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Review

Youth-Onset Type 2 Diabetes: Update on Epidemiology, Pathophysiology, Diagnosis, and Management Strategies

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Abstract

Youth-onset type 2 diabetes (T2D) is a growing public health challenge. This narrative review aims to provide a comprehensive overview of epidemiology, pathophysiology, diagnosis, complications, and therapeutic strategies in children and adolescents with T2D, highlighting the most recent evidence and the distinctive features that differentiate youth-onset from adult-onset disease. Over recent decades, its incidence has increased worldwide, closely linked to rising rates of childhood obesity, sedentary behavior, and socioeconomic disparities. The disease typically emerges around puberty, a period marked by physiological insulin resistance, and is influenced by a complex interplay of genetic, environmental, and developmental factors. Diagnosis can be delayed or missed due to overlapping features with type 1 diabetes and limitations in current screening tools. The clinical course is often aggressive, with early onset of microvascular and macrovascular complications. Management is particularly challenging due to the limited number of pharmacologic agents approved for pediatric use and the psychological and behavioral complexities of adolescence. While metformin remains the first-line treatment, newer therapies such as GLP-1 receptor agonists and SGLT2 inhibitors show promise in improving metabolic outcomes. In conclusion, early diagnosis, multidisciplinary management, and equitable access to effective therapies are essential to improve long-term outcomes in this vulnerable population.

Keywords: adolescence; beta-cell; complications; GLP-1 receptor agonists; glucose monitoring; insulin resistance; lifestyle; metformin; obesity; SGLT2 inhibitors

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1. Introduction

Type 2 diabetes (T2D) is a complex metabolic disorder characterized by the progressive decline in pancreatic β-cell function in the context of peripheral insulin resistance [1]. Historically considered as an adult-onset disease, the incidence of T2D among pediatric populations has risen at an alarming rate, paralleling the global increase in childhood obesity and sedentary lifestyles [2–5].

Youth-onset T2D exhibits distinct pathophysiological mechanisms compared to its adult counterpart, including a heightened degree of insulin resistance, accelerated β-cell dysfunction, and an increased susceptibility to early-onset microvascular and macrovascular complications [6–9].

The pathogenesis of pediatric T2D is driven by a complex interplay of genetic susceptibility, ethnic predisposition, and environmental factors, such as excessive caloric intake and insufficient physical activity [10]. Furthermore, metabolic dysregulation—characterized by ectopic lipid accumulation, chronic low-grade inflammation, and adipose tissue dysfunction—exacerbates insulin resistance and further increases functional demand on β-cells, accelerating disease progression [11].

Puberty represents a critical window for the manifestation of T2D due to transient physiological insulin resistance, which is typically counterbalanced by adaptive increases in basal and glucose-stimulated insulin secretion [12]. While insulin sensitivity is generally restored post-puberty [13], obese adolescents often exhibit persistent hyperinsulinemia and dysglycemia. Chronic hyperglycemia contributes to β-cell dysfunction through glucotoxicity and lipotoxicity, promoting oxidative stress, endoplasmic reticulum dysfunction, and ultimately β-cell apoptosis, thereby further compromising insulin homeostasis [14].

In recent years, youth-onset T2D has emerged as a major public health concern due to its rising prevalence and aggressive clinical course. Management is further complicated by the limited availability of approved therapies for pediatric use and the challenges of treatment adherence during adolescence, leading to suboptimal outcomes.

This narrative review aims to provide an in-depth analysis of the epidemiology, risk factors, clinical presentation, and management strategies in children and adolescents with T2D, highlighting the most recent evidence and the distinctive features that differentiate youth-onset from adult-onset disease.

2. Epidemiology

Pediatric diabetes is an escalating global public health concern. Over the past two decades, the incidence of T2D during childhood and adolescence have risen significantly, paralleling the global surge in obesity rates [15]. Projections indicate that, if current trends persist, the prevalence of youth-onset T2D could quadruple by 2050 [16].

In 2021, approximately 41,600 new pediatric cases of T2D were diagnosed globally. As indicated by the International Diabetes Federation (IDF), the Western Pacific region accounted for 30% of these cases, while 40% were reported in upper-middle-income countries. China, India, and the United States reported the highest incidence rates [17]. Conversely, the lowest incidence rates were observed among non-Hispanic White youth in the United Kingdom, Germany, and the United States [18–20]. These differences likely reflect a complex interplay of genetic susceptibility, environmental and socioeconomic factors, as well as variability in screening and diagnostic practices across countries and ethnic groups, which may lead to underdiagnosis in certain settings.

A summary of key epidemiological studies reporting incidence and prevalence of youth-onset T2D across different regions is provided in Table 1.

The SEARCH for Diabetes in Youth Study, a population-based surveillance study monitoring physician-diagnosed diabetes across six U.S. states and selected American Indian reservations, reported that the incidence of T2D among individuals aged 10 to 19 years increased from 9 cases per 100,000 person-years in 2002–2003 to 12.5 cases per 100,000 person-years in 2011–2012. This trend was consistently observed across all demographic subgroups, including age, sex, race, and ethnicity. The estimated prevalence of youth-onset T2D among individuals aged 10–19 years currently stands at 0.67 per 1000 individuals, an increase from 0.34 per 1000 in 2001, representing a relative rise of 95.3% over 16 years [21]. African American (0.85 per 1000; 95% CI, 0.74–0.97) and Hispanic (0.57 per 1000; 95% CI, 0.51–0.64) youth exhibited the highest absolute increases during 2001–2017 [22].

Table 1. Incidence and prevalence of youth-onset type 2 diabetes across different countries and populations.

Ref.	Country/Region	Years of Data	Study Design	Age Range	Key Findings
[21]	USA (SEARCH)	2001–2017	Population-based surveillance	10–19 y	Prevalence nearly doubled from 0.34 to 0.67 per 1000; relative increase 95%. Highest rates in Black (0.85/1000) and Hispanic (0.57/1000) youth.
[22]	USA (SEARCH)	2002–2015	Population-based surveillance	<20 y	Incidence of youth-onset T2D increased significantly across sex and race/ethnicity groups.
[23]	England	2012–2017	National registry	<40 y	122,780 cases <40 y (4.6% of all T2D); 0.5% <16 y, 0.7% 16–18 y. Younger individuals more often female, obese, socioeconomically disadvantaged, and from minority backgrounds.
[20]	India	2016–2018	National survey	10–19 y	Prevalence of prediabetes/diabetes: 12.3% in males, 8.4% in females. Higher prevalence in disadvantaged adolescent females.
[24]	USA (TODAY)	2004–2009	Multicenter RCT baseline cohort	10–17 y	704 participants, mean age 14 y, 65% female. Predominantly minority groups; 41% household income < $25,000.
[25]	Germany (North Rhine–Westphalia)	2002–2022	Regional registry	<20 y	Incidence increased from 1.3 to 2.8 per 100,000 person-years; annual percent change ~6.4%.
[26]	Mexico (Mexico City)	2013 vs. 2018	Single-center retrospective	8–17 y	Proportion of pediatric diabetes due to T2D rose from 20.2% to 33.0% over 5 years.
[27]	Saudi Arabia	2017–2020	National registry	<18 y	Among 2344 children and adolescents with diabetes, 6.4% had T2D
[28]	UK (London)	2008–2018	Single-center retrospective cohort	<18 y	Annual incidence of pediatric T2D doubled: from 2.6 (2008–2013) to 5.4 cases/year (2014–2018).
[29]	Israel	2008–2019	National observational study	10–18 y	Incidence rose from 0.63 to 3.41 per 100,000
[30]	Canada (Manitoba)	2009–2018	Population-based administrative data	<18 y	Incidence doubled from 16.0 to 31.1 per 100,000. Prevalence rose from 66.4 to 124.2 per 100,000. First Nations children most affected (incidence up to 121.2/100,000).

RCT: randomized controlled trial; T2D: type 2 diabetes.

A study from England analyzing data of the National Paediatric Diabetes Audit identified 122,780 individuals under 40 years with T2D, representing 4.6% of the total T2D population. Among these, 650 (0.5%) were under 16 years, 910 (0.7%) were aged 16–18 years, 8245 (6.7%) were aged 19–25 years, and 112,975 (92%) were aged 26–39 years. Compared to individuals over 40 years old, younger patients exhibited female predominance and a significantly higher prevalence of ethnic minority backgrounds, obesity, and socioeconomic disadvantage [23].

An Indian study analyzing data from the Comprehensive National Nutrition Survey documented a prediabetes/T2D prevalence of 12.3% among adolescent males and 8.4% among adolescent females. Body Mass Index (BMI) and subscapular skinfold thickness were identified as the most significant predictors of prediabetes and diabetes, while physical activity showed a protective effect. Adolescent females from socioeconomically disadvantaged backgrounds exhibited a significantly higher prevalence of T2D [20]. Similarly, the Treatment Options for Type 2 Diabetes in Adolescents & Youth (TODAY) study reported that approximately 40% of affected families had an annual household income of $25,000 or less, suggesting a strong link between socioeconomic status and clinical outcomes [24].

Recent regional studies further emphasize the growing burden of T2D, highlighting significant increases in incidence and prevalence across different populations. In North Rhine-Westphalia, Germany, incidence rates increased from 1.3 to 2.8 per 100,000 person-years between 2002 and 2022 [25]. In Mexico, the proportion of pediatric diabetes due to T2D increased from 20.2% to 33.0% over 5 years [26]. Saudi Arabia's Pediatric and Youth Diabetes Registry, comprising 2344 individuals, reports that 6.4% has T2D [27].

A retrospective study at Barts Health NHS Trust in London documented a doubled incidence of T2D, from 2.6 cases per year (2008–2013) to 5.4 cases per year (2014–2018) [28]. In Israel, incidence increased from 0.63 per 100,000 in 2008 to 3.41 per 100,000 in 2019 [29]. In Manitoba, Canada, T2D incidence nearly doubled from 16.0 to 31.1 per 100,000 per year between 2009–2010 and 2017–2018, with the most pronounced rise among First Nations children [30].

The COVID-19 pandemic has further exacerbated the pediatric T2D crisis. A significant increase in the incidence of T2D during this period has been recorded. It remains uncertain whether this rise was attributable to SARS-CoV-2 itself or to pandemic-related behavioral changes [31]. A multicenter retrospective study conducted across 24 hospital-based centers in the US analyzed data from youth aged $\leq$21 years who were newly diagnosed with T2D between March 2018 and February 2021. The findings revealed a 77.2% increase in new T2D diagnoses during the first year of the pandemic compared to the average of the previous two years. Additionally, the likelihood of presenting with metabolic decompensation and severe diabetic ketoacidosis significantly increased during the pandemic [32].

The underlying causes of this surge are likely multifactorial. SARS-CoV-2 has been hypothesized to increase hyperglycemia risk by interacting with angiotensin-converting enzyme 2 (ACE2) receptors expressed in key metabolic organs and tissues, including pancreatic β-cells [31]. However, the rising incidence of T2D may also be attributed to pandemic-related behavioral changes, such as reduced physical activity and increased weight gain. Indeed, studies have reported that the rate of BMI increase in children nearly doubled during the pandemic compared to pre-pandemic levels [33].

Epidemiological evidence from multiple studies corroborates this trend. A study conducted at the Children's Hospital of Chicago involving patients under 21 years of age reported that, prior to the COVID-19 pandemic, the mean annual incidence of newly diagnosed T2D cases was 54.2. During the pandemic period, this figure rose sharply to 159 cases per year, representing a 193% increase relative to the pre-pandemic baseline [34]. Similarly, in Germany, the incidence of T2D among individuals aged 6 to 18 years increased by 188% during the second year of the pandemic compared to preceding years [35].

In addition to the increase in new cases, the severity of clinical presentation worsened. Patients diagnosed with T2D during the pandemic exhibited higher initial glycated hemoglobin (HbA1c) levels and an increased prevalence of diabetic ketoacidosis at diagnosis. These trends may be attributed to delays in seeking medical care, and limited access to healthcare services [36].

3. Risk Factors

The development of T2D results from a complex interplay of genetic, epigenetic, and environmental factors. Although the etiopathogenesis of T2D in pediatric age remains partially unknown, several well-established risk factors have been identified.

Obesity is a fundamental modifiable risk factor for the onset of T2D, acting on the pathophysiology of insulin resistance and metabolic dysfunction [11]. A retrospective cohort study conducted on 369,362 participants aged 2 to 15 years revealed a fourfold increased risk of developing T2D among overweight or obese individuals compared to those with a normal BMI [37].

Adolescence is a crucial developmental phase marked by hormonal and psychological changes and at high incidence of obesity [12]. The considerable prevalence of overweight especially among adolescents is mainly related to pre-packaged foods consumption and high-calorie diets. During this developmental stage, dietary habits often deteriorate due to increased autonomy in food choices and greater exposure to ultra-processed foods.

In addition, poor activity lifestyle and sedentary behaviors amplify the risk of sustained weight gain and metabolic dysregulation among young males and females. A five-year longitudinal study involving 2516 adolescents highlights a gradual increase in leisure-time computer use, particularly among boys, from 11.4 to 15.2 h per week between early and mid-adolescence, and from 10.4 to 14.2 h per week between mid- and late adolescence [38]. Conversely, an observational study conducted on a cohort of 686 youth from Belgium, Greece, Hungary, the Netherlands, and Switzerland revealed that girls spent higher sedentary time (500 min/day) compared to boys (474 min/day) [39].

Even though BMI is traditionally considered as a marker of obesity, the distribution of adipose tissue is now acknowledged as a key indicator of metabolic risk. The excess of perivisceral fat depots predicts the development of cardiometabolic abnormalities, insulin-resistance, and T2D in children. A cohort study conducted on 520 young Japanese Americans without diabetes, identified body fat deposition as a significant predictor of eventual T2D onset [40].

Perihepatic and epicardial adipose tissue has also been associated with increased secretion of pro-inflammatory cytokines (TNF-α, IL-6) and reduced levels of insulin-sensitizing adipokines, such as adiponectin, resulting in impaired glucose intracellular uptake and increased susceptibility to T2D among obese adolescents [41].

Puberty is the physiological transition from childhood to adulthood, characterized by the maturation of the reproductive system. Females exhibit a higher susceptibility to T2D during puberty compared to males. This difference is probably associated with a combination of genetic, hormonal, and metabolic factors. Puberty usually occurs earlier in girls, and is associated with lower insulin sensitivity compared to boys at the same Tanner stage. However, following puberty, males face a greater risk of developing insulin resistance compared to females [42].

Prenatal conditions may also play a crucial role in shaping fetal metabolic programming and are significant contributors to the rising prevalence of youth-onset T2D. Maternal factors such as gestational diabetes and obesity can induce long-lasting alterations in the offspring's metabolic pathways through epigenetic modifications. Understanding the impact of prenatal influences on metabolic health highlights the necessity for early preventive strategies to mitigate the intergenerational transmission of metabolic disorders [43].

A retrospective case–control study investigated the associations between prenatal, obstetric, and perinatal factors and the risk of developing youth-onset T2D, revealing that exposure to maternal pregestational diabetes increases the risk by nearly sixfold, while exposure to gestational diabetes is associated with a fourfold elevated risk. Additionally,

the study identified breastfeeding as a protective factor against the development of T2D in youth [44].

Moreover, individuals with intrauterine growth restriction and those born small for gestational age may develop what is referred to as the "thrifty phenotype". According to this hypothesis, intrauterine malnutrition serves as a trigger for fetal adaptive mechanisms that are essential for short-term survival. However, these adaptations may also lead to long-term metabolic consequences, including an increased risk of insulin resistance and the subsequent early development of T2D [45].

Insufficient sleep has been identified as a contributing risk factor to the development of unhealthy dietary patterns, insulin resistance, and impaired glucose tolerance, particularly among adolescents. Furthermore, chronic sleep deprivation may exacerbate the difficulties in maintaining optimal blood glucose levels in children and adolescents already diagnosed with diabetes. A study enrolling 551 individuals with T2D revealed lower sleep quality assessed through the Pittsburgh Sleep Quality Index among participants with suboptimal glycemic control [46].

Ethnicity plays a significant role in determining the risk of developing T2D during childhood and adolescence. Epidemiological data consistently show that youth-onset T2D is most prevalent among Native American, Canadian First Nation, Indigenous Australian, Black, Hispanic, East and South Asian, Middle Eastern, and Pacific Islander populations. The elevated prevalence observed in these groups reflects a complex interplay of genetic, environmental, and lifestyle factors. In many of these populations, high obesity rates substantially contribute to T2D risk. Interestingly, East Asian children present an exception to this trend, as they exhibit relatively low obesity prevalence with a disproportionately high incidence of T2D. This pattern is likely attributable to a genetic predisposition to β-cell dysfunction, resulting in inadequate insulin secretion even in the context of minimal adiposity [47].

The Progress in Diabetes Genetics in Youth (ProDiGY) Consortium conducted the first genome-wide association study focused on T2D in children and adolescents, aiming to identify genetic variants associated with early-onset disease. The study identified several risk loci, including rs10992863 in PHF2, rs7903146 in TCF7L2, rs72982988 near MC4R, rs200893788 in CDC123, rs2237892 in KCNQ1, rs937589119 in IGF2BP2, rs113748381 in SLC16A11, and a locus in CPEB2, that influence insulin secretion and glucose metabolism. Whereas the majority of loci identified in youth-onset T2D overlap with those described in adult-onset disease, PHF2 (rs10992863) and CPEB2 appear to be specific to the early-onset form [48].

Furthermore, the N-acetyltransferase 2 (NAT2) A803 allele appears to predispose children to altered glucose tolerance by impairing pancreatic β-cell insulin secretion, as evidenced by a study involving 748 obese children and adolescents, revealing a higher prevalence of both impaired glucose tolerance (IGT) and elevated fasting plasma glucose among individuals carrying this allele, suggesting a potential genetic contribution to metabolic dysregulation in pediatric obesity [49].

In addition to lifestyle and genetic factors, certain medications are also known to increase the risk of early-onset T2D. In recent years, the growing use of antidepressants in children and adolescents has raised concerns about potential metabolic effects. A retrospective cohort study on Medicaid claims data assessing T2D risk among youth taking various classes of antidepressants, showed that long-term use of antidepressants—particularly serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)—was associated with a higher risk of developing T2D, especially with prolonged exposure. Long-term exposure to SNRIs and TCAs has been associated with weight gain, impaired insulin sensitivity, and disruption of glucose homeostasis, likely

mediated through serotonergic, noradrenergic, and histaminergic pathways that regulate appetite and energy balance [50]. Among other drugs, atypical antipsychotic agents (including aripiprazole, risperidone, olanzapine) are well known risk factors for weight gain and the early onset of T2D. Antipsychotic medications primarily exert their therapeutic effects through antagonism of dopamine D2 receptors. However, many also exhibit affinity for other neurotransmitter systems, including serotonergic (e.g., 5-HT2A), histaminergic (e.g., H1), and adrenergic (e.g., α1) receptors. These systems play key roles in the metabolic regulation and insulin secretion, and their modulation may underlie the metabolic side effects commonly associated with antipsychotic treatment [51].

4. Screening and Diagnosis

Youth-onset T2D presents as a more aggressive and rapidly progressive disease than its adult-onset counterpart [7]. Consequently, early screening and timely diagnosis are essential to prevent both acute and long-term complications.

According to the American Diabetes Association (ADA) guidelines, diabetes screening is recommended for all children aged ≥10 years who have BMI >85th percentile for age and sex and with at least one additional risk factor, as outlined in Table 2 [1].

Table 2. High-risk groups for youth-onset type 2 diabetes.

- Family history of type 2 diabetes
- Exposure to pregestational or gestational diabetes during pregnancy
- High risk ethnicity groups
- Signs of insulin resistance (acanthosis nigricans, fatty liver disease, hypertension, dyslipidemia, polycystic ovary syndrome)
- Small for Gestational Age or Large for Gestational Age
- Use of atypical antipsychotic agents (examples include aripiprazole, risperidone, olanzapine)

The methods currently employed for the screening and diagnosis of T2D in pediatric populations include measurement of HbA1c, fasting plasma glucose (FPG), and plasma glucose concentrations obtained during a 2-h oral glucose tolerance test (OGTT). The results of the tests identify different metabolic conditions based on the degree of glycemic dysregulation [52].

Updated diagnostic criteria of diabetes, according to ADA Guidelines, are summarized in Table 3. A diagnosis of diabetes in pediatric and adolescent populations is established when any of the standard diagnostic criteria are fulfilled on two separate occasions. Additionally, the presence of a random plasma glucose concentration ≥ 200 mg/dL (≥11.1 mmol/L) in conjunction with classic symptoms of hyperglycemia—such as polyuria, polydipsia, or unexplained weight loss—also constitutes diagnostic evidence of diabetes.

Table 3. Diagnostic criteria of diabetes and prediabetes.

Diagnostic Test	Prediabetes	Diabetes
HbA1c	5.7–6.4%	≥6.5%
Fasting plasma glucose	Impaired Fasting Glucose 100–125 mg/dL	≥126 mg/dL
2-h OGTT	Impaired Glucose Tolerance 140–199 mg/dL	≥200 mg/dL

HbA1c: glycated hemoglobin; OGTT: oral glucose tolerance test.

Alternatively, investigations may reveal a state of impaired glucose regulation called prediabetes, which is characterized by abnormalities in carbohydrate metabolism and is considered a potential intermediary stage in the progression to T2D. As defined by the

ADA Guidelines, prediabetes is identified based on specific glycemic thresholds indicative of impairment in glucose homeostasis that do not fulfill the diagnostic criteria for diabetes.

The optimal screening method for diabetes in obese youth remains controversial. Alternative glycemic markers, such as glycated albumin, 1,5-anhydroglucitol, and fructosamine, have been proposed as potential tools for T2D screening. However, current evidence has shown their effectiveness in detecting prediabetes is limited compared to traditional markers [53].

HbA1c, the end product of a glycosylation process involving the covalent binding between glucose and the N-terminal valine of the hemoglobin β chain, reflects the concentration of blood glucose over the preceding 8 to 12 weeks. The ADA guidelines highlight several advantages of HbA1c as a diagnostic marker of diabetes, including its convenience, as fasting is not required, and its lower intra-individual variability compared to other markers. A position article evaluated the use of HbA1c as a diagnostic tool for T2D in developing countries, focusing on its lower day-to-day variability as a key advantage. However, the authors also acknowledged several limitations, including reduced sensitivity and limited accessibility in certain regions. Across many low- and middle-income settings, limited access to standardized HbA1c assays constrains its diagnostic use; consequently, fasting plasma glucose remains the most widely implemented test. Additionally, HbA1c values may be underestimated in individuals with hematologic disorders such as sickle cell traits or X-linked glucose-6-phosphate dehydrogenase mutations [54].

An observational study conducted by Ehehalt et al. on a population of German overweight and obese children and adolescents, found that HbA1c is more reproducible and convenient as initial screening test for diabetes in high-risk pediatric populations due to its superior sensitivity, specificity, and practicality compared to OGTT. However, this study also highlighted that HbA1c diagnostic accuracy for prediabetes is limited, necessitating complementary tests [55].

The optimal HbA1c threshold for the early detection of T2D in youth remains a topic of ongoing investigation and debate. Recent evidence suggests that the risk of progression to T2D is approximately 4% among individuals with a baseline HbA1c of 5.7–5.9%, and increases to 8% in those with levels ranging from 6.0% to 6.4% [56]. Several studies have raised concerns about the sensitivity of the current diagnostic threshold of HbA1c of 6.5%, indicating that it may be less effective for early detection in pediatric populations. In a retrospective, single-center study analyzing data from 236 overweight or obese children and adolescents aged 4–17 years, a HbA1c level of 6.5% demonstrated a sensitivity of 87.2% and a specificity of 98.5% for detecting T2D. The optimal HbA1c cutoff identified was >6.2%, which yielded a sensitivity of 94.7% and specificity of 95.5% [57]. On the other hand, another study reported that lowering the HbA1c threshold to detect prediabetes resulted in a high rate of false positives, reducing its specificity and clinical utility. For HbA1c values between 6.0–6.5% (42 and 48 mmol/mol), additional confirmatory testing is necessary to accurately diagnose diabetes [55].

OGTT is a dynamic test that evaluates plasma glucose level 120 min after oral glucose intake and it is particularly useful for evaluating glucose tolerance. OGTT seems to be more sensitive than FPG in detecting early glucose dysregulation and it is the preferred diagnostic test for screening high-risk children when HbA1c and FPG are inconclusive. However, the requirement for fasting and multiple blood draws presents practical challenges in the pediatric population.

Recent studies have proposed novel approaches to interpreting OGTT results for the early diagnosis of T2D in youth. Emerging evidence suggests that evaluating 1-h plasma glucose concentration during the OGTT may offer a reliable alternative to the traditional 2-h measurement in identifying early-stage T2D [58]. Ravà et al. investigated the utility

of 1-h glucose levels as a predictor of impaired glucose tolerance and cardiometabolic risk in children with obesity. By analyzing the diagnostic accuracy of various thresholds, they proposed that a cutoff of 155 mg/dL (8.6 mmol/L) could represent a practical and meaningful marker for early T2D detection in the pediatric population [59].

Given that type 1 diabetes (T1D) remains the most prevalent form of diabetes in youth, a comprehensive diagnostic evaluation for T2D should include the assessment of pancreatic autoantibodies, such as glutamic acid decarboxylase antibody (GAD-65), insulinoma-associated antigen-2 antibody (IA-2), zinc transporter 8 antibody (ZnT8), and insulin autoantibody (IAA), to reliably exclude autoimmune diabetes [60,61]. The widespread prevalence of obesity across the general pediatric population has led to increasing overlap in phenotypic features between T1D and T2D. Notably, excess adiposity is no longer a distinctive feature of T2D alone, as a significant proportion of youth with T1D now also present with overweight or obesity at onset. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study reported that approximately 12% of individuals who initially met diagnostic criteria for T2D, tested positive for GAD-65 and/or IA-2 antibodies, suggesting underlying autoimmune β-cell dysfunction despite the clinical phenotype being consistent with T2D [62].

5. Clinical Presentation

The clinical course of T2D diagnosed during adolescence is more aggressive compared to adult-onset cases [61]. Data from the TODAY study have demonstrated that youth-onset T2D progresses more rapidly, with a faster decline in β-cell function [62].

The clinical phenotype of children and adolescents diagnosed with T2D is typically characterized by overweight, defined by a BMI at or above the 85th percentile for sex and age, or obesity, defined as a BMI at or above the 95th percentile for age and sex, in accordance with the Centers for Disease Control and Prevention (CDC) growth charts. In addition, many affected individuals exhibit central adiposity, as indicated by a waist circumference exceeding the 90th percentile for age and sex. This anthropometric profile is frequently accompanied by clinical and biochemical markers of insulin resistance including acanthosis nigricans, dyslipidemia, and arterial hypertension.

The clinical presentation of T2D at onset in children and adolescents varies widely, from asymptomatic to severe conditions including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS).

DKA is an acute metabolic complication of diabetes characterized by hyperglycemia (blood glucose > 200 mg/dL or 11 mmol/L), venous pH < 7.3 or serum bicarbonate <18 mmol/L, ketonemia (blood ß-hydroxybutyrate $\geq$ 3 mmol/L) or moderate or large ketonuria. Ketosis-prone diabetes (KPD) is a form of diabetes that exhibits features of both T1D and T2D. Subjects typically present with DKA at onset and phenotype of obesity-associated T2D, with exact underlying mechanisms remaining under investigation. The Aβ classification system categorizes KPD based on the presence or absence of β-cell autoantibodies (A+ or A−) and β-cell functional reserve (β+ or β−). Pathophysiologically, A−β+ KPD appears to reflect transient β-cell secretory failure on a background of insulin resistance, with ketoacidosis driven by impaired ketone oxidation and altered substrate handling rather than excess ketogenesis [63]. Data from the Rare and Atypical Diabetes Network (RADIANT) showed that 45% of children diagnosed with T2D presenting with DKA met the criteria for the A−β+ KPD, highlighting the importance of considering this diagnosis in youth as well as in adults [64].

Another possible clinical presentation of T2D is euglycemic DKA (EDKA), a rare but serious metabolic complication characterized by significant ketoacidosis with blood glucose levels < 250 mg/dL. While traditionally associated with T1D, euglycemic DKA

has been increasingly reported in individuals with T2D. Vomiting, abdominal pain, fatigue could represent the clinical presentation of this condition so EDKA could be mistaken with gastroenteritis or infection. EDKA could be caused by the use of SGLT2 inhibitors, prolonged fasting or eating disorders, inadequate insulin treatment [65].

HHS is a serious and potentially fatal complication of diabetes characterized by extreme elevations in serum glucose concentrations (>600 mg/dL) and hyperosmolality without significant ketosis and acidosis. The incidence of HHS has risen in parallel with the increasing prevalence of childhood obesity and T2D, with reports indicating that up to 2% of children may present with HHS at diagnosis [66]. This severe condition often presents with neurological manifestations, severe dehydration, with sepsis or infection often acting as a trigger. Identified risk factors that may lead to HHS are delayed diagnosis of T2D and poor access to care. In children and adolescents presenting with HHS, aggressive fluid resuscitation is often necessary to prevent hemodynamic instability and circulatory collapse. During rehydration serum sodium concentrations should be closely monitored and progressive decline in serum glucose is expected [67].

6. Complications

Long-term complications of T2D may occur earlier compared to T1D (Figure 1) [62]. Furthermore, early-onset T2D is associated with a more severe phenotype compared to adult counterpart, as suggested by data from an Australian cohort of 193 youth with T2D, where nine individuals had already developed at least one diabetes-related complication at the time of diagnosis [68].

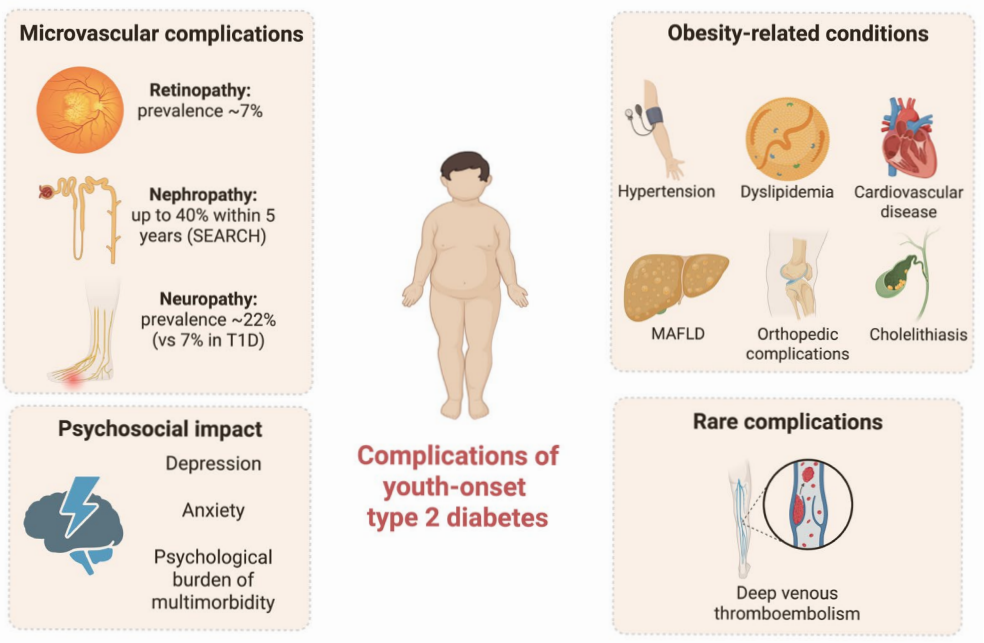

Figure 1. Complications of youth-onset type 2 diabetes. Summary of microvascular, obesity-related, psychosocial, and rare complications associated with pediatric type 2 diabetes.

Diabetic nephropathy, characterized by persistent albuminuria and declining renal function, is a significant concern in youth with T2D. Different researchers have showed evidence of early kidney damage in youth with T2D. The SEARCH study has shown that up to 40% of adolescents with T2D develop microalbuminuria within five years after diagnosis. Additionally, albuminuria progression seems to be more common in T2D versus T1D [22]. The TODAY study is a landmark clinical trial that followed adolescents with T2D over

several years. By the third year, about 6% of participants had developed microalbuminuria, and the prevalence increased over time [62].

Diabetic retinopathy is a serious microvascular complication of T2D, and although traditionally considered a late-onset complication, it has increasingly been reported in children and adolescents with T2D. A recent systematic review and meta-analysis of 27 observational studies including children and adolescents with T2D showed that diabetic retinopathy was present among 6.99% of participants, with prevalence increasing significantly with longer diabetes duration [69].

Diabetic peripheral neuropathy is another potential complication of T2D in pediatric age. A study by Jaiswal et al. found that its prevalence was 7% in youth with T1D and 22% in youth with T2D [70].

Besides its association with T2D, obesity is a chronic condition that may lead to several complications. Arterial hypertension, dyslipidemia, cardiovascular disease, metabolic dysfunction-associated fatty liver disease (MAFLD), genu valgum, flatfoot, and cholelithiasis are some of the obesity-associated comorbidities in youth.

Sporadic cases of deep venous thromboembolism in the context of T2D have also been documented in the pediatric population. A reported case involved a 15-year-old male who presented with swelling and pain in the left calf and was ultimately diagnosed with extensive deep venous thromboembolism. A concurrent diagnosis of T2D was made, supporting the hypothesis of a potential interplay between metabolic dysregulation and an underlying genetic predisposition to thrombosis [71].

Finally, the association between T2D and other obesity-related conditions in young age may also represent a significant psychological burden. Data from the Pediatric Diabetes Consortium T1D and T2D registries confirmed that youth with T2D had higher rates of depressive symptoms and anxiety compared to those with T1D [72].

7. Management

Given the known association of youth-onset T2D with both microvascular and macrovascular complications within the first years of disease, maintaining optimal glycemic control in this population is crucial [73]. Management of T2D needs a comprehensive approach that involves education, lifestyle modifications, regular physical activity, and, when indicated, intensive glucose monitoring and pharmacologic treatment [7] (Figure 2). However, in pediatric populations, achieving therapeutic goals can be challenging due to the limited availability of approved treatment options and the complexities associated with growth and development [73].

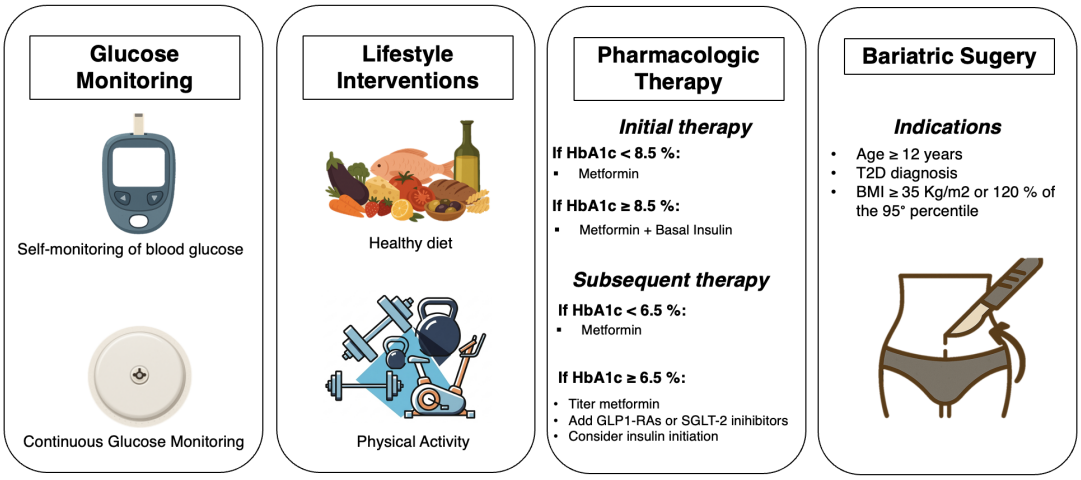

Figure 2. Graphical summary of management strategies for youth-onset type 2 diabetes.

7.1. Lifestyle

Lifestyle modification represents the first-line intervention in individuals with prediabetes, aiming to delay or prevent the progression to T2D, and a cornerstone of therapeutic management in youth with established T2D, in association to pharmacologic treatment.

Several interventional studies have demonstrated the benefits of structured lifestyle programs in youth at risk for, or with, established T2D. Large-scale community-based prevention trials reported reductions in obesity-related outcomes [74], whereas smaller randomized programs in high-risk adolescents consistently improved physical activity, insulin sensitivity, health-related quality of life, and body composition, even when effects on BMI or HbA1c were modest [75,76].

However, not all lifestyle interventions have proven effective. The Feel4Diabetes program did not significantly increase physical activity, highlighting barriers such as socioeconomic disadvantage, limited parental education, and lack of time [77–79].

Data from the TODAY study underscore that sustained adherence to dietary and physical-activity recommendations is associated with improved glycemic control; nevertheless, overall adherence remains challenging [80,81]. Psychosocial factors, including depression, stressful life events, and limited family or peer support, are significant obstacles to long-term behavioral change [82–84].

Nutritional strategies remain central to both prevention and treatment. Observational and interventional evidence indicates that meal timing, glycemic index, and breakfast consumption influence insulin sensitivity and weight regulation [85–88]. Emerging studies further suggest potential benefits of adjunctive dietary supplements, such as a polysaccharide macromolecule complex, in delaying T2D progression, although the evidence remains preliminary [89]. Vitamin D deficiency is frequently reported in youth with obesity and T2D and has been associated with reduced insulin sensitivity and adverse metabolic outcomes in observational studies. Some interventional trials suggest that vitamin D supplementation may improve insulin resistance, yet evidence remains inconsistent and insufficient to establish a protective role in preventing or delaying T2D onset [90].

Physical activity is a critical determinant of metabolic health. A combination of aerobic and resistance training appears most effective in reducing insulin resistance, while both endurance and high-intensity interval training have been shown to improve glycemic control, body composition, and cardiorespiratory fitness [91–93]. Additional interventional studies have demonstrated favorable effects on lipid profiles, hepatic fat, neurocognitive function, and cardiovascular parameters [94–98].

7.2. Glucose Monitoring

In recent years, technological advancements have substantially transformed diabetes management, offering increasingly sophisticated tools for monitoring and treatment. Among these, continuous glucose monitoring (CGM) systems have represented a major step forward, particularly in pediatric T1D, where they are now widely considered as the standard of care. By assessing glucose concentrations in the interstitial fluid, CGM devices allow real-time monitoring of glycemic levels, providing users and healthcare providers with valuable information to support diabetes management [99].

Although CGM systems have been extensively validated in T1D, recent evidence has also highlighted their potential role in T2D, including in pediatric populations. Glucose sensors are being explored both as diagnostic tools, offering a less invasive alternative to the OGTT to evaluate response to glucose intake, and as monitoring instruments in people with established T2D, including individuals on insulin as well as those receiving non-insulin hypoglycemic therapies.

A recent study involving 39 overweight or obese youth with prediabetes evaluated the performance of CGM as a screening tool for T2D during an OGTT, comparing its results with conventional plasma glucose measurements. While CGM was generally well tolerated, its clinical applicability was limited by challenges in accurately identifying the timing of glucose ingestion and by the lack of standardized and recognized dysglycemia thresholds [100].

The benefits of CGM use in youth with established T2D are still under debate. A study exploring the feasibility and outcomes of CGM use in adolescents with T2D reported improvements in HbA1c after three months, along with increased patient satisfaction [101]. These beneficial effects were further supported by Chesser et al., who demonstrated enhanced Pediatric Quality of Life Inventory (PedsQL) scores in a cohort of adolescents and young adults with uncontrolled T2D (HbA1c > 7%) [102].

In contrast, Manfredo et al. found that CGM use in youth with T2D did not yield significant improvements in short- or long-term glycemic control, although it did contribute to promoting behavioral improvements [103].

7.3. Metformin

Metformin, combined with lifestyle modifications, is the first line treatment in pediatric subjects with T2D and HbA1c values < 8.5% [7]. Metformin belongs to a class of oral hypoglycemic agents known as biguanides, and is approved by FDA for pediatric use in children aged 10 years and older [104]. Metformin hypoglycemic effect relies on its ability to inhibit hepatic gluconeogenesis and lipogenesis while increasing fatty acid oxidation. It also acts by increasing glucose uptake and fatty acid oxidation in skeletal muscle and adipose tissue, decreasing glucose intestinal absorption and increasing its elimination, facilitating glucose utilization by intestinal cells and promoting GLP-1 secretion [104].

It can be administered with a starting daily dose of 500 mg that can be increased up to the maximum tolerated dose and not exceeding 2000 mg per day. Potential side effects of biguanides are transient abdominal pain, diarrhoea, and nausea, while their use is contraindicated in subjects with diabetic ketoacidosis, eGFR < 30 mL/min, cardiac insufficiency, respiratory insufficiency and in individuals who receive radiographic contrast materials [7].

Metformin is the most commonly prescribed oral medication for the treatment of pediatric T2D, as highlighted by the SEARCH study, which reported that 64.9% of enrolled youth with T2D received metformin monotherapy, while 70.4% were treated with metformin in combination with insulin [105]. Kelsey et al., examining clinical characteristics in a large cohort of adolescents with recent-onset T2D screened for the TODAY study, demonstrated that metformin therapy, when combined with proper diabetes education, improved short-term glycemic control and reduced cardiovascular risk factors [106].

Despite being the first-line therapy and one of the few medications available in youth-onset T2D, a significant limitation of metformin therapy is the high rate of therapeutic failure [107]. Bacha et al., analyzing data from the Pediatric Diabetes Consortium T2D Registry involving 276 youths with T2D, identified two predictive factors associated with successful long-term glycemic control using metformin alone: lower baseline HbA1c values and shorter duration of diabetes at the time of diagnosis [108]. These findings were further supported by an analysis of data from the TODAY study, which identified the HbA1c cutoff of 6.3% during metformin therapy as a useful indicator of high risk for therapeutic failure [109]. In this context, the advantage of metformin as a widely available and low-cost therapy must be balanced against its limited long-term durability, with therapeutic failure remaining a frequent outcome in adolescents.

Moreover, adherence to oral metformin regimens remains challenging for many adolescents. Venditti et al. identified key barriers to optimal adherence, including forgetfulness, inconsistent meal timing, irregular sleep patterns, and daily schedule disruptions. Conversely, the presence of strong family support and consistent daily routines emerged as effective strategies to enhance adherence and improve treatment outcomes among adolescents with T2D [110].

7.4. GLP-1 Receptor Agonists (GLP-1 RAs)

Recently, GLP-1 receptor agonists (GLP1-RAs) have emerged as a valuable therapeutic option for managing obesity and T2D in pediatric populations. In line with the latest ISPAD guidelines, these medications are recommended for adolescents unable to achieve or maintain HbA1c levels below 6.5% with first-line therapies [7]. GLP1-RAs facilitate weight loss and support β-cell function, thereby contributing to better regulation of blood glucose levels. Apart from pancreatic β-cells, GLP1-RAs exert their effects on multiple organs such as brain, heart, liver, stomach, and intestine with the result of favoring appetite suppression, delaying gastric emptying, improving heart function, and decreasing liver fat content [111]. FDA-approved molecules belonging to this class are liraglutide, semaglutide, exenatide, and dulaglutide, that can be administered in children aged 10 years and older. GLP1-RAs may be responsible for gastrointestinal side effects, such as nausea, vomiting and diarrhea and, less frequently, may cause dizziness, headache and dyspepsia [7]. Although GLP-1 receptor agonists offer superior efficacy in terms of weight reduction and glycemic control, their high cost and limited reimbursement in several healthcare systems currently restrict their widespread applicability in pediatric populations.

Miller et al. analyzed clinical and demographic features of a cohort of 11,380 preadolescents and adolescents treated with GLP-1 RAs, showing that the majority had a previous T2D diagnosis, a history of metformin use, or a BMI exceeding the 95th percentile [112].

The effects of GLP-1 RAs on glucose control and body weight were evaluated in a meta-analysis led by Dai et al., which included 14 randomized controlled trials involving 1262 adolescents with overweight/obesity and/or T2D. The results showed significant improvements in HbA1c levels, fasting glucose and body weight. Interestingly, liraglutide exhibited superior efficacy in terms of glucose control, while exenatide was more effective in promoting weight loss [113]. Another meta-analysis analyzing five studies involving a total of 415 children with T2D reached similar conclusions, also reporting negligible gastrointestinal side effects reported [114].

Additionally, a Korean study investigated the efficacy of once-weekly dulaglutide in five pediatric subjects with T2D, four of whom had previously been treated with metformin. After a 12-month follow-up, dulaglutide was found to significantly improve HbA1c levels [115].

7.5. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors act by promoting the excretion of glucose through the renal tubules, thereby lowering blood glucose levels independently of insulin secretion. According to the most recent ISPAD guidelines, their use should be considered when the therapeutic goal of maintaining HbA1c below 6.5% is not achieved, either as monotherapy or in combination with GLP-1 RAs [7,116].

Dapagliflozin, an SGLT2 inhibitor indicated for the treatment of diabetes, cardiac insufficiency and kidney disease in adults, has recently been investigated in pediatric populations and is currently approved by FDA and EMA for use in children aged 10 years and older [7]. A systematic review by Grube et al., including five studies on the use oral dapagliflozin in children aged 0 to 17 years, suggested good safety and efficacy profiles

for the drug [117]. A clinical trial involving 24 adolescents with T2D aged 10 to 17, treated with daily doses of 2.5, 5 or 10 mg of dapagliflozin, showed a dose-dependent increase in urinary glucose excretion and a reduction in mean fasting plasma glucose across all treatment groups, with only six subjects experiencing mild adverse effects [118]. The T2NOW clinical trial, which compared dapagliflozin with saxagliptin in youths aged 10 to 17 with T2D, found superior glycemic outcomes with dapagliflozin [119]. In the follow-up extension of the trial, 52 weeks of dapagliflozin therapy did not adversely affect growth, pubertal development, bone markers, or overall maturation up to one year after treatment discontinuation [120]. Nonetheless, available pediatric studies are short in duration, and long-term safety and durability of metabolic benefits remain to be established. In addition, cost-related barriers may limit real-world uptake, particularly outside well-resourced healthcare systems.

Canagliflozin, another SGLT2 inhibitor, was evaluated in a clinical trial involving a pediatric population randomized to receive either 100 mg or 300 mg daily. After 14 days of treatment, both doses showed effectiveness in reducing the mean 24-h renal threshold for glucose and increased urinary glucose excretion, while maintaining good tolerability and acceptability [121].

7.6. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

By inhibiting the degradation of incretin hormones, DPP-4 inhibitors enhance glucose-dependent insulin secretion and have become a valuable therapeutic option in adults with T2D. More recently, their potential applicability in the pediatric population has begun to receive increasing attention.

Tamborlane et al., in a randomized controlled trial involving 39 adolescents with T2D aged 10 to 18 years, compared linagliptin to placebo at once-daily doses of 1 mg and 5 mg over a 12-week period. The study reported dose-dependent improvements in HbA1c and fasting plasma glucose, with no adverse effects observed [122]. Similarly, sitagliptin, evaluated at single doses of 50, 100, or 200 mg in a trial including 35 adolescents with T2D, showed good overall tolerability [123]. It should be noted, however, that pediatric-specific data on DPP-4 inhibitors remain extremely limited, and most efficacy and safety considerations are extrapolated from adult studies.

7.7. Insulin Therapy

According to ISPAD guidelines, basal insulin is recommended alongside metformin as initial therapy for youth with T2D who present with an HbA1c $\geq$ 8.5% at diagnosis. Additionally, the initiation of basal insulin—and, if needed, short-acting insulin—is suggested when lifestyle modifications, metformin, SGLT-2 inhibitors, and GLP1-RAs fail to achieve HbA1c levels < 6.5%. In cases of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome at presentation, intravenous insulin followed by multiple daily injections of long- and short-acting insulin is indicated [7].

A randomized controlled trial evaluated whether early combination therapy with glargine and metformin, compared to metformin monotherapy, could preserve β-cells destruction—a key aspect of T2D pathophysiology. The study, which enrolled 91 overweight or obese youths with impaired glucose tolerance or recently diagnosed T2D, showed that neither approach arrested progressive β-cell damage [124].

Concerns regarding hypoglycemia often arise with insulin use in T2D. Shahid et al. evaluated the real-world impact of hypoglycemia in a cohort of 22 adolescents with T2D receiving insulin therapy. Over a 3-month follow-up period, nine episodes of hypoglycemia were recorded, of which only five were symptomatic. Interestingly, a positive correlation was observed between the frequency of hypoglycemia and lower BMI [125].

Given the substantial advances in diabetes technology, closed-loop insulin delivery systems have already demonstrated clinical benefits in adults with T2D [126]. However, further research is needed to assess their efficacy and safety in pediatric populations with T2D.

7.8. Bariatric Surgery

Given the evidence that bariatric surgery can lead to improvement or even remission of T2D in adults, its potential application in pediatric populations has become a topic of interest within the scientific community [127]. Bariatric surgery is currently recommended for youth with T2D and a BMI $\geq$ 35 kg/m^2 or $\geq$120% of the 95th percentile, who are over 12 years of age [7]. Even though data on long-term effects of bariatric surgery remain limited, researchers have also hypothesized a possible role for bariatric surgery also in T2D prevention [128].

Inge et al., in a clinical trial comparing medical therapy and bariatric surgery in severely obese adolescents with T2D, found that surgery was more effective in improving glycemic control, promoting weight loss, and reducing comorbidities. However, 23% of participants undergoing surgery required additional surgical interventions during the two-year follow-up period [129].

A study focusing on laparoscopic sleeve gastrectomy in 64 pediatric patients with T2D reported significant reductions in HbA1c and random blood glucose levels following the procedure [130]. Similarly, Carbajo et al. observed a 100% remission rate after five years in a cohort of obese adolescents who had undergone one-anastomosis gastric bypass. Notably, only one case of iron deficiency anemia was reported, with no instances of malnutrition or growth impairment—supporting the relative safety of the procedure in selected patients [131].

8. Conclusions

Youth-onset T2D is rising worldwide, with evidence from large studies showing a rapid increase over the past two decades. Early-onset disease carries a more aggressive course, with higher rates of complications such as nephropathy, retinopathy, and MAFLD, and is strongly linked to obesity, minority ethnicity, and socioeconomic disadvantage. These findings underline the urgent need for prevention, timely diagnosis, and effective interventions to reduce the long-term burden.

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