Africa have focused on T1DM. In 2004, a review of population-based studies of childhood T2DM identified 4 studies conducted in the 1980s that reported either no cases or a very low prevalence of youth-onset T2DM in Togo, Tanzania and Mali[50]. The available data suggest that the prevalence and/or detection of youth-onset T2DM in sub-Saharan Africa remains low relative to high-income countries. However, the proportion of school-aged children who are overweight or obese is rising across sub-Saharan Africa[51], suggesting that the prevalence of obesity-related diseases, including T2DM, will increase among African youth.

East Asia

As the incidence of T1DM in East Asian countries is very low[52–56], diabetes in these countries is largely attributed to T2DM. Data from the Korean National Health and Nutrition Examination Survey (KNHANES) showed an increasing prevalence of diabetes among adolescents from 0.19% in 2007 to 0.43% in 2018, in parallel with a rising prevalence of obesity[52].

In China, the prevalence of youth-onset T2DM, estimated by review of hospital records from 14 medical centres, increased 2.5-fold between 2005 and 2010[54]. A national cross-sectional survey reported a prevalence of diabetes among Chinese children aged 10-17 years of 0.13% in 2013-2014[53].

The incidence of youth-onset T2DM in India in 2006-2012 was estimated using registry data from centres in New Delhi and Chennai. After correction for under-ascertainment, the incidence of T2DM among people aged <20 years was estimated to be 0.5 per 100,000 per year[57].

In Japan, a large number of children aged 6-15 years with T2DM have been identified over the past four decades. A study that used data from urine glucose testing of nearly 12 million

primary and junior high school students in Tokyo estimated an incidence of 2.58 per 100,000 children per year during 1974-2015[55].

Australia and New Zealand

Estimation of the prevalence and incidence of T2DM in Australia and New Zealand is facilitated by the existence of several national population-based government registries. The Australian National Diabetes Service Scheme (NDSS) is a population-based registry that captures 80-90% of people with diabetes in Australia. The NDSS reported that during 2003-2019, the prevalence of T2DM was stable among people aged <20 years and among those aged 20–45 years. However, the stable prevalence of T2DM among those aged <20 years might partly reflect the poor representation of Indigenous Australians in the NDSS.

No national studies of the prevalence of youth-onset diabetes among Indigenous Australians are available and the few regional studies have reported vastly variable data. A hospital-based study from the Top End of the Northern Territory, using data collected from 2007-2011, reported a prevalence of T2DM among people aged <25 years of 0.05%. Most of the youths with T2DM (83%) were Indigenous Australians, who comprised 30% of the Northern Territory population[58]. A retrospective cross-sectional study conducted in Northern Australia between 2016-2017 reported prevalences of T2DM of 0.14% and 1.41% among Indigenous Australians aged <15 years and 15-24 years, respectively[59]. In this study, the prevalence of T2DM was higher in girls than in boys (0.944% versus 0.416%) and varied considerably across regions. For example, among 15–24-year-olds, the prevalence of T2DM ranged from a very high 3.11% in Central Australia to 0.83% in Far North Queensland. The reasons for these regional differences are unclear but might be related to variations in socioeconomic factors.

Data from Western Australia suggest that Indigenous children have a 20-fold higher mean incidence of T2DM than non-Indigenous children[60]. The incidence of T2DM increased among Indigenous and non-Indigenous Australian youth between 1990 and 2012. However, the mean rate of increase in incidence was greater among Indigenous children (12.5% per year) than non-Indigenous children (10.9% per year).

The Virtual Diabetes Registry (VDR) is a robust source of diabetes prevalence data in New Zealand that contains administrative data about people suspected of having diabetes who are identified through their use of diabetes-related health services. Data from the VDR collected between 2015 and 2020 indicate that the prevalence of diabetes among those younger than 20 years in New Zealand is highest among Maori people (0.24%), Pacific Islanders (0.23%) and those of European descent (0.27%)[61]. However, these data are not stratified by diabetes type so the impact of youth-onset T2DM on these estimates cannot be assessed.

Near and Middle East

The Near and Middle East region encompasses 20 countries[62]: Algeria, Bahrain, Egypt[63], Iran[64,65], Iraq[66], Israel[67,68], Jordan, Kuwait[69,70], Lebanon[71], Libya[13], Morocco, Oman[72], Palestinian Authority, Qatar[73,74], Saudi Arabia[75–77], Syria, Tunisia, Turkey[78,79], United Arab Emirates (UAE)[80,81] and Yemen[82]. Regional comparisons reported by the International Diabetes Federation indicate that the prevalence of diabetes in this region is the highest

worldwide and is increasing rapidly[83]. High prevalences of youth-onset T2DM have been documented among children and adolescents in Kuwait[70] (0.035%) and Qatar[73] (0.053%). In addition, high incidences of youth-onset diabetes have been reported in Kuwait[69] (8.0 per 100,000 people aged 10-14 years per year), Libya[13] (1.8 per 100,000 people aged 10-14 years per year, 5.9 per 100,000 people aged 15-19 years per year), and Qatar[73] (4.2 per 100,000 people aged <18 years per year). A national observational study of Israeli children and adolescents aged 10-18 years with T2DM reported a 10-fold increase in the incidence of youth-onset T2DM among Israeli Arabs between 2008 (0.66 per 100,000) and 2019 (6.4 per 100,000) and a 3.5-fold increase among Israeli Jews during the same period (0.62 per 100,000 in 2008 versus 2.3 per 100,000 in 2019)[67].

Similar to western countries, a higher frequency of youth-onset T2DM has been reported among girls than among boys in Iran[65], Israel[67], Turkey[78,79], and Egypt[70]. However, in the UAE[80], Iraq[66], and Kuwait[70] a higher frequency of youth-onset T2DM was reported among boys. These findings might reflect differences in the frequency and distribution of obesity among male and female children in these countries[84]. In the UAE, for example, the prevalence of morbid obesity (BMI ≥99th percentile) among children aged 11-14 years was 9.6-fold higher in boys than in girls[85]. In Kuwait, 41.4% of boys aged 6-18 years had obesity compared to 28.9% of girls in the same age group[84]. Although data on youth-onset T2DM in the Near and Middle East are sparse, the available data indicate a high and growing risk of T2DM among children and adolescents.

Key studies of youth-onset T2DM

The limitations associated with adequately characterizing youth-onset T2DM using data from national disease registries and regional surveillance studies together with the urgent need to expand understanding of this disease beyond small high-risk populations, necessitates rigorously conducted multicenter studies to provide more detailed and nuanced characterization of this emerging problem. Two such studies, the SEARCH for diabetes in youth study and the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial, have provided important insights.

The SEARCH for diabetes in youth study

Data from the SEARCH study has greatly expanded our understanding of the epidemiology of paediatric diabetes, the risk factors that contribute to childhood-onset diabetes and diabetes-related complications[86,87]. SEARCH was conducted between 2001 and 2020 and included >2,500 participants with youth-onset T1DM and 300 with youth-onset T2DM at five centres across the US. In addition, SEARCH included active surveillance of patients with incident diabetes, enabling direct comparisons of epidemiology and complications by diabetes type and providing insights into the differences between paediatric and adult-onset diabetes[86,87].

SEARCH reported that in 2002-2012, few cases of T2DM were identified in children under the age of 10 years; however, the incidence of T2DM was greater than that of T1DM among Asian and Pacific Islander, American Indian, and non-Hispanic Black children aged 10-14 years[88]. For those aged 15-19 years, a higher incidence of T2DM than T1DM was observed

for every group except non-Hispanic white people[88]. The differences between racial and ethnic groups persisted over time, with the most recent SEARCH estimates from 2015 showing a higher incidence of T2DM than T1DM among youths aged 10-19 years in all racial and ethnic groups apart from non-Hispanic white people [89]. SEARCH reported that between 2002 and 2015, the age, sex, and race or ethnic group adjusted incidence of T2DM among youths in the US increased by 4.8% annually, compared with an annual increase in the incidence of T1DM in this population of 1.9%[88,89].

The SEARCH study estimated that in 2017, 0.067% of youths in the US had T2DM, suggesting that the prevalence of this disease doubled in just 16 years[19]. This finding parallels the reported increase in childhood obesity in the US from 13.9% in 1999-2000 to 18.5% in 2015-2016[90]. Non-Hispanic Black and Mexican American teenagers experienced the greatest increases in prevalence of obesity and severe obesity between 1999 and 2018, which may contribute to the reported racial and ethnic differences in the incidence and prevalence of T2DM[91,92].

Similar to adult T2DM, risk factors for youth-onset T2DM include obesity and inactivity. However, risk factors that are unique to children might also contribute to the risk of T2DM in childhood. The SEARCH Case-Control Study found that exposure to maternal gestational diabetes was associated with a 5.7-fold increase in the odds of youth-onset T2DM[93]. Exposure to maternal diabetes and/or pre-pregnancy maternal obesity accounted for 47% of youth-onset T2DM in this study. SEARCH also found that breastfeeding of any duration was associated with significantly lower odds of youth-onset T2DM[94]. However, the odds ratio was attenuated after adjustment for current BMI z-score in the offspring, suggesting that the protective effect of breastfeeding is mediated in part by the weight of the child[94]. Poor maternal diet[95], exposure to environmental chemicals[96,97], limited access to healthy foods, limited facilities for physical activity and reductions in the walkability of neighbourhoods might also contribute to the continued rise in youth-onset T2DM[98–100]. SEARCH found that the incidence of youth-onset T2DM was highest in rural areas with low population density[98]. The researchers suggested that this increased incidence in rural areas could be attributed to lower access to healthy foods, fewer recreational resources, and greater dependence on automobiles for transportation compared to urban areas. Exposure to pesticides used in agriculture might also be higher in rural communities. Findings from the SEARCH study highlight the importance of surveillance of childhood diabetes within populations and provide insights into the complex and heterogeneous nature of youth-onset T2DM.

The TODAY trial

The TODAY multicenter randomized control trial compared the efficacy of three treatment regimens to achieve durable glycemic control in children and adolescents with T2DM[101]. Between July 2004 and February 2009, the trial investigators enrolled 699 youths aged 10-18 years with a T2DM duration of <2 years, BMI ≥85th percentile, fasting C-peptide >0.6 mmol/L and negative pancreatic antibodies. The participants were randomly assigned to metformin monotherapy, metformin plus rosiglitazone or metformin plus an intensive lifestyle intervention and followed for an average of 3.9 years. The primary outcome of

loss of glycemic control (defined as HbA1c ≥8% for 6 months or sustained metabolic decompensation requiring insulin) was reached by 46% (n=319) of participants, comprising 51.7%, 46.6% and 38.6% of those in the metformin alone, metformin plus lifestyle intervention and metformin plus rosiglitazone groups, respectively[101]. The finding that metformin monotherapy failed to achieve durable glycaemic control in half of the trial participants is consistent with the rapid β-cell dysfunction that is experienced by young people with T2DM (discussed further below).

In 2011, 572 (82%) of the TODAY trial participants were enrolled in an observational follow-up study, TODAY2, that was conducted in two phases to characterize the burden of vascular complications experienced by youths with T2DM as they transition to adulthood. Between 2011-2014, the participants received all diabetes care from the study and were treated with metformin with or without insulin to maintain glycaemic control. From 2014-2020, 518 participants transitioned to a fully observational study with annual study visits and medical management by their healthcare providers. The average follow-up of the combined studies was 10.2 years. The TODAY2 data demonstrate that diabetes-related complications develop early and accumulate rapidly during the course of youth-onset T2DM, with 15-year cumulative incidences of hypertension, DKD, dyslipidemia and neuropathy of 67.5%, 54.8%, 51.6% and 32.4%, respectively (FIG. 1)[20]. The 15-year cumulative incidence of any microvascular complication was 80.1% at a mean age of 26.4 years[20]. Serious cardiovascular events were uncommon (3.73 events per 1000 person-years) but occurred in 17 participants despite their young age. Collectively, these data demonstrate the serious health consequences of youth-onset T2DM as patients transition to young adulthood and the challenges of treating T2DM in this age group[20].

Complications and their risk factors

DKD is the most common and aggressive complication in youths with T2DM, but the incidence of other diabetes-related complications is also increased in these individuals, adversely affecting their health at an early age. In SEARCH, the prevalence of DKD, diabetic retinopathy, peripheral neuropathy, hypertension and arterial stiffness were all higher in young adults with T2DM than in those of similar age and diabetes duration with T1DM (FIG. 2), even after adjustment for sociodemographic factors[21]. At a mean age of 21 years, three quarters of participants with T2DM and one-third of those with T1DM had at least one microvascular complication or cardiovascular comorbidity[21]. The only complication that did not have a higher prevalence in patients with T2DM than in those with T1DM was cardiac autonomic neuropathy.

Diabetic kidney disease

Albuminuria is the earliest clinical marker of DKD and occurs very early in the disease course of youth-onset T2DM compared with youth-onset T1DM and adult T2DM[102,103]. In adults with T2DM, albuminuria typically develops after a minimum diabetes duration of 5 years; however, studies of youth-onset diabetes have reported albuminuria in some patients at the time of diagnosis[104]. In 2021, a systematic review reported that the prevalence of albuminuria among patients of all ethnicities with youth-onset T2DM was 22.2% (95% CI

17.3-27.4%)[105]. In a multi-ethnic cohort of US patients with diabetes who were diagnosed before the age of 20 years, the odds of elevated albuminuria after a mean diabetes duration of 7.9 years were 2.6-fold higher in those with T2DM than in those with T1DM[21,106]. The TODAY2 study, which also included a multi-ethnic cohort of participants, reported a 15-year cumulative incidence of albuminuria in patients with youth-onset T2DM of 54.8%[20]. Although nonalbuminuric DKD has been widely reported in T1DM and in adult T2DM, to our knowledge no data are available on nonalbuminuric DKD in patients with youth-onset T2DM.

Observational studies of Indigenous peoples in the US, Canada and Australia with T2DM and long-term follow-up data, have reported higher rates of progression of DKD to kidney failure among those who developed T2DM in youth compared with those who developed T2DM in adulthood[103,107,108]. In Canada, the incidence of kidney failure is 4-fold higher in youth with T2DM, most of whom are First Nations people, than in youth with T1DM[98]. Similarly, studies in Pima Indians from Arizona reported a 5-fold greater risk of kidney failure and a 2-fold greater risk of death between the ages of 25-54 years among those with youth-onset T2DM compared with those with older-onset T2DM[109, 110]. The aggressive nature of kidney complications in youth-onset T2DM was further confirmed by studies of kidney biopsy samples from Pima Indians with T2DM; those from patients with youth-onset diabetes had more severe structural lesions, including greater glomerular basement membrane width, higher mesangial fractional volume, lower glomerular surface density available for filtration, and lower podocyte density per glomerulus compared with those from patients with adult-onset T2DM irrespective of age at time of biopsy and diabetes duration[111]. DKD was the leading cause of death among Pima Indians with diabetes until the mid-1980s when it was superseded by cardiovascular disease largely as a result of improved availability of kidney replacement therapies in these communities[112]. Nevertheless, DKD remains the most prevalent end-stage complication of diabetes and contributes substantially to morbidity and mortality in this population[113].

The Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) collects data from all kidney replacement therapy units in Australia with opt-out consent, resulting in almost complete data. ANZDATA is linked to the Australian NDSS and the Australian National Death Index, providing a robust national database that enables characterization of youth-onset T2DM and risk of kidney failure[114]. A study that analysed linked data for 2,782 people with diabetes who were diagnosed between the ages of 15 and 35 years at a tertiary diabetes center in New South Wales, Australia, showed that the risk of kidney replacement therapy and kidney-related death was 2-fold higher in those with T2DM than in those with T1DM[115]. This difference remained significant after adjustment for sex, ethnicity, duration of diabetes and the ‘first available’ measurements of haemoglobin A1c (HbA1c), blood pressure and lipids, but was attenuated with the addition of BMI as a covariate, illustrating the important role of obesity in the development and progression of DKD in youth-onset T2DM.

Cardiovascular disease and mortality

Cardiovascular disease is the leading cause of death among adults with T2DM and its contribution to the morbidity and mortality that is associated with youth-onset T2DM is under intense scrutiny. An echocardiogram study that included 479 SEARCH participants with a median duration of diabetes of 11.6 years reported that those with T2DM had greater left ventricular (LV) mass and worse diastolic function, a precursor to heart failure, than those with T1DM[116]. This difference persisted after adjustment for differences in BMI, blood pressure, and HbA1c. Both patient groups showed abnormal diastolic function compared with healthy individuals, but the percentage of any dysfunction was greater among those with T2DM (58.1%) than among those with T1DM (47.5%).

In the SEARCH study, 133 of 14,721individuals with T1DM and 55 of 4,141 individuals with T2DM died during a median follow-up of 8.5 years[117]. Diabetes was the underlying cause of 42.1% of deaths among those with T1DM and 9.1% of deaths among those with T2DM. The standardized mortality ratio was greater for T2DM than for T1DM in this cohort[117]. Similarly, in a study of 24,415 individuals with diabetes who were recruited from a tertiary hospital-based clinic in New South Wales, Australia, 824 had youth-onset diabetes defined as diabetes diagnosed between 15 and 30 years of age: 354 had youth-onset T2DM and 470 had youth-onset T1DM. Those with youth-onset T2DM had 2-fold higher mortality than those with T1DM of similar age of onset and 50% of deaths among those with youth-onset T2DM and 30% of deaths among those with T1DM were due to cardiovascular disease[118].

The TODAY trial participants underwent echocardiography a median of 4.5 years after diagnosis of T2DM and at an average age of 18 years. In this cohort of adolescents with T2DM, mean LV mass, LV shortening fraction and left atrial internal dimension were in the high normal range and 16.2% of participants had adverse LV geometry[119]. Adverse measures of cardiac structure and function were associated with higher BMI and blood pressure and no effect of treatment group on cardiac target organ injury was observed, suggesting a need for more aggressive therapy. Repeat echocardiograms that were performed approximately 5 years after the initial echocardiograms at a mean participant age of 23 years and diabetes duration of approximately 9.5 years demonstrated substantial worsening of cardiac function from adolescence to early adulthood. Of particular concern, ejection fraction was <52% in 11.7% of male participants and diastolic function (E/Em) had declined since the initial echocardiograms were performed[120].

The TODAY2 long-term follow-up study of the TODAY cohort, reported an incidence of all adjudicated heart, vascular, and cerebrovascular events of 3.73 per 1,000 person-years during an average follow-up of 10.2 years[20]. These events comprised 17 serious cardiovascular events (4 myocardial infarctions, 6 congestive heart failure events, 3 coronary artery disease events, 4 stroke events) and one death owing to myocardial infarction. This high rate of cardiovascular disease occurred despite the young age of the participants (mean age at the end of the study period of 26.4±2.8 years and mean diabetes duration of 13.3±1.8 years). Together, the available data indicate that youth-onset T2DM is associated with an increased risk of cardiovascular disease and death in young adulthood.

Retinopathy

Diabetic retinopathy is a major cause of vision loss worldwide[121]. The prevalence and progression of diabetic retinopathy in youth with T1DM is well characterized and intensive glycaemic control has been shown to slow the progression of this complication[122]. However, the impact of diabetic retinopathy in youth-onset T2DM is less certain. Studies of retinopathy in youth-onset diabetes have reported a similar prevalence in T2DM and T1DM[123] and both a higher[124] and lower prevalence in T2DM than in T1DM[125]. SEARCH reported a higher prevalence of diabetic retinopathy in T2DM (42%) than in T1DM (17%) at similar diabetes duration (~7 years)[126]. The prevalence of retinopathy was lower in non-Hispanic white participants than in other racial and ethnic groups irrespective of diabetes type and this difference was not explained by glycemia, suggesting that socioeconomic factors and disparities related to race and ethnicity might have a role in this variability.

The impact of diabetic retinopathy in youth-onset and older-onset T2DM is also variable. In a study of 2,508 Pima Indians, those with youth-onset T2DM (age at onset <20 years) had less than half the risk of diabetic retinopathy identified by direct ophthalmoscopy than those with adult-onset T2DM (age at onset 20-59 years)[109]. On the other hand, a study that analysed clinical records from a diabetes centre in south India reported a higher prevalence of diabetic retinopathy in patients with youth-onset T2DM (age at onset <25 years) than in sex and diabetes duration-matched patients with older-onset T2DM (age at onset >50 years), with an odds ratio of 2.1 after adjustment for clinical covariates[127].

Estimates from clinical trials suggest that the risk of retinopathy in patients with youth-onset T2DM might be greater than published estimates of the risk in those with older-onset T2DM. The TODAY2 study reported a prevalence of diabetic retinopathy of 51% (identified by digital fundus photography of seven standard stereoscopic fields) at a mean diabetes duration of 12 years with 9% of retinopathy cases being moderate or severe[20]. By contrast, NHANES reported a prevalence of retinopathy of 28.5% among individuals with T1DM or T2DM aged ≥40 year with a mean diabetes duration of 15 years[128].

Neuropathy

Diabetic neuropathy is often subclinical or mild in youth with diabetes. However, early recognition of diabetic neuropathy is important for initiation of treatment to reduce the morbidity and mortality associated with this complication, which often appears in young adulthood among those who developed diabetes in youth[129]. In TODAY2, 32.4% of the 500 participants with youth-onset T2DM developed diabetic neuropathy (assessed by annual Michigan Neuropathy Screening Instrument [MNSI] and Semmes-Weinstein monofilament examinations) within a mean of 13.3 years following their diagnosis of diabetes[20].

The odds of diabetic neuropathy diagnosed using the MNSI was 2.52 times higher among participants in SEARCH with youth-onset T2DM than in those with youth-onset T1DM of similar diabetes duration after adjustment for established risk factors[21]. Similarly, individuals with T2DM developed neuropathy sooner than those with T1DM in a Canadian cohort identified using a large healthcare administrative database[130]. By contrast, although cardiovascular autonomic neuropathy was prevalent in youth-onset diabetes in SEARCH, no

statistically significant difference was observed between those with youth-onset T2DM (age-adjusted prevalence = 15.7%) and those with T1DM (age-adjusted prevalence = 14.4%)[131].

SEARCH was the first study to compare cognitive function in young adults with T1DM and T2DM[132]. Those with youth-onset T2DM had lower fluid cognitive scores (assessed using the NIH Toolbox Cognition Battery), reflecting reductions in executive function, than those with T1DM. This association was attenuated by adjustment for age, race, ethnicity, adiposity, parental education and depressive symptoms[132], suggesting that these differences are mediated by adiposity and mental health and might reflect the impact of social inequities that are associated with race and ethnicity.

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is very common in patients with youth-onset T2DM; one study found that 48% of tested individuals had elevated alanine aminotransferase (ALT), a surrogate for NAFLD, and a third had ALT values that were three times the upper limit of normal[133]. Another study found that 20% of African Americans, 71% of Hispanic and 88% of non-Hispanic White people with youth-onset T2DM had elevated ALT at diagnosis[134]. In the TODAY study, liver fat was not assessed, and exclusion criteria included aspartate aminotransaminase (AST) or ALT levels >2.5 times the upper limit of normal, preventing enrolment of patients with substantial NAFLD. Nevertheless, after a mean follow-up of 3.8 years, liver transaminase levels had increased to >2.5 times the upper limit of normal in 13% of the 699 study participants.

Data from the TODAY study suggested a lower prevalence of elevated liver transaminases in the metformin plus rosiglitazone group than in the metformin and lifestyle intervention and metformin only groups[101]. Despite reductions in liver transaminase levels suggesting improvement in NAFLD with rosiglitazone, increases in subcutaneous adipose tissue and abdominal visceral adipose tissue were greater in the metformin plus rosiglitazone group than in the other two groups[135]. This finding indicates that in contrast to its reported effects on body composition in adults[136–139], roglitazone treatment does not lead to fat redistribution from the viscera and liver to subcutaneous fat in youths.

Risk factors

In patients with youth-onset T2DM, hyperglycemia and hypertension are important risk factors for DKD[140–143], cardiovascular disease[20,120,144,145] and diabetic retinopathy[123,124,127,146]. Poor glycemic control is a well-established risk factor for diabetic neuropathy in T1DM but its role in T2DM is less clear. SEARCH demonstrated that diabetes duration was significantly associated with diabetic neuropathy in youth with T1DM and T2DM, but glycemic control over time was only associated with diabetic neuropathy in youth with T1DM[144]. The optimal targets for glycemic and blood pressure control in youth-onset T2DM have not been identified, but mean HbA1c values in youth with T2DM are often above current recommended adult targets due in part to the challenges of chronic disease management during adolescence[20,147].

The excess burden of diabetes-related complications in young adults with T2DM compared with those with T1DM might be related to a greater number and/or severity of vascular

risk factors early in T2DM. In the TODAY study, the 15-year cumulative incidence of dyslipidemia was 51.6%[20] and hypertension (defined as blood pressure ≥95th percentile for age, sex, and height or systolic blood pressure ≥130mmHg and/or diastolic blood pressure ≥80mmHg on three consecutive occasions or elevated blood pressure followed by initiation of anti-hypertensive therapy) was documented in 18.7% of participants at baseline with a 15-year cumulative incidence of 67.5%[20,145]. Adverse echocardiographic changes in TODAY were associated with hypertension, obesity, female sex, Hispanic ethnicity and non-Hispanic Black race, worse glycemic control, and elevated heart rate[120]. The SEARCH study reported a higher prevalence of poor glycemic control, adiposity, hypertension, and dysplipidemia in youth with T2DM compared to youth with T1DM of similar disease duration[148–151].

Dyslipidaemia is also associated with diabetic neuropathy in youth. SEARCH found that increased LDL-cholesterol was associated with diabetic neuropathy (defined by the MNSI) in youth with T1DM, whereas decreased LDL-cholesterol was associated with diabetic neuropathy in youth with T2DM[144]. The reasons for the differing association of LDL-cholesterol with diabetic neuropathy by type of diabetes are unknown. Elevated triglycerides were also associated with cardiovascular autonomic neuropathy in youth with T1DM and T2DM[152]. No ethnic differences in the prevalence of diabetic neuropathy diagnosed by the MNSI were observed in youth-onset T1DM or T2DM in SEARCH, but the prevalence of cardiovascular autonomic neuropathy in youth-onset T2DM was higher in Hispanic and non-Hispanic White people than in Asian and Pacific Islander, non-Hispanic Black people, and other racial and ethnic groups. In SEARCH, tobacco use was reported among youth with T1DM and T2DM[153] and was associated with diabetic neuropathy in both types of diabetes[144].

Metabolic syndrome is a risk factor for NAFLD. In the TODAY study, the baseline prevalence of metabolic syndrome (according to the NCEP ATP III definition) was 75.8% and this prevalence did not improve over time with diabetes treatment[135]. Elevated ALT as a surrogate for NAFLD was more frequent in those with metabolic syndrome, as was elevated C-reactive protein, IL-6, and PAI-1[135]. Thus, the metabolic syndrome and markers of NAFLD and inflammation were frequently abnormal in patients with youth-onset T2DM and did not respond to multiple diabetes treatments, suggesting a need for new therapies.

Mechanisms of the aggressive phenotype

Longer diabetes duration is associated with a greater burden of diabetes complications[154–158]. However, a more aggressive clinical course is observed in youth-onset than in adult onset T2DM even after controlling for duration of diabetes[127,159–163]. Several factors might contribute to this aggressive T2DM phenotype (FIG. 3).

β-cell function and insulin resistance

Inherently worse pancreatic β-cell function, leading to rapid β-cell failure, might be partly responsible for the severe glycemic phenotype in youth with T2DM[163–166]. This hypothesis is supported by the observation that poor β-cell function, and not insulin sensitivity, was a driving factor for loss of glycemic control in youth in the TODAY[167] and Restoring Insulin

Secretion (RISE) studies[168–170]. By contrast, lower insulin sensitivity was associated with loss of glycaemic control among adults in the RISE study (FIG. 4)[171].

Alternatively, a higher degree of obesity and insulin resistance might be required to develop T2DM at a young age compared to in adulthood when the pancreas might be less healthy. More severe insulin resistance might cause β-cells to secrete more insulin, driving earlier β-cell failure, and lowering insulin clearance. Data from RISE clearly show worse insulin resistance, a higher requirement for insulin secretion, and lower insulin clearance in youth-onset versus adult-onset T2DM[168,172–175]. As puberty is associated with a marked increase in insulin resistance, the demand on the pancreas might be greatest during adolescence.[168,172–175]

Genetic factors

The role of genetic factors in the aggressive phenotype of youth-onset T2DM must also be considered. The Progress in Diabetes Genetics in Youth (ProDiGY) study, which analysed data from a multi-ethnic cohort of participants in the TODAY, SEARCH and Type 2 Diabetes Genetics Exploration by Next-generation sequencing in multi-Ethnic Samples (T2DM-GENES) studies, identified seven genome-wide significant loci in or near *PHF2 TCF7L2, MC4R, CDC123, KCNQ1, IGF2BP2, and SLC16A11*, that were associated with this phenotype[176]. The variant in *PHF2* was novel, whereas the other variants have previously been associated with T2DM in adults. *MC4R* is a gene that strongly influences obesity. The effect size of the variant in *MC4R*, rs72982988, for T2DM in youth was greater than that reported in adults, suggesting that the role of obesity-related genes might differ between youth-onset and adult-onset T2DM. Notably, a unique polymorphism in the gene that encodes hepatocyte nuclear factor 1-alpha (*HNF-1α G319S*) that is found in many Canadian First Nations youth has been associated with a form of maturity-onset diabetes of the young that mimics T2DM[177].

Treatment intensity and adherence

Other factors that might contribute to the poor glycemic control and high rates of complications in youth-onset T2DM include lower adherence to medication, lifestyle interventions[178,179] and self-monitoring[168] compared with adult patients. A study in 212 young adults (mean age 26 years) with T2DM reported that 69.8% were low adherent to oral hypoglycaemia medications. In this study, low adherence was most common among women, non-Hispanic Black people and those who did not have healthcare coverage[180]. The factors that are associated with low adherence among patients with youth-onset T2DM are incompletely understood but likely include high rates of depression[181] and poverty[182]. In the TODAY cohort, 70% of youth with T2DM lived in single-parent households and 42% lived in households with an annual income of less than US$25,000[182].

Youth with T2DM might also receive less aggressive treatment than adults owing to a lack of regulatory approval of newer T2DM therapies for this population as well as a lack of provider comfort with prescribing traditionally adult medications for these patients[183–186]. A study that compared individuals with youth-onset versus adult-onset T2DM who were matched for sex and diabetes duration, reported that those with younger onset had

significantly higher HbA1c, cholesterol, triglycerides, and LDL cholesterol and lower HDL cholesterol[127] than those with older onset of T2DM.

Socioeconomic and environmental factors

Youth with T2DM are historically a more disadvantaged group than adults with T2DM[172], and therefore are likely to have less access to quality healthcare, healthy food choices[187] and physical activity as well as lower activity levels[188]. Studies published in the past 20 years report that US youth [189,190], particularly girls and African Americans[191,192], have very low levels of habitual physical activity.

Poor sleep has also been implicated in youth-onset T2DM owing to its association with insulin resistance. As adolescents currently obtain well below the recommended amount of sleep and have markedly shifted circadian rhythms, which are likely worsened by environmental exposures such as evening use of computers and phones, their circadian patterns are out of sync with typical school schedules[193–196]. Lower socioeconomic status is also associated with poor sleep quality in the general population[197]. However, further studies of sleep quality in patients with youth-onset T2DM are needed.

Exposure to other stressors that are more common in populations that are historically disadvantaged, medically underserved and at increased risk of youth-onset T2DM might also increase the aggressiveness of the disease. These stressors include depression, low birth weight and adverse childhood exposures, including systemic racism and environmental pollutants (for example, dichlorodiphenyl-dichloroethylene, polyfluroalkyl and perfluoroalkyl substances)[198–201].

In utero exposure to diabetes

Exposure to diabetes *in utero* is associated with higher BMI in children and accelerates progression to diabetes by various mechanisms, potentially including epigenetic modifications. This *in utero* exposure can therefore result in a vicious cycle of increasing T2DM prevalence in successive generations[202–211].

Exposure to diabetes *in utero* might preferentially harm poorly replicating, terminally differentiated cells such as those in the brain, pancreas, and nephron, leading to impaired development that can accelerate the appearance and severity of diabetes complications[212,213]. In the kidneys, impaired nephron development can lead to reduced nephron mass and/or functional capacity, thereby increasing the risk of DKD later in life[212,214,215]. *In utero* exposure to diabetes has been associated with elevated albuminuria in Pima Indians with T2DM[214] and with single-nephron hyperfiltration in the children of French women who had T1DM during pregnancy.

Management of youth-onset T2DM

Given the aggressive clinical course of youth-onset T2DM, the challenges associated with managing chronic disease in the young, and the frequent development of end-stage diabetes complications in mid-life in these patients, effective diabetes management strategies are

important. Current management strategies include lifestyle interventions, pharmacological therapies and metabolic bariatric surgery (MBS).

Lifestyle interventions

The ADA, International Society of Pediatric and Adolescent Diabetes (ISPAD), American Heart Association (AHA) and American Society of Nephrology (ASN) guidelines recommend a combination of lifestyle modifications and drug therapy in youth with T2DM[216–218]. Their guidelines emphasize the importance of regular moderate-intensity aerobic exercise as a first-line standard-of-care intervention for hypertension. This recommendation is supported by meta-analyses showing that aerobic exercise training in adults reduces casual systolic blood pressure by 2-8 mm Hg on average, with the largest systolic blood pressure-lowering effects observed in those with the highest baseline systolic blood pressure[219]. Regular aerobic exercise also improves vascular endothelial function in nondiabetic middle aged and older adults[220,221] and may mitigate risk of DKD in middle aged and older adults with T2DM[222], in large part by decreasing oxidative stress and increasing shear stress-mediated nitric oxide production[223,224]. Further studies are needed to evaluate the effects of aerobic exercise on vascular endothelial function and risk of DKD in youth with T2DM.

Despite the encouraging findings in adults, the TODAY trial showed that an aerobic exercise intervention did not attenuate hypertension or microvascular complications in youth with T2DM[20]. The physical activity target of the TODAY trial was 200 minutes per week of moderate to vigorous intensity exercise for most participants and up to 300 minutes per week for those who already engaged in regular, physical activity at the time of study enrollment[20,101]. Only 53.6% of participants in the TODAY trial met the physical activity target and this failure might be a major contributor to the suboptimal response in the metformin plus lifestyle intervention group in this trial[20,101]. Notably, youth-onset T2DM has a female predominance, but the lifestyle intervention in TODAY was significantly less effective and associated with worse adherence in girls than in boys[20,101]. An observational study in Canadian First Nations youth with T2DM identified improved glycemic control and blood pressure in those who engaged in vigorous-intensity physical activity[225].

The most commonly reported barrier to regular aerobic exercise is lack of time[226–231]. Other frequently cited barriers include logistical barriers such as lack of facility access (including as a result of lack of transportation, prohibitive cost, and schedule constraints) and mobility issues[228,232–234]. Psychological barriers are also common and include low motivation, depression, and poor exercise self-efficacy[181,235]. Poor physical function is an important contributor to failure to meet physical activity targets and is associated with comorbid conditions such as obesity, neuropathic pain, fatigue, and cardiovascular disease[236]. Lifestyle strategies to lower risk of microvascular and macrovascular complications in youth-onset T2DM should consider approaches to overcome these barriers to adherence.

Dietary modification targeting a daily caloric deficit and enhanced nutrient intake is an important part of the management of youth-onset T2DM[237]. Dietary interventions might be more effective in lowering BMI in these patients when coupled with increased physical activity[237]. Although diet and physical activity can lower BMI and mitigate risk of diabetes

complications, these lifestyle modifications are not recommended as monotherapy and should always be used in conjunction with pharmacotherapy for youth-onset T2DM owing to the aggressive nature of the disease.

Pharmacological management

As hyperglycemia is rarely sufficiently controlled by diet and exercise in youth-onset T2DM, pharmacological interventions are typically required. A major limitation, however, is the paucity of trial data regarding optimal pharmacological management of youth-onset T2DM. This limitation is unnecessarily perpetuated by the frequent exclusion of adolescents from clinical trials of T2DM medicines. Thus, many treatment recommendations for youth with T2DM are based on data extrapolated from trials conducted in adults rather than on evidence of efficacy in youths. In addition, several drugs that are available for adults with T2DM are not approved for the treatment of youths owing to limited efficacy and safety data in this population, reducing the options that are available to normalize glycemia in youth-onset T2DM.

Metformin.—The biguanide metformin is the first-choice agent to treat hyperglycemia in youth-onset T2DM[238]. Metformin activates adenosine monophosphate-activated protein kinase in insulin-sensitive tissues (predominantly liver and skeletal muscle) and therefore reduces hepatic glucose production and increases insulin-stimulated glucose-uptake in skeletal muscle[239].

Insulin.—Insulin is a safe and effective treatment to lower hyperglycemia in youth-onset T2DM and is the first choice of therapy when HbA1c is high at diagnosis (e.g. >8.5% or 69 mmol/mol) or if ketoacidosis is present[238]. Data from the TODAY study show that insulin therapy can be successfully stopped when glycemic targets are met in up to 90% of youth with T2DM[240]. The RISE study showed that 3 months of insulin glargine treatment followed by 9 months of metformin compared with 12 months of metformin treatment alone did not prevent deterioration of β-cell function during treatment or following treatment cessation. This finding suggests that alternate approaches are necessary to halt the progressive disease course seen in youth with T2DM[241].

GLP-1 receptor agonists.—Injectable glucagon-like peptide-1 (GLP-1) receptor agonists harness the beneficial metabolic effects of the gut hormone GLP-1. In the Evaluation of Liraglutide in Pediatric with Diabetes (Ellipse) trial[61], liraglutide (1.8 mg daily) plus metformin with or without concomitant insulin treatment, reduced HbA1c levels by 1% at week 26 and induced small reductions in weight in adolescents (aged 10-17 years) with T2DM[242]. Likewise, in the Assessment of Weekly Administration of LY2189265 in Diabetes – Pediatric Study (AWARDS-PEDS) in youth (aged 10-18 years) with T2DM who were being treated with lifestyle modifications with or without metformin or insulin therapy, weekly administration of dulaglutide 0.75 mg or 1.5 mg reduced HbA1c at 26 weeks by 0.6% or 0.9%, respectively, without an effect on BMI[243]. Another trial in youth (aged 10-17 years) with T2DM who received a stable dose of oral therapy (metformin and/or sulfonylurea) and/or insulin for at least two months prior to enrollment, reported that exenatide long-acting release (LAR) 2 mg weekly induced a 0.7% reduction in HbA1c levels

compared with placebo[244]. The adverse effects observed in these studies were similar to those observed in adults and included gastrointestinal effects such as nausea and diarrhea[245]. The long-term safety and cardiovascular and kidney effects of GLP-1 receptor agonists have not been studied in youth with T2DM.

Liraglutide and exenatide LAR have both been approved for the treatment of youth-onset T2DM in the US. Off-label use of GLP-1 receptor agonists is required for patients aged <18 years in many countries.

Thiazolidinediones.—Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor (PPAR)-gamma receptor activators that increase peripheral insulin sensitivity and improve β-cell function, resulting in durable glycemic control in adults[246,247]. In youth with T2DM in the TODAY study, glycemic failure rates decreased by 13% when rosiglitazone added to metformin was compared to metformin alone[101]. However, TZD therapy is associated with increased risk of fractures, fluid retention and heart failure in adults[248]. Although these adverse effects were not observed in the TODAY study, TZDs have not been approved for youth-onset T2DM despite their beneficial effects on insulin sensitivity that could benefit insulin-resistant adolescents.

Sulfonylureas.—Binding of sulfonylureas to ATP-dependent K^+ channels on the cell membrane of pancreatic β-cells causes them to close, inducing insulin secretion. A study in patients with youth-onset T2DM reported similar reductions in Hba1c levels with the sulfonyluera glimepiride compared to metformin; however, patients in the glimepiride group experienced greater weight gain and more episodes of hypoglycemia[249]. Sulfonylureas are currently not recommended for treatment of hyperglycemia in adolescents in many countries due to limited safety data.

SGLT2 inhibitors.—Oral sodium-glucose cotransporter 2 (SGLT2) inhibitors block glucose uptake in the proximal tubule of the kidneys, thereby inducing glycosuria and lowering plasma glucose concentration. Several studies have evaluated the glucose-lowering effects of these agents in youth with T2DM; however, the results of some of these studies are not yet available. A clinical trial that enrolled participants aged 10-24 years with T2DM, reported that 10 mg of dapagliflozin in addition to standard care had no effect on HbA1c levels compared with placebo in the intention-to-treat analysis, but reduced HbA1c by 1.13% relative to placebo among protocol-compliant participants after 24 weeks[250]. Another study in 27 youth with T2DM reported that empagliflozin acutely lowered estimated glomerular filtration rate (eGFR) and increased fractional sodium excretion[251]. This finding is of interest because natriuresis is thought to contribute to the beneficial cardiovascular effects of SGLT2 inhibition and an acute reduction in eGFR is thought to reflect a reduction of intraglomerular pressure that likely underlies the kidney protective effects of SGLT2 inhibitors reported in adults. Given the paucity of published data, SGLT2 inhibitors are not yet approved for treatment of youth onset-T2DM.

Metabolic bariatric surgery

MBS (sometimes called bariatric surgery) can promote weight loss and improve metabolic health. This intervention seems to be the most effective treatment for T2DM in adults[252]. Over 25 years of data from the Swedish Obese Subjects (SOS) study have shown that in adults with obesity (7.4% of whom had T2DM), MBS, irrespective of operation type, induces durable reductions of 25% in body weight, 30% in mortality, and 50% in microvascular complications compared with usual obesity care[253]. Furthermore, this study reported T2DM remission at 15 years of follow-up in 30% of patients in the MBS group compared with 6.5% of those in the nonsurgical treatment group[254]. The Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study reported T2DM remission in 23% of adults 5 years after vertical sleeve gastrectomy compared to 5% of adults following intensive medical treatment[255,256]. Extrapolating these data to youth is challenging given the numerous differences between youth-onset and adult-onset T2DM.

Teen-LABS, a prospective, observational cohort study of youth with obesity undergoing MBS, reported a T2DM remission rate of 94% at 3 years following Roux-en-Y gastric bypass (RYGB) in 29 youth with T2DM and no cases of incident T2DM among 153 youth without T2DM at enrollment[257]. A retrospective comparison of data from Teen-LABS participants with T2DM (n=30) and a matched subset of participants from the TODAY study (n=63), suggested that youth with T2DM who undergo RYGB surgery have better outcomes, including reductions in hypertension, dyslipidemia and risk of DKD and cardiovascular disease[258–260]. The Teen-LABS and TODAY studies were not designed to be directly compared and have important differences in study design, outcomes collected, and cohort characteristics. Nonetheless, they offer a first suggestion of a management strategy that might provide an efficacious treatment in this challenging high-risk patient population.

The Surgical or Medical Treatment for Pediatric Type 2 Diabetes (ST_2OMP) study is intended to address the limitations of the Teen-LABS and TODAY comparison and fill gaps in our understanding of MBS in youth[261,262]. ST_2OMP is prospectively comparing teenagers choosing medical therapy to those choosing vertical sleeve gastrectomy. The medical therapy incorporates an aggressive multi-drug, treat-to-target intervention with the goal of achieving an HbA1c <6.5% and includes off-label use of SGLT-2 inhibitors and on-label use of GLP-1 agonists. The primary outcome of the study is glycemic control at 1 year and the secondary outcomes will compare diabetes related comorbidities. Outcome data from ST_2OMP are expected in 2024-2025.

Conclusions

The incidence and prevalence of youth-onset T2DM is increasing worldwide. Children and adolescents who are overweight or obese, the majority of whom live in developing countries, are at increased risk of this disease[19,159,263]. The prevalence of overweight or obesity among children and adolescents aged 5-19 years increased more than four-fold between 1975 and 2016, reaching 18% globally[264]. In the US, where nearly 14 million youth are obese, the rising prevalence and severity of obesity and other metabolic conditions are projected to increase the incidence of youth-onset T2DM by 600% between 2017 and 2060[18,265]. The

Assessing the Burden of Diabetes by Type in Children, Adolescents, and Young Adults (DiCAYA) Network is monitoring this expected increase[266].

Youth-onset T2DM has a more adverse clinical course than youth-onset T1DM and a more extreme metabolic phenotype than adult-onset T2DM, including greater insulin resistance and more rapid deterioration of β-cell function[241,267]. These factors increase the risk of vascular complications among patients who develop youth-onset T2DM[20,21,159,241,268,269]. However, the available therapeutic options to manage T2DM in youth and prevent the development of these complications are limited. The current mainstays of therapy to mitigate risk of DKD in patients with T2DM include renin-angiotensin-aldosterone system blockade, SGLT2 inhibitors and GLP1 receptor agonists[270–273]. However, the only medications that are approved by the US FDA, European Medicines Agency and Health Canada for the treatment of youth with T2DM are metformin, insulin and GLP-1 receptor agonists.

Data from the TODAY and RISE studies show that the physiology underlying the development of T2DM in youth differs from that of adult-onset T2DM, suggesting that different treatments might be needed. Establishing a fuller understanding of the unique pathophysiology of youth-onset T2DM is a necessary first step to enable the design of clinical trials to identify efficacious management strategies for patients[241,267,274]. Prevention of T2DM in youth is also a top priority. The identification of children and adolescents who are at greatest risk of developing youth-onset T2DM will facilitate the development of more effective interventions to prevent or delay the onset of the disease and to decrease the risk of complications in those who do develop T2DM in youth. The development of effective strategies to overcome barriers to adherence will also be an essential component of these efforts.

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Competing interests

P.B. has acted as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli-Lilly, LG Chem, Sanofi, Novo Nordisk, Horizon Pharma, XORTX. P.B. serves on the advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk and XORTX. D.H.v.R. has acted as a consultant and received honoraria from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck and Sanofi, and received research operating funding from AstraZeneca, Boehringer Ingelheim, Eli Lilly Diabetes Alliance and Merck. The other authors declare no competing interests.

Glossary

Standardized mortality ratio

The ratio of the number of deaths observed in a population over a given period to the number that would be expected over the same period in the general population.

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Key points

- The incidence and prevalence of youth-onset type 2 diabetes mellitus (T2DM) is increasing worldwide; the disease has been reported in all racial and ethnic groups but Indigenous peoples and people of colour are disproportionately affected.
- Important drivers of the epidemic of youth-onset T2DM epidemic include the increasing frequency, severity and earlier onset of childhood obesity, the increasing frequency of intrauterine exposure to diabetes, sedentary lifestyles, structural racism and other psychosocial factors
- Individuals who develop T2DM during childhood or adolescence often have a more aggressive clinical course than those with type 1 diabetes mellitus or those who develop T2DM in adulthood.
- Youth-onset T2DM has a more extreme metabolic phenotype than adult-onset T2DM with greater insulin resistance and more rapid deterioration of β-cell function; intermediate complications often develop in late childhood or early adulthood, and end-stage complications, including kidney failure, develop in mid-life.
- Due to limited efficacy and safety data, several drugs that are available for the treatment of adults with T2DM have not been approved for the treatment of youth, reducing the options that are available to normalize glycemia in these patients.
- Managing youth-onset T2DM and mitigating the risk of microvascular and macrovascular complications requires the development of more effective interventions as well as strategies to overcome barriers to adherence that are not typically encountered in adult patients.

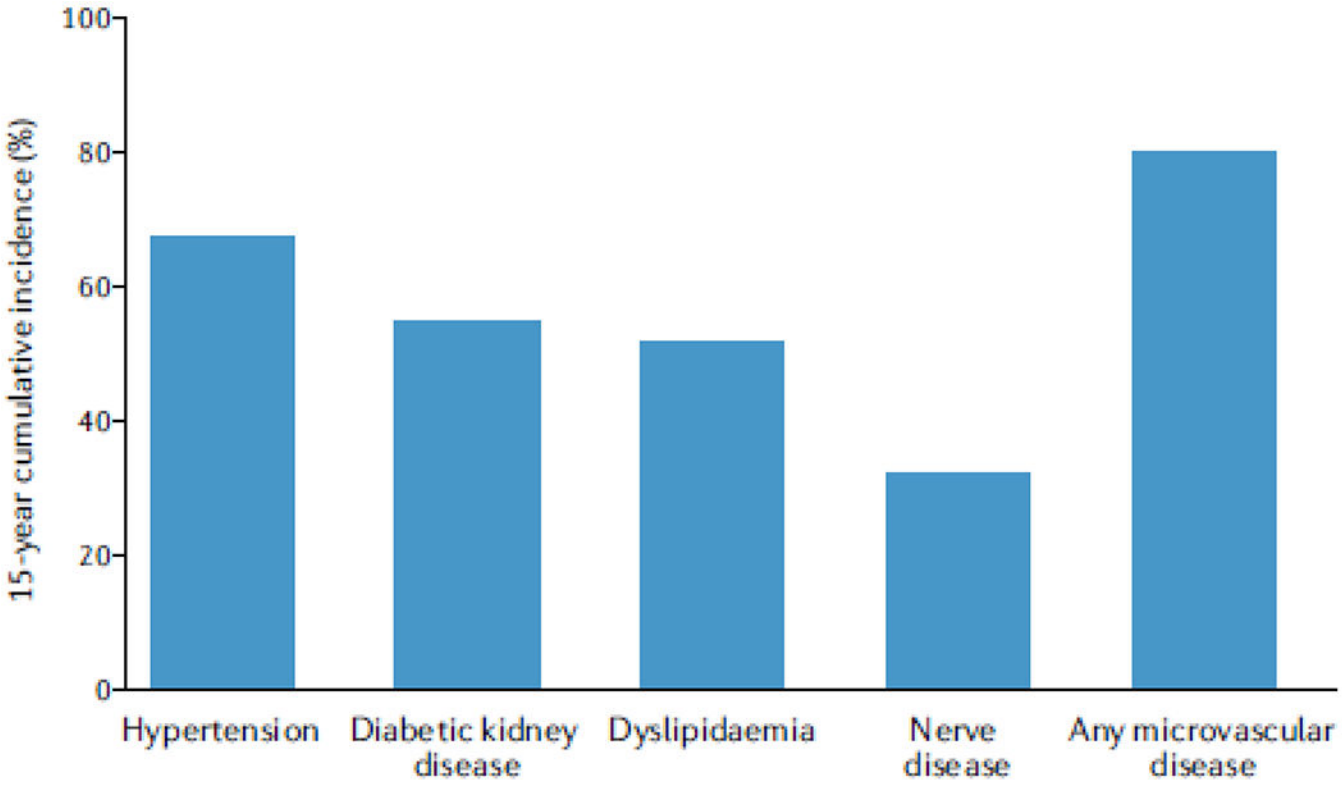

Figure 1 |. Long-term complications of youth-onset T2DM.

The 15-year cumulative incidences of hypertension, diabetic kidney disease, dyslipidemia (that is, low-density-lipoprotein or triglyceride dyslipidemia), neuropathy and any microvascular disease in participants with youth-onset type 2 diabetes mellitus (T2DM) in the TODAY trial[20].

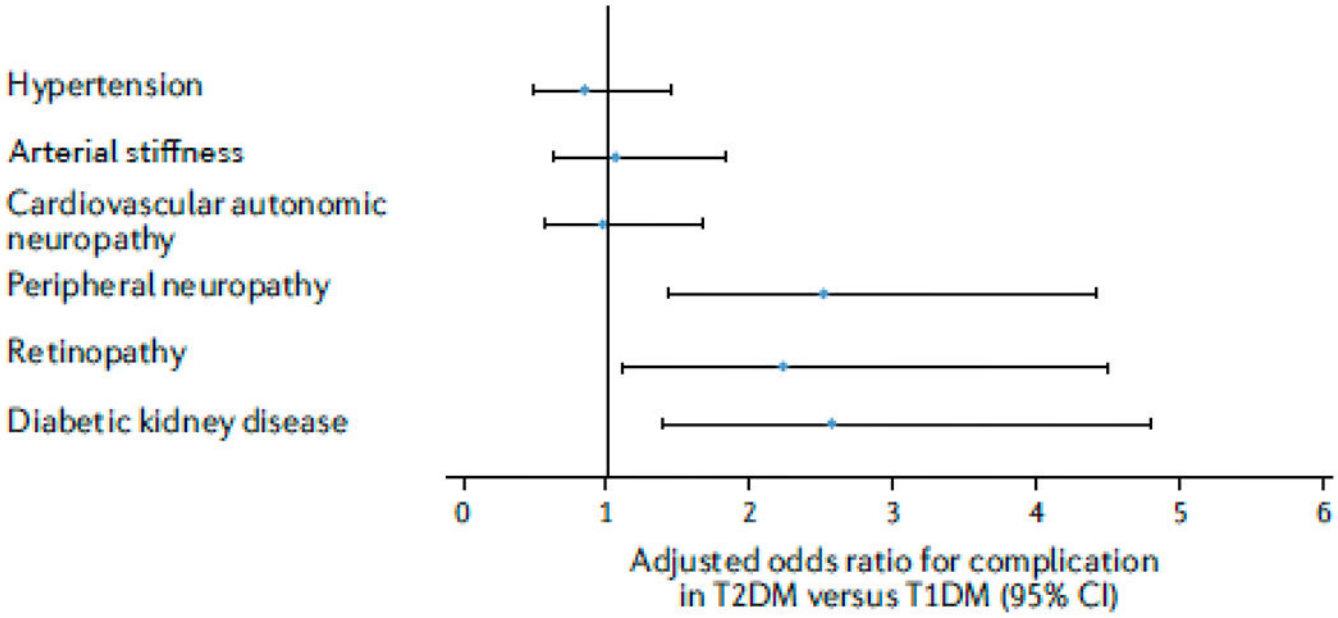

Figure 2 |. Odds of long-term complications in children and adolescents with T2DM versus those with T1DM.

Forest plot showing odds ratios and 95% confidence intervals of diabetes complications in adolescents and young adults with type 2 diabetes mellitus (T2DM) versus those with T1DM in the SEARCH study[21,106]. After adjustment for established risk factors measured over time, participants with T2DM had significantly higher odds of diabetic kidney disease (DKD; defined as the presence of albuminuria (≥30 μg/mg of creatinine) or reduced kidney function (estimated glomerular filtration rate ≤60 ml/min/1.73m^2)), retinopathy (determined using graded digital fundus images), and peripheral neuropathy (defined using the Michigan Neuropathy Screening Instrument) than those with T1DM. The odds of cardiovascular autonomic neuropathy (heart rate variability abnormalities), arterial stiffness (pulse wave velocity ≥90th centile of controls) and hypertension (blood pressure levels ≥95th centile for age) did not differ significantly between the two groups.

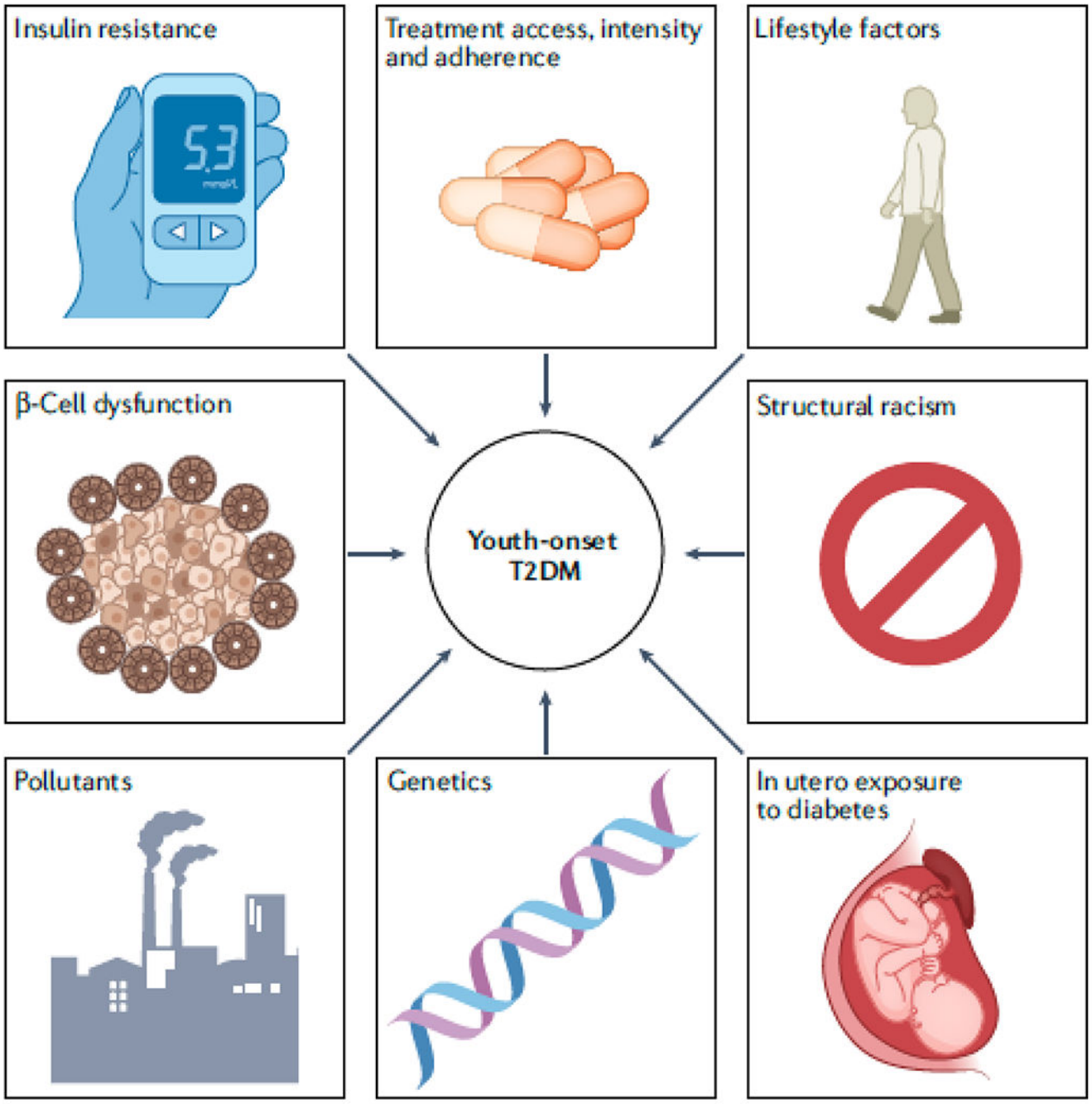

Figure 3 |. Potential mechanisms responsible for the aggressive clinical phenotype in youth-onset T2DM.

Several factors might contribute to the more aggressive phenotype in youth onset versus adult-onset type 2 diabetes mellitus (T2DM). The more severe glycaemic phenotype in youth-onset than in adult-onset T2DM might be partly explained by worse pancreatic β-cell function, leading to more rapid β-cell failure[163–166]. Early development of insulin resistance might lead to increased insulin secretion, driving β-cell failure and thereby lowering insulin clearance. Demand on the pancreas might be highest during adolescence owing to the marked insulin resistance of puberty[168,172–175]. Lower adherence to medical therapy,

lifestyle modifications[178,179] and self-monitoring[168] as well as less aggressive medical treatment and fewer treatment options[183–186] might also contribute to poorer glycaemic control and higher rates of complications in youth compared with adults with T2DM. Youth with T2DM are generally a more disadvantaged group than adults with T2DM[172] so might have less access to quality healthcare, healthy food choices[187] and opportunities for physical activity[188]. Other factors that are associated with historical disadvantage, including depression, poorer sleep quality[197], low birth weight, and childhood exposure to stressors, including systemic racism, and environmental pollutants[198–201], might also increase the risk of youth-onset T2DM and the aggressiveness of the disease. Exposure to diabetes *in utero* is associated with higher BMI in childhood and increased risk of insulin resistance and T2DM in youth[202–207]. In utero exposure to diabetes might also result in impaired nephron development, which increases the risk of DKD in later life[212,214,215,275], as well as other developmental disruptions that could accelerate the appearance and severity of diabetes complications[212]. Genetic factors might contribute to the more aggressive clinical phenotype that is associated with youth-onset compared with adult-onset T2DM[176].

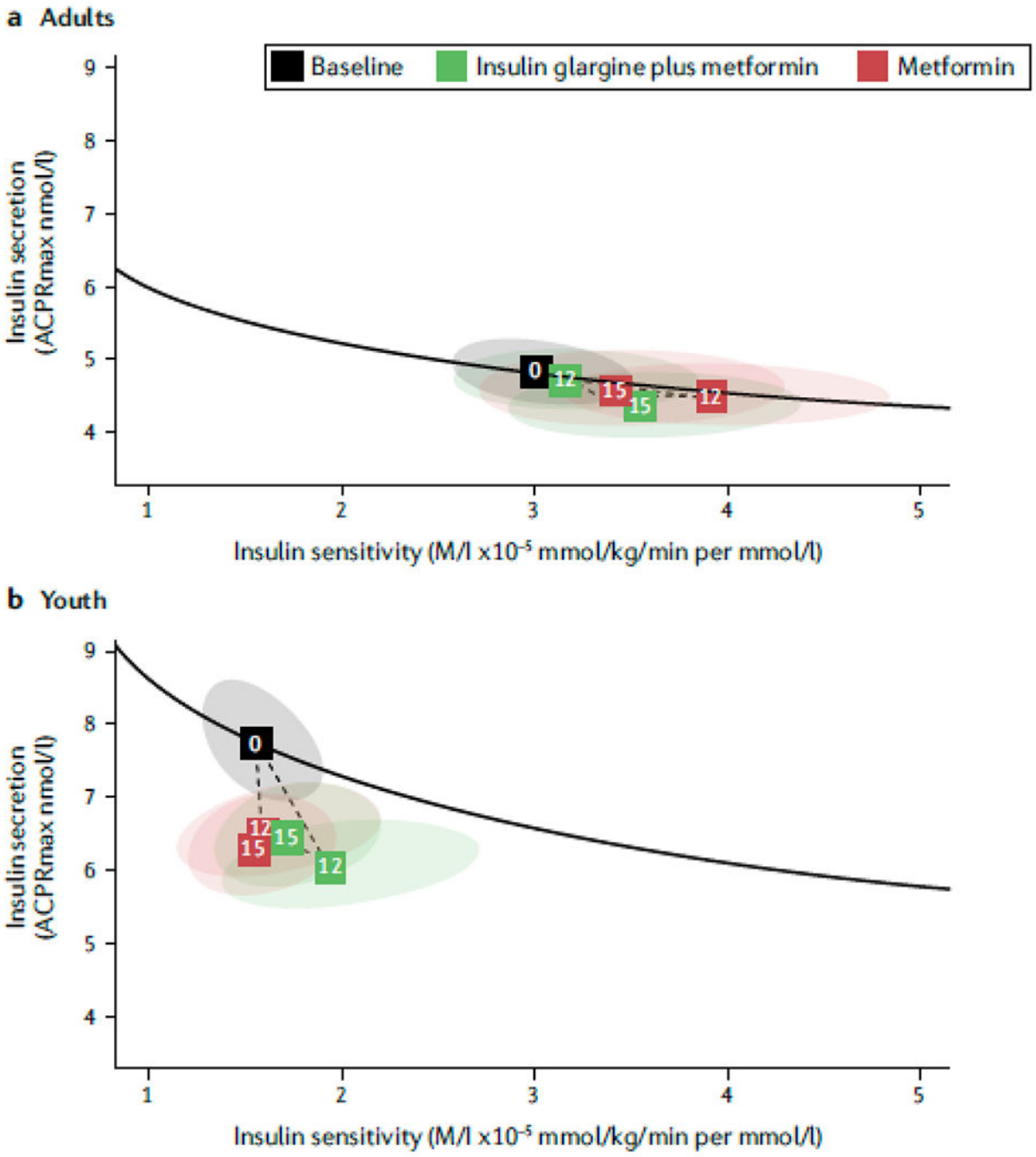

Figure 4 |. Greater loss of β-cell function in youth-onset versus adult-onset T2DM.

The Restoring Insulin Secretion (RISE) Study used hyperglycemic clamps to examine insulin sensitivity and β-cell function in **a** | adults and **b** | youth with impaired glucose tolerance or recently diagnosed T2DM at baseline, after 12 months of treatment for hyperglycemia with either insulin glargine and metformin or metformin alone, and at 15 months of follow-up (3 months after discontinuation of treatment)[175]. Insulin secretion determined using an arginine stimulation test (acute c-peptide response to arginine at maximal glycemic potentiation [ACPRmax]) is shown on the y axes and insulin sensitivity

(glucose infusion rate by steady state insulin concentrations [M/I]) is shown on the x-axes. The solid black lines in the vector plots illustrate the relationship between insulin secretion (that is, β-cell response) and insulin sensitivity at baseline. The numbered boxes represent the mean values for each cohort at baseline (0), 12 months (12) and 15 months (15) and the ellipses around the boxes represent the 95% confidence intervals. The dotted lines show the trajectory of mean values from baseline to 12 months of intervention and to 15 months of follow-up. Values above the solid black line represent improved β-cell function and those below this line represent worse β-cell function compared to baseline. At baseline, youth were markedly more insulin resistant and had much higher insulin secretion than adults despite similar levels of glycemia. After 12 months of treatment, β-cell function had deteriorated in youth but not in adults. The two interventions did not differ substantially in their effects on β-cell function in either age group. The difference in β-cell function outcomes in response to treatment in youths and adults supports a more adverse trajectory of β-cell deterioration in youth. Reprinted with permission from ref [175], American Diabetes Association.