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Review Article

Diabetes Mellitus - Modern Approaches to the Diagnosis

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Abstract

The incidence of type 1 diabetes (T1D) continues to rise, with 18% of new diagnoses occurring in children aged 9 years and younger. In 2014, Current Diabetes Reports published a review of diabetes care in young children with T1D, highlighting the challenges of T1D care, current research in this population, and opportunities for future research and clinical care. Since 2014, numerous changes in the clinical presentation of diabetes have impacted young children. Research has reinforced the importance of maintaining glucose levels within a narrow target range for young people with T1D of all ages

Kew Words: diabetes mellitus; patients; children

Introduction

The incidence of type 1 diabetes (T1D) continues to rise, with 18% of new diagnoses occurring in children aged 9 years and younger [1]. In 2014, Current Diabetes Reports published a review of diabetes care in young children with T1D, highlighting the challenges of T1D care, current research in this population, and opportunities for future research and clinical care [2]. Since 2014, numerous changes in the clinical presentation of diabetes have impacted young children. Research has reinforced the importance of maintaining glucose levels within a narrow target range for young people with T1D of all ages [3]. Current glycemic goals recognized by the American Diabetes Association (ADA) and the International Society of Pediatric and Adolescent Diabetes (ISPAD) recommend that young children maintain HbA1c levels < 7.0% whenever possible and without risk of severe hypoglycemia [3, 4]. In addition, young children with T1D are among the fastest adopters of diabetes technology, including insulin pumps and continuous glucose monitors [5, 6], with significant implications for both glycemic control and psychosocial functioning in parents and children. However, recent data from the T1D Exchange showed a mean A1c of 8.2% in children under 6 years of age [5], suggesting that this age group would benefit from increased attention and interventions to support diabetes management. Many of the challenges of diabetes management in young children identified in the 2014 article still remain [2]. Parents continue to bear the primary responsibility for diabetes management in young children. Diabetes management is complicated by the normative development of toddlers and preschoolers, including rapid physical and neurological development, difficulty verbalizing thoughts and feelings, frequent and unpredictable physical activity, picky eating, and behavioral problems and fears [2]. In addition, many clinical management programs for T1D do not offer individualized patient education specifically designed to meet the needs of young children. Given these unique management and developmental aspects, parents of young children are increasingly becoming targets of behavioral interventions. In the United States, some of these new intervention trials were funded in response to a 2013 Request for Applications from the National Institutes of Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) calling for interventions to improve diabetes management in families of young children with T1D [7]. Type 2 diabetes mellitus (T2D), previously known as non-insulindependent diabetes or adult-onset diabetes, is a disorder resulting from insulin resistance and relative (rather than absolute) insulin deficiency in the absence of autoimmune destruction of beta cells. It is a polygenic disorder involving the interaction of genetic and environmental risk factors that lead to the underlying pathophysiology of hepatic and muscle insulin resistance and subsequent beta-cell failure. Most patients with the disorder are obese, and T2DM often remains undiagnosed for many years while the patient progresses asymptomatically through earlier stages of hyperglycemia known as "prediabetes." Prediabetes includes impaired fasting glucose (IFG; fasting glucose level of 5.6 to <7 mmol/L) and impaired glucose tolerance (IGT; 2-hour glucose level of 7.8 to <11.1 mmol/L on an oral glucose tolerance test). T2DM in children and adolescents appears to be a more aggressive disease than late-onset T2DM. Progression from IFG or IGT to T2DM in children and adolescents does not necessarily progress linearly over time and occurs morrapidly than in adults, typically within 12–21 months. 3–5 T2DM and prediabetes' with dysregulation of glucose or insulin metabolism are inextricably linked with obesity and are increasingly seen in young people attending specialist obesity services

Physiological problems

Early onset of T1D places young children at increased risk for neurocognitive sequelae. Using both comprehensive neurocognitive testing and high-resolution structural magnetic resonance imaging (MRI), Mauras and colleagues found that young children with T1D did not differ from their peers without T1D on measures of cognitive and executive function, but children with T1D exhibited differences in brain growth [8]. Slower brain growth was associated with higher cumulative hyperglycemia and glucose variability among young children with T1D [8]. Another study found similar structural findings but also found subtle cognitive differences in children with T1D compared with children without T1D, including participants who were newly diagnosed with T1D (T1D duration in the study ranged from 1 month to 8 years). This study also found a trend toward an association between DKA and a history of severe hypoglycemia and IQ scores. This research suggests that glycemic controls may have detrimental effects on the developing brain [9]. In a longitudinal study, Kirchhoff and colleagues observed differences in cognitive function between young adults with T1D and their age-matched relatives without diabetes, with cognitive decline associated with both increased hyperglycemia and earlier age at T1D onset, which may pose challenges to the cognitive developmental trajectory [10,11]. Young children are at increased risk of diabetic ketoacidosis (DKA) at T1D onset [12, 13]. DKA at T1D diagnosis has been associated with higher A1c levels over time and a negative impact on cognitive function [14, 15]. Hey and colleagues found that DKA when diagnosed in young children was associated with lower cognitive scores as assessed by IQ tests, the Detectability and Commission subtests of the Conners' Continuous Performance Test II, and the Dot Locations subtest of the Memory Scale for Children (Mtime since diagnosis = 2.8 years) [15]. Developing or improving public health education programs to help families and primary care physicians recognize early signs of T1D and DKA may be helpful in reducing the negative impact on cognitive development in young children [16]. Given the developmental expectations of young children, including limited language abilities and unpredictable eating and activity patterns, there is often more concern about hypoglycemia than in older children with T1D [17]. In addition, young children often take smaller, more accurate doses of insulin and have higher insulin sensitivity than older youth [2]. Recent studies have shown that parents may intentionally keep their young children's blood glucose levels higher to avoid low blood glucose and the adverse effects of hypoglycemia [17,18]. Parental fear of hypoglycemia may interfere with achieving updated glycemic targets that recommend narrower glycemic ranges [19], which is problematic given the aforementioned research linking chronic hyperglycemia to negative cognitive impacts. As noted previously, since the 2014 review, the recommended A1c target for young children (children ≤ 6 years) has changed from < 8.5 to < 7%, reflecting the current target for all people with type 1 diabetes regardless of age. The A1c target was changed to avoid long-term vascular complications, hyperglycemia, and hypoglycemia to ensure that children have the best chance of living a healthy life with minimal diabetes-related complications, especially as they approach adulthood. While this more conservative A1c target may be more challenging for families to achieve, the International Society of Pediatric and Adolescent Diabetes notes that the lower target is intended to be an ambitious goal because people in the lower glycemic target range tend to have lower A1c levels.

Nutrition

Diet quality and parental monitoring of mealtime behavior are important aspects of diabetes management in young children. Research has shown that although parents of young children generally know what healthy eating entails, they do not always follow healthy eating patterns due to barriers to feeding and mealtimes. One nutrition study assessing breakfast diet quality in a sample of young children with T1D found that less than half of the children met dietary recommendations for protein and fat (46% each), and even fewer met dietary recommendations for carbohydrates (23%). Parent-identified challenges to feeding their child with T1D a healthy diet may include (1) the cost and availability of healthy foods, (2) picky eating habits in young children, (3) a desire to maintain the same food options as siblings and peers, and (4) difficulty getting young children to try new foods. Not surprisingly, mealtime behaviors can be stressful for parents. Younger children are associated with more frequent problematic mealtime behaviors, which are associated with higher glycemic control in young children with type 1 diabetes. Parents also report concerns about administering insulin before meals because appetite changes, especially in this age group of young children. In recent years, research has identified useful techniques used during mealtimes to maintain glycemic control within the normal range. Seccold and colleagues found that glycemic control targets were more likely to be met when children were given insulin before meals and followed a consistent mealtime schedule rather than snacking throughout the day. Implementing effective approaches, such as providing support to parents of young children with problematic eating behaviors through trained counselors or parent coaches, focusing on the nutrient composition of children's foods, and maintaining mealtime routines, may also help improve glycemic control in young children.

Physical activity

Ensuring that physical activity is performed in a safe and healthy manner is an additional challenge in the management of T1D in young children, as parents may be concerned about hypoglycemia caused by physical activity. Although there has been minimal research on physical activity in young children, physical activity is beneficial for maintaining healthy weight and glycemic control in older children and adolescents with T1D. The Physical Activity Guidelines Advisory Committee's national guidelines recommend that most young children engage in light, moderate, and/or vigorous activity for 3 hours per day, and ISPAD recommends that children with T1D engage in the same amount of exercise as children in the general population. However, Tully and colleagues (2018) examined physical activity in a small sample of young children aged 3 to 7 years with T1D and found that this sample spent a greater proportion of the day being sedentary and were less active than published samples of young children without T1D.

Psychosocial functioning Treatment of type 1 diabetes in young children is often described as comprehensive and relentless, and parents of children with type 1 diabetes endorse significant burdens associated with type 1 diabetes treatment [20]. Harrington and colleagues analyzed survey data from 597 young children under 7 years of age with type 1 diabetes, finding that the following burdens were endorsed by more than half of all parents: (1) worrying about low blood sugar, (2) worrying about future complications, (3) feeling upset when diabetes treatment is "not on track," and (4) negative impact on sleep quantity and quality [21]. These burdens can have negative impacts on both family functioning (e.g., family well-being, family conflict) and individual parental psychosocial functioning (e.g., mood, stress, quality of life). Research suggests that parental adjustment is associated with type 1 diabetes treatment outcomes in young children and quality of life [22]. In one study, higher levels of parenting stress were associated with lower diabetes-related quality of life in both parents and children [23]. Additionally, Jazer and colleagues found that sleep quality in young children with T1D was associated with parental sleep and well-being [24]. Thus, parental psychosocial functioning appears to be a key factor in the well-being of young children with T1D. Due in part to developmental limitations for child self-report in young children, studies to date have relied primarily on parent report of the child's psychosocial functioning, with fewer studies examining adjustment or quality of life in young children themselves. In one study, parents rated young children with T1D as having lower health-related quality of life compared to a control group of children without T1D [25].

However, in other studies, parental ratings have provided evidence of diabetes-related resilience, demonstrating no difference in quality of life or health-related functioning between young children with and without type 1 diabetes [26]. Developmentally appropriate measures are needed to assess parent and child functioning in this unique population of young children, and some new measures have emerged in recent years. For example, Enlow and colleagues developed and validated the Parent and Preschooler Diabetes Adjustment Scale to assess caregiver adaptation to the challenges and demands of raising a young child with type 1 diabetes [27].

Individual characteristics of parents

Unlike the treatment of type 1 diabetes in older children, effective treatment of type 1 diabetes relies solely on parents or other caregivers. Individual characteristics of parents are thought to influence how parents cope with the challenges of managing type 1 diabetes. Some of these characteristics are modifiable and amenable to intervention (e.g., social support, parenting style, parental coping, child behavior problems), whereas others are much less amenable to intervention (e.g., sociodemographic characteristics). A number of studies, discussed below, provide evidence suggesting that the inclusion of individual characteristics of parents (i.e., sociodemographic factors, social support, parenting, and premorbid psychiatric problems) is relevant to the model.

Sociodemographic factors

Most studies examining associations of parental sociodemographic characteristics (i.e., race, ethnicity, marital status, socioeconomic status) with T1D outcomes have focused on older youth, but a few have examined YC-T1D. In one study, YC-T1D with married parents, compared with single parents, were more likely to have higher blood glucose (BG) levels in target range and better glycemic control. A study examining parents of youth diagnosed with T1D, including YC-T1D, found that receipt of public assistance, single parent marital status, and caregiver education less than high school predicted future diabetes-related emergency department (ED) hospitalizations. When controlling for racial differences, poorer glycemic control was better explained by lower socioeconomic status and single parent marital status in older youth with DM. In addition to influencing T1D outcomes, demographic variables also appear to influence parental functioning. The only YC-T1D study of this type found that single mothers and mothers of non-white children with T1D, including YC-T1D, endorsed significantly worse physical and psychological well-being. Taken together, parental marital status, educational attainment, socioeconomic status, and racial/ethnic minority status appear to be associated with parental coping, T1D management behaviors, and T1D outcomes. Although these studies were cross-sectional and causality cannot be implied, certain sociodemographic characteristics may be considered risk or protective factors for influencing parental T1D coping and management behaviors and outcomes, as reflected in our model. Social support

Social support influences how parents of older children cope with type 1 diabetes [28–30], although empirical studies examining this construct in parents of children with type 1 diabetes (YC-T1D) are limited. Qualitative studies show that parents report feelings of isolation shortly after diagnosis [31, 32]. Mothers may be particularly prone to these feelings when children are younger than 4 years [31, 32]. In another qualitative study, parents of children with type 1 diabetes also described isolation when caring for children with type 1 diabetes and noted that family and friends had minimal understanding of type 1 diabetes management [33]. More research examining the impact of social support on type 1 diabetes management and outcomes (e.g., glycemic control, incidence of hypoglycemic events) is needed. However, given existing research that suggests that parents of children with type 1 diabetes experience feelings of isolation and misunderstanding from family and friends, minimal social support is considered a risk factor in our model and may be a constructive intervention point [34, 35].

Parenting styles

Several studies have examined the associations between parenting styles and T1D outcomes. A review of studies linking parenting styles to glycemic control and adherence concluded that higher family cohesion, parental warmth, and an "authoritarian" parenting style were associated with better T1D health outcomes, whereas higher overall family conflict, parental restriction, criticism, and an "authoritarian" parenting style predicted worse outcomes [36]. A study of parenting behavior in 35 families of children (aged 2–8 years) with T1D found significant positive correlations between parents' use of ineffective/coercive parenting strategies (e.g., persuasion and interruptible commands) and deviations in children's dietary intake and glycemic control [37]. Given the association between parenting style and T1D outcomes, this construct is considered a risk/protective factor and a potential intervention point in our model.

Sleep disruption

Implementing nighttime blood glucose monitoring and managing type 1 diabetes may impair sleep quality and quantity in parents of children with YC-T1D [38]. In a study of 71 parents of children with YC-T1D, parents who reported more frequent nighttime blood glucose monitoring also endorsed higher anxiety and increased parenting stress [39]. In another study, the same group found that 79% of parents reported that nighttime blood glucose monitoring disrupted their own sleep, although glycemic control was not associated with either the number of nighttime blood glucose monitoring or sleep disruption [40]. A larger study of 134 parents of children with YC-T1D found that parents reported less sleep than recommended and more sleep problems compared with standardized norms for healthy adults, and that poorer sleep quality was associated with worse glycemic control and greater fear of hypoglycemia [38]. It is unclear whether there is a direct relationship between parental sleep quality and glycemic control. It is possible that parental sleep disruption may enhance glycemic control by promptly interrupting glycemic excursions or hinder glycemic control by reducing attention to T1D demands during waking hours. Thus, although it is unclear whether there is a direct relationship between sleep quality and glycemic control, disrupted sleep may be considered a risk or protective factor for T1D outcomes, as supported by our model.

Type 1 diabetes therapy

Start of therapy

Insulin therapy should be started as soon as type 1 diabetes is diagnosed, as the child's metabolism can deteriorate rapidly. A specialist diabetes team with experience in children should be called in as soon as possible.

Treatment goals

Initial treatment and long-term care should be provided by a specialist paediatric diabetes team, continuously from ages 1–18 years, and in some cases up to 21 years. Specialist care has been shown to result in fewer days spent in hospital and readmissions, lowe HbA1c values, better disease control and fewer complications.

Team management of type 1 diabetes should include:

Insulin therapy**,** Individualised metabolic self-monitoring, Age-appropriate structured education, and Psychosocial support for affected families. The following medical goals are at the forefront of the care of children with diabetes: prevention of acute metabolic disturbances, prevention of diabetes-related microvascular and macrovascular secondary diseases and normal physical development (growth in height, weight gain, onset of puberty). The

patient's psychosocial development should be as little affected as possible by diabetes and its therapy, and integration and inclusion in kindergarten, school and vocational training should be ensured. Individual therapy goals should be formulated jointly with the child or adolescent and their family (HbA1c value, target ranges for blood glucose levels, behavioral changes that accompany a risky lifestyle, integration efforts, etc.). The HbA1c target of <7.5% was changed in 2018 by ISPAD to a new target of <7.0%, the ADA recommendations are still <7.5%, while the English NICE guidelines suggest a target of <6.5%. An additional parameter for assessing the metabolic state is the time spent in the target range (TIR = time in range). As a rule, the target range is defined as 70–180 mg/dL. An individual goal for the duration of TIR is recommended. Preprandial glucose values should be between 70 and 130 mg/dL (4.0–7.0 mmol/L), and postprandial values - from 90 to 180 mg/d (5.0–10.0 mmol/L). Before bedtime, values of 80–140 mg/dL (4.4–7.8 mmol/L) are recommended the average frequency of glucose monitoring should be 5 to 6 times a day, but in individual cases it can be significantly higher.

Continuous treatment of type 1 diabetes

Continuity of diabetes treatment in a child or adolescent with diabetes, both over time and at different stages of life and development, is crucial to ensure a metabolic situation as close to normoglycemia as possible and free psychosocial development.

Treatment of diabetes during physical activity/sport Regular exercise improves metabolic control and should be a given for children and adolescents with diabetes. Regular swimming has been shown to significantly reduce HbA1 levels. Since blood glucose levels are reduced by energy consumption during physical activity, the risk of hypoglycemia increases. The strongest predictor of hypoglycemia is the initial glucose value, which should be at least 120 mg/dL (6.6 mmol/L); otherwise, additional carbohydrates may be required. Individual therapy plans with insulin dose adjustments and appropriate behavioral rules should be created for each patient.

Insulin treatment

Standard treatment for children with type 1 diabetes is intensified insulin therapy. All insulin therapy should be given as part of a comprehensive diabetes care and with family support. Insulin therapy should be individually tailored to each child. For pediatric patients, human insulin or insulin analogues should be used. For intravenous insulin therapy, regular insulin should be used.

Rapid-acting insulin and insulin analogue There are differences between rapid-acting human insulin and rapid-acting insulin analogues in the onset and duration of action in children, and they can be used flexibly for prandial replacement in children depending on th situation. Rapid-acting insulin analogues should be used for insulin pump therapy.

Long-acting insulin and insulin analogs Both NPH insulin and long-acting insulin analogs can be used alone for routine insulin replacement in children.

Insulin pump therapy

Insulin pump therapy for children and adolescents is safe and effective. It has a positive effect on the incidence of hypoglycemia, ketoacidosis and metabolism. Especially in young children, insulin pump therapy allows better regulation of insulin dose, especially at night, thereby helping to prevent hypoglycemia. Insulin pump therapy is recommended for the following indications Young children, especially neonates, infants and preschoolers, Children and adolescents with marked increases in blood glucose in the early morning hours (dawn phenomenon), Severe hypoglycemia, recurrent hypoglycemia and nocturnal hypoglycemia (despite intensifie conventional therapy = ICT), HbA1c value outside the target range (despite ICT), Severe fluctuations in blood glucose despite ICT, regardless of the HbA1c value, Incipient microvascular or macrovascular secondary diseases Limitation of quality of life due to previous insu therapy Children with severe fear of needles, Pregnant adolescents (ideally before conception if pregnancy is planned), and Competitive athletes.

Demographics

The prevalence of T2DM in children and adolescents has increased worldwide in parallel with rising obesity rates. [41–43] In Australia, the incidence of T2DM in patients aged 0–17 years was approximately two per 100,000 person-years, with the annual adjusted crude incidence increasing by 27% between 1990 and 2002. [44] Early-onset T2DM most commonly occurs in adolescence and rarely earlier. Plasma insulin levels rise steadily from a prepubertal baseline, peaking at puberty and then returning to prepubertal levels by the third decade of life.[45] Insulin sensitivity declines by approximately 30% during puberty.[46] It is therefore no coincidence that this physiological, pubertal-related insulin resistance coincides with the peak age of early onset of T2DM, and that prepubertal T2DM is much less common. Among the 1.2 million young people in the SEARCH for Diabetes study, there were no children aged 4 years or younger with T2DM, and only 19 cases of T2DM were reported in children aged 5–9 years between 2002 and 2003.

Diagnosis of Type 2 Diabetes Mellitus in Children and Adolescents

The presentation of T2DM ranges from asymptomatic hyperglycemia in a healthy child, perhaps detected on random testing, to ketoacidosis in up to 25% of patients. These individuals are also at risk for hyperglycemic hyperosmolar nonketotic state, which is associated with high mortality. The diagnosis of T2DM in young people requires a diagnosis of diabetes followed by classification of the diabetes type. It is worth noting that the prevalence of T1DM is approximately 10-fold higher than the prevalence of T2DM in most pediatric populations. Therefore, the diagnosis of T1DM should be made in the acute setting if there is any doubt regarding the subclassifications of diabetes. Delay in treatment of T1DM in young people increases the risk of diabetic ketoacidosis. Less common causes of diabetes, such as monogenic diabetes due to mutations in hepatocyte nuclear factor 4 alpha (HNF4A) and HNF1A (previously known as maturity-onset diabetes of the young) and maternally inherited mitochondrial disorders, should be considered in those presenting in adolescence, especially if there is strong familial clustering of diabetes. There are currently four generally accepted ways to diagnose diabetes according to the recommendations of the International Society of Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association, based on the measurement of hyperglycemia and the presence of symptoms. Several clinical characteristics such as age, ethnicity, obesity, family history of T2DM and the presence of islet cell antibodies are important factors in differentiating T1DM from T2DM.

Lifestyle changes

Although lifestyle changes (diet and exercise) are critical for the management of T2DM, less than 10% of young adults with T2DM achieve their glycemic goals with lifestyle changes alone. This may be due to high rates of loss to follow-up, factors related to socioeconomic status, and high rates of comorbid depression. Involvement of an experienced dietitian is essential. Dietary recommendations may begin with avoiding sugar-sweetened sodas and juices, increasing fruit and vegetable intake, portion control, and changing family eating behaviors, such as eliminating junk food from the household. It is well established that regular exercise without calorie restriction or weight loss is associated with reduced insulin resistance and improved insulin sensitivity in overweight or obese young adults, regardless of T2DM status. Exercise recommendations, such as 60 minutes

of moderate-intensity exercise per day and reducing screen time to less than two hours per day, are important parts of a diabetes management plan. However, there is little evidence regarding the effectiveness of lifestyle interventions in young people with T2DM. Although observational studies suggest that higher activity levels are associated with better glycemic control in young people with T2DM, the only large-scale intervention trial to evaluate lifestyle interventions in 699 young people with T2DM did not support this finding. The study found that 24 months of intensive lifestyle interventions (200–300 minutes of moderate-to-vigorous exercise per week and 1200–1500 calories daily) in addition to metformin monotherapy did not improve long-term glycemic control over 24 months of followup. Similarly, cardiovascular risk factors such as dyslipidemia and inflammatory markers were not improved by lifestyle interventions in addition to metformin monotherapy.

Normalization of glycemia young people with confirmed T2DM are typically treated with metformin and/or insulin therapy, determined by symptoms, severity of hyperglycemia, and presence of ketosis. Metformin monotherapy is the treatment of choice for those who are metabolically stable (glycosylated hemoglobin [HbA1c] <9%), starting at 500 mg daily and titrating up to 1000 mg twice daily over four weeks.[417] Metformin reduces hepatic gluconeogenesis, increases insulin-stimulated glucose uptake into fat and muscle, and does not usually cause hypoglycemia.[48] The initial anorexic effect may also contribute to weight loss.45 Long-term metformin use is associated with a 1–2% reduction in HbA1c. Insulin therapy is required for those with HbA1c >9%, severe hyperglycemia (serum glucose >15 mmol/L) or ketosis/ketoacidosis on admission (serum ketones ≥1.0 mmol/L and/or serum pH <7.3 ± bicarbonate <15 mmol/L)[49]. Different insulin regimens, such as basal insulin (initial dose 0.25–0.5 U/kg) or prandial insulin, are effective in achieving metabolic control. Although there are no data to date comparing different insulin regimens in adolescents, this needs to be tailored to the patient's needs. Studies in adults have shown that the basal glargine regimen is as effective as prandial insulin lispro, with the added benefits of simplicity and a lower risk of hypoglycemia. It is worth noting that although starting insulin injections will improve glycemic control and increase diabetes awareness, early insulin therapy may also result in poorer treatment adherence, resulting in less patient contact and worse long-term diabetes control. Therefore, the decision to initiate insulin therapy should be made carefully, balancing the medical benefits with the adolescent and family dynamics. Other available oral antidiabetic agents are either not approved for use in individuals under 18 years of age or are still being studied. Sulfonylureas are associated with hypoglycemia and greater weight gain (compared to metformin) and may potentially accelerate the loss of beta-cell function.[50] Other medications such as thiazolidinediones, α-glucosidase inhibitors, incretin mimetics, and dipeptidyl peptidase-4 (DPP-IV) inhibitors, although promising, require further study as long-term safety data are lacking and they are not approved for use in individuals under 18 years of age. The overall goal of initial treatment is to achieve HbA1c <6.5%. Home blood glucose monitoring (HBG) training is needed to monitor fasting and postprandial blood glucose levels to achieve target BG (4–8 mmol/ L) and HbA1c ranges (<6.5%). A multidisciplinary approach involving pediatric and adult endocrinologists, diabetes specialists, dietitians, social workers, and psychologists, as well as lifestyle modification, is needed to achieve this goal.

Management of comorbidities

Young adults with newly diagnosed T2DM have a high prevalence of diabetes-related complications and obesity at diagnosis[51]. Reports show the presence of hypertension in 10–32% of patients, microalbuminuria in 14–22%, retinopathy in 9.3%, dyslipidemia in 85%, and non-alcoholic fatty liver disease in 22% when T2DM is diagnosed in individuals younger than 30 years[52]. Therefore, more aggressive screening for microvascular and macrovascular complications should be performed at diagnosis and regularly thereafter than in young adults with T1DM. Other comorbidities associated with obesity and insulin resistance are also common, such as polycystic ovary syndrome in women, obstructive sleep apnea syndrome (OSA), psychiatric illness, and orthopedic problems. The prevalence of OSA may be as high as 60% in obese young adults [53], with the risk of OSA increasing by 12% for every 1 kg/m2 increase in body mass index (BMI). [54] Similarly, neuropsychiatric comorbidity is common, occurring in 26% of young people with T2DM, and up to 14.7%, many of whom are girls, have depressive symptoms. [55] Adolescents with T2DM reported greater depression and had lower quality of life scores compared with adolescents with T1DM. [56] Depressed mood is also associated with poorer glycemic control, more emergency department visits, and poor adherence to diabetes treatment recommendations. [57] Therefore, screening for these issues at diagnosis of T2DM is essential, and ongoing annual surveillance is required.

Acute complications

Diabetic ketoacidosis

Diabetic ketoacidosis is a potentially life-threatening condition. It should be treated promptly in a specialized facility by a diabetology team experienced in treating children. There should be a written treatment plan for diabetic ketoacidosis in children and adolescents.

Biochemical criteria for ketoacidosis include:

- pH<7.3,
- Bicarbonate<15 mmol/L,
- Hyperglycemia>11 mmol/L,>200 mg/dL, and Ketonuria and serum ketones.
- Ketoacidosis is classified into 3 severity grades:
- Mild (pH<7.3; bicarbonate<15 mmol/L),
- Moderate (pH<7.2; bicarbonate<10 mmol/L), and Severe (pH<7.1; bicarbonate 5 mmol/L).
- The following treatment goals should be achieved in ketoacidosis:
- Stabilization of the cardiovascular system with an initial volume bolus using isotonic saline,
- Followed by slow balanced infusion therapy and electrolyte replacement,
- Slow normalization of blood glucose levels,
- Balancing acidosis and ketosis,
- Avoiding complications of therapy (cerebral edema, hypokalemia), and Diagnosis and therapy of provoking factors.

During treatment of severe diabetic ketoacidosis, clinical observation and monitoring should be performed at least hourly. Patients with severe ketoacidosis and increased risk of cerebral edema should be treated immediately in an intensive care unit or a specialized diabetes unit with comparable equipment by a diabetology team experienced in paediatrics. Patients with suspected cerebral edema should be treated in an intensive care unit in collaboration with an experienced diabetology team. Patients with obvious signs of cerebral edema should be treated with mannitol or hypertonic saline until further diagnostic measures (MRI) are initiated. There are case reports or case series showing therapeutic efficacy in symptomatic cerebral edema with early intravenous mannitol (0.5–1 g/kg) over 10–15 min and repeated if necessary (after 30 min).

Hypoglycemia

Hypoglycemia is the most common acute complication in diabetes [Diabetes Control and Complications Study Group 1994]. According to the latest recommendations of the Hypoglycemia Study Group

[International Hypoglycemia Study Group (2017)], a distinction is made between blood glucose values in the following groups: Stage 1: <70 mg/dL (3.9 mmol/L), requires attention and treatment, if necessary, Stage 2: <54 mg/dL (3 mmol/L), always requires immediate treatment and Stage 3: with impaired consciousness, always requires immediate treatment. Mild hypoglycemia can be corrected by the patient with fast-acting carbohydrates. Severe hypoglycemia may only be corrected with external assistance due to associated limitation or loss of consciousness. In addition to loss of consciousness, severe hypoglycaemia may also be accompanied by a seizure. Children and adolescents with type 1 diabetes should always carry fast-acting carbohydrates in the form of dextrose or similar substances to be able to act immediately in the event of mild hypoglycaemia and thus prevent severe hypoglycaemia. Parents or other primary caregivers should be instructed in the use of glucagon injections or other emergency measures. Caregivers, for example in day care centres and nurseries, and teachers in schools should also be instructed in the risks and treatment options for hypoglycaemia. In case of hypoglycaemia perception disorder, a temporarily higher blood glucose level should be set [Australasian Paediatric Endocrine Group et al. 2005; Clarke et al. 2008]. The use of a continuous glucose monitoring system with a hypoglycaemia stop function should also be considered.

Nutritional recommendations

Nutrition counseling for children and adolescents with diabetes is an important part of a comprehensive treatment plan and should include the following components: Information about the effectiveness of carbohydrates, fats and proteins in relation to blood glucose levels, Promotion of healthy eating habits at family meals and in community settings: regular, balanced meals and snacks (fruits, vegetables, raw vegetables), prevention of eating disorders (especially uncontrolled, binge eating) and prevention of overweight, Consideration of cultural eating habits Sufficient energy for age-appropriate growth and development, Working towards a normal BMI, which includes regular physical activity, A good balance between energy intake and energy use according to insulin profiles, Nutrition during illness and exercise, and Reduction of the risk of cardiovascular disease. Nutritionists (dietitians/ecotrophologists) with in-depth knowledge of child and adolescent nutrition and insulin therapy should provide such advice Nutritional recommendations should include all dietary components and their proportion in daily energy intake [German Society for Nutrition/Deutsche Gesellschaft für Ernährung (DGE) 2015].

Conclusion

In summary, childhood diabetes mellitus is a multifaceted disease that requires a multidisciplinary approach to diagnosis and treatment. With due attention to early diagnosis, individualized treatment, lifestyle, and psychosocial support, the quality of life of children with diabetes can be significantly improved and the risk of developing serious complications can be reduced. This also highlights the need for further research in this area to improve prevention and treatment methods

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