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REVIEW

The changing face of paediatric diabetes

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Abstract

The purpose of this review is to provide an update on the changing face of paediatric type 1 diabetes and type 2 diabetes. Paediatric diabetes is on the rise, with extensive research dedicated to understanding its pathophysiology, comorbidities and complications. As obesity continues to increase among all youth, differentiating between type 1 diabetes and type 2 diabetes has become increasingly difficult but remains important for optimising treatment, anticipating complications and predicting disease risk. Novel treatments are emerging, with the ultimate goal being to achieve glycaemic control, limit weight gain, improve quality of life and reduce comorbidities. In this review, we focus on updates regarding the epidemiology, clinical presentation, comorbidities and complications of paediatric type 1 diabetes and type 2 diabetes and conclude with current and emerging treatments.

Keywords Complications · Diabetes · Insulin · Metformin · Paediatrics · Review · Type 1 diabetes · Type 2 diabetes

Abbreviations

DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
GLP-1	Glucagon-like peptide-1
MBS	Metabolic bariatric surgery
MDI	Multiple daily injections
RISE	Restoring Insulin Secretion
RYGB	Roux-en Y gastric bypass
SGLT2	Sodium–glucose cotransporter 2
Teen-LABS	Teen-Longitudinal Assessment of Bariatric Surgery
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
TZD	Thiazolidinedione

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This review provides an update on paediatric type 1 and type 2 diabetes. Type 1 diabetes is typically characterised by insulin deficiency and is thought to result when an environmental trigger initiates an autoimmune response to the pancreatic beta cells in a genetically susceptible individual [1]. On the other hand, youth onset type 2 diabetes is typically characterised by insulin resistance followed by varying degrees of beta cell failure [2]. While 10–20% of individuals with type 1 diabetes have a family member with type 1 diabetes, more than 90% of youth with type 2 diabetes have a relative with type 2 diabetes [3]. Both genetics and the environment are thought to contribute to the risk of type 1 and type 2 diabetes, though a recent study found that heritability did not contribute to the variance of type 2 diabetes among twins diagnosed before 45 years of age [4]. Viral infections, diet, exposure to maternal diabetes in utero, endocrine disruptors and obesity have each been linked to diabetes, the latter most strongly linked to type 2 diabetes [5].

Epidemiology

The incidence of type 1 diabetes in youth varies according to geography, age, sex and ethnicity and continues to increase worldwide at a rate of 1–3% per year [6]. The highest incidences

of type 1 diabetes occur in Sweden and Finland (37–65 per 100,000 children) with a slight male predominance (3:2 male to female ratio in incidence at age ≥13 years) [7, 8]. Venezuela and parts of China have the lowest incidence (<2 per 100,000 children) [9]. In the USA, the incidence of type 1 diabetes among non-Hispanic white children and adolescents was 27 per 100,000 per year in 2012 [10]. The incidence in African-American and Hispanic children was 50–70% of that of non-Hispanic white children (~19 and 15 per 100,000 per year, respectively) and lowest in Native American and Asian/Pacific Islander youth (6.5 per 100,000 per year) [10], with largely no overall differences by sex [10]. Parts of Canada, such as Newfoundland, have a higher incidence of type 1 diabetes (36 per 100,000 per year) than the USA [11].

The annual increase of youth-onset type 2 diabetes in the USA is currently 4.8% [10]. The rise in type 2 diabetes largely parallels the rise in childhood obesity and in 2012 the estimated incidence in the USA was 12.5 per 100,000 children. The largest increases have been observed in non-Hispanic black, Native American and Asian/Pacific Islander youth, followed by Hispanic youth, with a low and stable incidence in non-Hispanic white youth from 2002 to 2012 [10]. In the USA, youth-onset type 2 diabetes is twice as common in females as in males [10]. Youth-onset type 2 diabetes is seen across the world in both developed and under developed nations [12]. In India and Japan nearly 50% of youth-onset diabetes (<25 years old) is attributed to type 2 diabetes, with type 2 diabetes diagnosed twice as often as type 1 diabetes among adolescents [13, 14].

Clinical presentation

Establishing the type of diabetes is important for choosing the best treatment, anticipating complications and predicting disease risk in relatives. Typical characteristics of youth with type 1 diabetes, type 2 diabetes and MODY are shown in Table 1 [15].

Youth with type 1 diabetes are more likely to be white and to present with polyuria, polydipsia, polyphagia and weight loss [16]. Features of the metabolic syndrome are rare unless significant obesity is also present. Diabetic ketoacidosis (DKA) is seen in up to 50% of youth at presentation [17, 18]. Forty-five per cent of children present with type 1 diabetes before 10 years of age [19] but there are two peaks in the age of presentation, the first at 4–6 years and the second at 10–14 years.

Type 2 diabetes should be considered in pubertal youth with obesity, a family history of type 2 diabetes, features of the metabolic syndrome, and absent pancreatic autoantibodies. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, of the 699 youth with type 2 diabetes enrolled, 97% of youth were overweight/obese, 90% had a family history of type 2 diabetes and only 20% were non-Hispanic white [3]. At enrolment, a third of youth with type 2 diabetes had an elevated blood pressure or hypertension (BP >90th percentile for age, sex and height), 80% had low HDL-cholesterol (<1.03 mmol/l), and 21% had elevated triacylglycerol levels (>1.69 mmol/l) [3].

Polydipsia and polyuria are seen in about 67% of youth with type 2 diabetes at presentation, while a third are diagnosed through routine screening of asymptomatic youth with obesity [18]. DKA and hyperglycaemic hyperosmolar state are present at diagnosis in 6–11% and 2% of youth with type 2 diabetes, respectively [17, 18]. Median age of type 2 diabetes presentation is 13.5 years, coinciding with the peak of puberty and physiological insulin resistance, with an earlier presentation in girls vs boys due to sex differences in the age of pubertal onset [3, 18, 20]. Pre-pubertal children rarely have type 2 diabetes, even if obese [3, 18, 20].

In overweight youth, the clinical presentations of type 1 and type 2 diabetes may overlap [21]. Currently 36% of youth with type 1 diabetes in the USA are overweight or obese (22.9% overweight, 13.1% obese), and the frequency is higher among female youth (40.8% overweight or obese), based on data from 5529 adolescents in the Type 1 Diabetes Exchange, a large US-based clinical registry [21]. Youth with type 1 diabetes in Germany, Austria and Canada also show high BMI z scores compared with youth without diabetes [22]. Insulin resistance, while usually present in type 2 diabetes, is also seen in many youth and adults with type 1 diabetes [23–25].

C-peptide level can be helpful in differentiating between diabetes types but may be low at diagnosis of type 2 diabetes and normal during the honeymoon phase of type 1 diabetes. However, 2 years following a diagnosis of diabetes, the C-peptide level is generally still modestly elevated in people with type 2 diabetes, while in type 1 diabetes individuals it is usually low.

Screening for diabetes autoantibodies is recommended in all individuals with clinically suspected type 2 diabetes to help to differentiate it from type 1 diabetes [26, 27]. Of the 1206 youth with a clinical diagnosis of type 2 diabetes screened in the TODAY study, 118 (~10%) had GAD65, insulin and/or insulinoma-associated antigen 2 (IA-2) autoantibodies [28]. The presence of antibodies suggests autoimmune type 1 diabetes and predicts a more rapid decline in beta cell function and higher risk for development of other autoimmune disorders [29]. Ninety per cent of youth who develop type 1 diabetes before puberty have islet antibodies detectable before age 5 years [30], with a peak onset of antibody emergence at age 2 years. Progression to type 1 diabetes at 10 year follow-up after islet autoantibody seroconversion in 585 children with multiple islet autoantibodies was 69.7% (95% CI 65.1%, 74.3%), and in 474 children with a single islet autoantibody was 14.5% (95% CI 10.3%, 18.7%) [31]. Risk scores to predict the diagnosis of type 1 diabetes based on type and concentration of antibody are available [32].

The US SEARCH for Diabetes in Youth study developed an aetiological approach to classifying diabetes types in youth

Table 1 Classical presentation of diabetes types in children and adolescents

	Classical type 1 diabetes	Classical type 2 diabetes	Monogenic diabetes
Age at presentation	Two peaks: age 4–6 years and 10–14 years	Onset after puberty, rare before age 10 years	Onset before age 25 years
Weight	Usually normal weight, can be overweight or obese	>90% are overweight or obese	Usually normal weight, can be overweight or obese
Autoantibodies	Present	Absent	Absent
Insulin resistance	Less common	Present	Absent
Risk of DKA	High	Low	Low
C-peptide after diagnosis	Low	Detectable	Detectable
Family history of diabetes	Infrequent (10–15%)	Frequent (90%)	Frequent, usually in multiple generations

based on the presence of autoimmunity and insulin resistance (estimated by waist circumference, serum triacylglycerol and HbA_{1c}) [15]. Using this method, 70% of youth aligned with traditional descriptions of type 1 diabetes (autoimmune positive, 'insulin sensitive') or type 2 diabetes (non-autoimmune, 'insulin resistant'). However, 20% of their cohort had autoimmune positivity with 'insulin resistance', likely representing youth with type 1 diabetes plus obesity and/or family history of type 2 diabetes, and 10% of youth were non-autoimmune and 'insulin sensitive', a group requiring further testing for other types of diabetes such as MODY.

Youth-onset vs adult-onset type 2 diabetes

Compared with adults, youth with type 2 diabetes appear to have a more severe phenotype with greater reductions in insulin sensitivity and insulin clearance, higher insulin secretion, a more rapid decline in beta cell function overtime (measured by hyperglycaemic clamp), and overall poorer responses to medical treatments [33–39]. In the TODAY study where treatment with metformin alone, metformin plus lifestyle intervention, or metformin plus rosiglitazone was compared, treatment failure (defined as an HbA_{1c} of >64 mmol/mol [>8%] or metabolic decompensation requiring insulin therapy) [40] occurred in 52%, 39% and 47% of youth, respectively. Treatment failure for all three arms occurred within 11 months on average [41], with an estimated annual rate of beta cell function decline of ≈20–35% [42]. This is in stark contrast to adults with type 2 diabetes in A Diabetes Outcome Progression Trial (ADOPT), where metformin treatment failure rates were 21%, less than half of the 52% reported in TODAY [43] and where the rate of decline in beta cell function was only 7–11% per year.

The Restoring Insulin Secretion (RISE) study included both adults and youth, allowing for direct comparisons of beta cell function using oral glucose tolerance tests and hyperglycaemic clamps in people with impaired glucose tolerance (prediabetes) or recently diagnosed type 2 diabetes. At baseline, despite similar BMI and dysglycaemia, youth in the RISE study demonstrated 50% lower insulin sensitivity than adults as well as augmented beta cell responses even after accounting for insulin sensitivity, suggesting greater demand on beta cells compared with adults [34, 35]. Furthermore, when youth were evaluated on or after 12 months of treatment with metformin alone or insulin glargine followed by metformin, youth experienced a deterioration of beta cell function that continued after treatment withdrawal. In contrast, beta cell function in the adults improved during treatment, although it was not sustained after treatment withdrawal [33, 36]. These studies highlight differences in beta cell function outcomes and responses to medications by age group and point to a more adverse trajectory of beta cell deterioration in youth.

Comorbidities and complications

Data from the SEARCH study consistently show a higher prevalence of comorbidities in young adults with type 2 diabetes vs type 1 diabetes, even after adjusting for established cardiovascular risk [44, 45]. At age 21 years, those with type 2 diabetes vs type 1 diabetes showed higher rates of diabetic kidney disease (DKD), retinopathy, peripheral neuropathy, arterial stiffness and hypertension [46, 47] (Fig. 1). There is clear evidence of elevated left ventricular mass, abnormal cardiac geometry and impaired diastolic function, reduced cardiopulmonary fitness, abnormal limb blood flow, arterial stiffness and higher blood pressure, as well as renal hyperfiltration, in both diabetes types compared with peers without diabetes with a similar BMI [24, 48–59]. However, some comorbidities including low HDL-cholesterol and elevated triacylglycerol, hepatic fat [54] and liver transaminases [60], and non-alcoholic steatohepatitis (NASH) [61] are not typically present in youth with type 1 diabetes, especially in those with a normal BMI. Moreover, blindness and amputation have only been reported by early adulthood in youth-onset type 2 diabetes [44, 62], and rates of DKD, neuropathy, retinopathy and cardiovascular death are all currently higher in young adults with type 2 diabetes vs type 1 diabetes. Life expectancy and quality of

life may be reduced in adults with type 1 and type 2 diabetes [63–65], but each is highly dependent on age, glycaemic control and the presence of additional complications (e.g. concomitant renal disease).

Treatment

The treatment of both type 1 and type 2 diabetes in childhood includes optimising glycaemic control and BMI through physical activity and a healthy diet [26, 27]. However, studies demonstrating the effectiveness of lifestyle modification in youth are lacking and most youth with diabetes are not meeting blood glucose goals [47, 66]. Microvascular and macrovascular complications of diabetes are known to be influenced by hyperglycaemia [67–69] but lower average glucose levels may increase the risk of hypoglycaemia. Hypoglycaemia in type 1 diabetes has in turn been correlated with insulin resistance [70] and increased weight gain, arguing for management strategies that optimise glucose control, minimise hypoglycaemia and limit weight gain.

Type 1 diabetes The mainstay of therapy for type 1 diabetes is insulin. Intensive basal-bolus insulin regimens via multiple daily injections (MDI) of prandial and basal insulin or continuous subcutaneous insulin infusion are currently recommended for type 1 diabetes [71]. However, currently available insulins have imperfect pharmacodynamics; thus, current research includes developing ultra-rapid insulins and glucose-responsive 'smart' insulins that have the ability to 'turn on' and 'turn off' in response to a low or high blood glucose level [72]. Insulin is also currently delivered peripherally rather than through the portal vein, causing underexposure of the liver and overexposure of the periphery to insulin, a postulated contributor to the elevated hepatic glucose output and peripheral insulin resistance, respectively, in type 1 diabetes. A hepatic-directed insulin is under study to help circumvent the peripheral delivery barrier [73].

Sensor augmented pump therapy, i.e. combining an insulin pump with a continuous glucose-monitoring system, has been shown to be superior to MDI with blood glucose self-monitoring in reducing HbA_{1c} without increased frequency or severity of hypoglycaemia, provided the sensor is used >60% of the time. These are the currently available systems (further details are provided elsewhere [74, 75]):

1. Low-glucose suspend systems – basal insulin delivery is suspended when blood glucose reaches a predefined low sensor threshold and resumes after a set period.
2. Predicted low-glucose suspend systems – basal insulin delivery is suspended when an algorithm predicts that blood glucose will drop below a specified low sensor threshold within 30 min and resumes once blood glucose is no longer low or falling.
3. Hybrid closed-loop systems – an overarching goal of type 1 diabetes management has been to eventually develop an artificial pancreas that integrates blood sugar measurement, an automated algorithm and a device designed to deliver one or more hormones to maintain blood glucose within a specific target range in order to minimise hypoglycaemia and hyperglycaemia and improve quality of life. The Medtronic 670G insulin pump with Guardian 3 sensor introduced in 2017 includes a hybrid closed-loop insulin delivery system that automatically adjusts basal insulin delivery every 5 min based on sensor glucose. Early studies show improvement in HbA_{1c} in both adults and adolescents without DKA or hypoglycaemia [76].

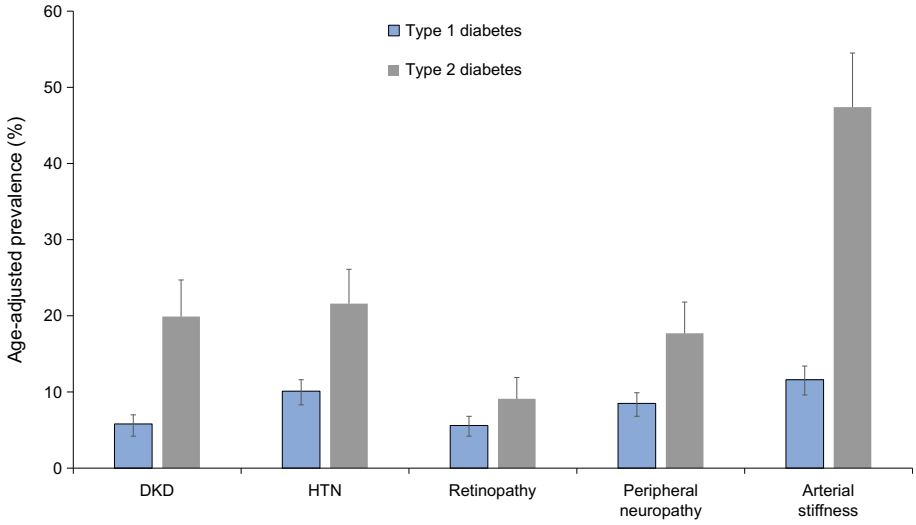

Fig. 1 Age-adjusted prevalence of complications in youth-onset diabetes by type. Data from the SEARCH for Diabetes in Youth Study [46]. Data are prevalence with 95% CIs. HTN, hypertension. This figure is available as a downloadable slide

Metformin has been the most studied adjunctive agent in type 1 diabetes. A recent meta-analysis of 13 randomised controlled metformin trials in type 1 diabetes found significant improvements in BMI and reductions in insulin requirements, total cholesterol and LDL-cholesterol [77], but little or no decrease in HbA_{1c}. Short-term paediatric data suggest similar metabolic improvements in youth [78, 79], along with improvements in insulin sensitivity [53] and vascular health on imaging [79], but data on long-term benefits of metformin in type 1 diabetes are currently lacking.

New therapies are on the horizon. Pramlintide is a synthetic analogue of amylin, which is co-secreted with insulin postprandially to inhibit glucagon release, slow gastric emptying and signal satiety and is deficient in type 1 diabetes. In adults with type 1 diabetes, pramlintide resulted in a decrease in postprandial hyperglycaemia and glucagon, HbA_{1c} and weight compared with insulin-only therapy [80, 81]. Other agents being investigated in type 1 diabetes are thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, drugs used in type 2 diabetes [82, 83].

Continued interest remains in preventing or delaying the development of type 1 diabetes. One avenue has examined early life feeding practices hypothesised to trigger autoimmunity. Weaning to cow's milk formula free of bovine insulin decreased the incidence of diabetes-associated autoantibodies by age 3 in children with HLA-conferred susceptibility to type 1 diabetes [84], but trials weaning to a hydrolysed milk formula and delaying gluten exposure in infancy have shown no benefit [85, 86]. TrialNet is studying hydroxychloroquine, a drug noted to improve glucose and lipid metabolism in rheumatic diseases, to prevent dysglycaemia in youth with two or more diabetes-associated antibodies (ClinicalTrials.gov no. NCT03428945). In addition, as an imbalance between autoreactive effector and regulatory T cells may be crucial in the breakdown of peripheral tolerance in type 1 diabetes, other experimental therapies have focused on regulatory T cell number and function, selective T cell co-stimulation modulating agents and interventions to induce tolerance [87]. Use of anti-thymocyte globulin just after type 1 diagnosis resulted in partial preservation of beta cell function and reduced HbA_{1c} 2 years after therapy in individuals with new-onset type 1 diabetes [88] and, recently, anti-CD3 therapy has been reported to delay progression from antibody positivity and dysglycaemia to diabetes-range hyperglycaemia by ~2 years [89].

Type 2 diabetes Using lifestyle intervention alone to achieve or maintain normal blood glucose in type 2 diabetes is difficult [90–92]. Thus, current paediatric guidelines suggest initial use of metformin, with basal insulin added for ketosis, ketonuria or an HbA_{1c} >69 mmol/mol (>8.5%) [27, 93]. However, in the TODAY study, metformin alone and metformin plus lifestyle were ineffective in maintaining durable glycaemic control in 57% and 47% of adolescents with type 2 diabetes [41], respectively. Moreover in the RISE study, neither metformin alone nor insulin followed by metformin were effective at improving beta cell function in youth with type 2 diabetes or impaired glucose tolerance [33]. While rosiglitazone enhanced the efficacy of metformin in TODAY, the combined dual therapy was still ineffective at maintaining durable control in over a third of adolescents [41]. TZDs may be a particularly helpful choice in highly insulin-resistant patients, including adolescents, with recent data showing benefit on early nephropathy when combined with SGLT2 inhibitors [94].

GLP-1 receptor agonists are approved in adults and have shown weight loss and cardiovascular benefits [95, 96]. GLP-1 is secreted by intestinal enteroendocrine L cells and the brain postprandially to increase insulin secretion and inhibit glucagon production, delay gastric emptying and signal satiety. The effects are brief because of rapid degradation by dipeptidyl peptidase-4 (DPP-4). In June 2019, liraglutide, a GLP-1 agonist, was approved in the USA for treatment of type 2 diabetes in children aged over 10 years. Approval was largely based on the results of the Ellipse trial, a randomised controlled trial of 134 youth with type 2 diabetes, which showed improved glycaemic control with add-on liraglutide compared with placebo (0.64 percentage point lowering in HbA_{1c} vs increase of 0.42; 64% vs 37% of participants with HbA_{1c} <53 mmol/mol [7%], respectively); with an overall good safety profile [97]. Weight loss was not observed, but the dose was not maximised in most participants due to the titration algorithm employed.

SGLT2 inhibitors lower blood glucose by causing decreased reabsorption of glucose from the urine. Studies in adults show reductions in HbA_{1c}, glycaemic variability, body weight and insulin doses, increased time in the target glycaemic range, and improvements in cardiovascular risk factors and mortality compared with placebo [95, 96]. The weight loss and glucose lowering with SGLT2 inhibitors appears less than that observed with GLP-1 receptor agonists [98], but this class of drugs appears very effective for treatment of DKD in adults [99, 100]. SGLT2 inhibitors are approved in Europe and Japan for adults with type 1 diabetes.

An emerging therapy for type 2 diabetes is metabolic bariatric surgery (MBS). MBS is recommended in adults with type 2 diabetes with obesity. MBS is also considered for less obese adults (BMI 30.0–34.9 kg/m^2) if blood glucose is inadequately controlled [101]. MBS is also now considered for adolescents with type 2 diabetes and severe obesity (BMI ≥35 kg/m^2 or BMI ≥120% of the 95th percentile for age and sex) [102].

Initial MBS outcomes in youth with type 2 diabetes show weight loss and remission of diabetes [103, 104]. Teen-Longitudinal Assessment of Bariatric Surgery (-LABS) is an

observational study of youth undergoing MBS, currently with 5 years of follow-up data [105]. Of the 161 youth who underwent Roux-en Y gastric bypass (RYGB), 29 had type 2 diabetes [103]. A 94% type 2 diabetes remission rate (defined as being free of diabetes medication and having an HbA_{1c} <48 mmol/mol [6.5%] or a fasting blood glucose <7.0 mmol/l [126 mg/dl]) occurred at 3 years, with no incident type 2 diabetes cases in the youth without type 2 diabetes [103]. While direct comparisons of MBS with medical therapy have yet to occur, a retrospective comparison of youth in the TODAY study and Teen-LABS was published [106]. Over 2 years, HbA_{1c} fell from 51 mmol/mol (6.8%) on medication to 37 mmol/mol (5.5%) off medication in Teen-LABS, but increased from 44 mmol/mol (6.2%) to 62 mmol/mol (7.8%) on medication in TODAY. During the same time, hypertension decreased from 45% at baseline to 20% in Teen-LABS vs a near doubling in TODAY, from 22% to 41% [106]. Similarly, dyslipidaemia decreased from 72% to 24%, and the proportion of youth in Teen-LABS with elevated urinary albumin excretion decreased from 26% to 5%, with no change seen for either in TODAY [106]. These initial results suggest a beneficial effect of MBS on blood glucose and comorbidities. However, these results evaluated RYGB which is no longer the preferred MBS in adolescents [107] as vertical sleeve gastrectomy now accounts for more than 80% of MBS procedures in the USA [107]. Furthermore, whether bariatric surgery is superior to newer glucose-lowering medications with weight-loss benefit (i.e. GLP-1 agonists or SGLT2 inhibitors) in reducing blood glucose is not known. Two cases of youth with type 1 diabetes undergoing bariatric surgery have been reported. Weight loss similar to youth without diabetes was reported, but without improvements in glycaemic control or dependency on exogenous insulin [108].

Conclusions

The incidence and prevalence of youth-onset type 1 and 2 diabetes and its complications continue to rise. Healthy eating, physical activity and obesity prevention should be implemented for both forms of diabetes. New technologies and therapies should be considered in all adolescents with diabetes. Key areas for research include understanding: (1) the factors that predict the development of early comorbidities and complications in youth-onset diabetes; (2) the contributions of epigenetics and the environment; (3) effective strategies to reduce and treat obesity in both forms of diabetes; (4) drugs, treatments and technology that prevent, slow or reverse disease progression; and (5) the long-term impact of disease on quality of life, reproductive health and the offspring of young adults with youth-onset diabetes.

Summary

- Being overweight or obese is common in youth with type 1 or type 2 diabetes
- Identifying diabetes type is important for treatment and anticipating complications
- Comorbidities and complications are present in youth and should be screened for as per paediatric guidelines
- New medications, technology and treatments are on the horizon and should be studied in youth-onset diabetes

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