Acute and Chronic Adverse Outcomes of Type 1 Diabetes

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KEYWORDS

• Type 1 diabetes • Complications • Diabetic ketoacidosis • Severe hypoglycemia • Macrovascular • Microvascular

KEY POINTS

- The Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that improving glycemic management is associated with lower rates of complications.
- Acute complications can occur in youth and adolescents, and chronic complications can occur as early as the adolescent period.
- Guidelines exist for screening and management of complications.
- New technologies, including continuous glucose monitors and insulin pumps, have the potential to better understand/address glycemic patterns and decrease rates of both acute and chronic complications.

INTRODUCTION

Despite significant advances in diabetes treatment and technology in recent history, type 1 diabetes (T1D) continues to be associated with significant complications, both acute and chronic. In the acute setting, complications associated with T1D include hypoglycemia and diabetic ketoacidosis (DKA). Chronic complications can be categorized as either microvascular or macrovascular. Microvascular complications of T1D most commonly manifest as retinopathy, neuropathy, and nephropathy,[1] while macrovascular complications include various types of cardiovascular disease such as coronary artery disease, cerebrovascular disease, and peripheral vascular disease.[2]

The Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that interventions aimed at maintaining glucose levels as close to the non-diabetic range as safely possible were associated with lower rates of both microvascular and macrovascular

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Endocrinol Metab Clin N Am ■ (2023) ■–■
https://doi.org/10.1016/j.ecl.2023.09.004 **endo.theclinics.com**

complications.[3] However, achieving target hemoglobin (Hb)A1c levels remains a difficult challenge at any age, especially during youth and young adulthood.[4] As the prevalence of T1D continues to increase, concern for complications also rises.[2] Despite recent improvements in diabetes care, T1D continues to be associated with risk for substantial medical burden.[1] This article reviews the acute and chronic complications that are seen in youth and adults with T1D.

ACUTE COMPLICATIONS

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is one of the most serious acute complications of T1D and is classically characterized by the triad of hyperglycemia, metabolic acidosis, and hyperketonemia.[5] Typical diagnostic criteria include elevated glucose of greater than 250 mg/dL, ketones detected in serum or urine, and metabolic acidosis (serum bicarbonate <18mEq/L and/or pH < 7.30).[6] DKA can be further classified as mild, moderate, or severe based on the severity of a patient's metabolic acidosis and the presence of altered mental status.[7] DKA typically presents with symptoms of nausea, vomiting, abdominal pain, declining mental status, and altered breathing patterns.[8] Patients may also report a history of polyuria, polydipsia, polyphagia, weakness, malaise, or lethargy.[8]

Approximately 30% of people with new-onset T1D present with DKA, with higher rates in children compared to adults.[5] In adults with known T1D, the incidence of DKA ranged from 0 to 263 per 1000 person-years (PYs) and prevalence ranged from 0 to 128 per 1000 people.[6] In children with established T1D, data published in 2015 from a German database of 31,330 individuals showed that in those aged 0.5 to 20 years the rate of ketoacidosis is 4.82 per 100 PYs.[9]

There are several established risk factors for DKA in people with previously diagnosed T1D. Non-modifiable risk factors include age, socioeconomic status, sex, and ethnicity.[9] Risk of DKA increases after early childhood (>5 year old) and then plateaus between 13 and 25 year old. After 25 years, the risk of DKA decreases as age increases.[9] People with socioeconomic disadvantages and females have also been shown to be at higher risk for DKA.[9] Modifiable risk factors for DKA include prior DKA admissions, elevated HbA1c, co-morbid psychiatric disorders, and acute infections.[9] The practice setting where people with T1D receive care may also be associated with risk of DKA. Individuals who are cared for in settings with less experience treating T1D had higher rates of DKA. Additionally, regular contact with an endocrinologist may protect against DKA, as people with poor clinic attendance and less contact with their diabetes health care team were more likely to have recurrent DKA.[9] The advancement of diabetes technology has associated with a decrease in DKA, with data from the type 1 diabetes exchange registry showed that individuals using a pump were less likely to report an episode of DKA compared to those using injection therapy (2% vs 4%; $P = .002$).[10]

DKA can be associated with significant morbidity and mortality, underscoring the importance of prompt treatment. The most common cause of death in DKA is cerebral edema.[11] Cerebral edema occurs in 0.7% to 1% of children with DKA, particularly in those with new-onset diabetes and presents with headache followed by altered mental status and lethargy.[7] Continued deterioration may lead to seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest.[7] Mannitol is used in the treatment of cerebral edema.[7] Other complications of DKA are numerous and include electrolyte derangements (such as hypokalemia and hyperkalemia), thrombosis, stroke, and sepsis.[11]

Treatment of DKA is typically by protocol and specific to each institution. Nevertheless, the goals of treatment are the same, which include resolution of dehydration and correction of hyperglycemia, ketosis, and acidosis.[8] The 3 main components of treatment are intravenous hydration, insulin, and electrolyte management.

Of note, in pediatrics, the fluid resuscitation regimen is controversial, due at least in part to the lack of consensus regarding the cause of cerebral edema, which is a more common complication in the pediatric population.[8] Due to the proposed association between cerebral edema and the osmotic shifts from the rate of fluid or electrolyte replacement, the Pediatric Emergency Care Applied Research Network FLUID study compared the acute and long-term neurologic outcomes with subsequent rapid or slow fluid replacement of either 0.45% or 0.9% saline.[12] Ultimately, it did not show a significant difference between the various fluid administration protocols and neurologic outcomes.[12]

Severe Hypoglycemia

Hypoglycemia is the most common life-threatening acute complication of T1D treatment.[11] It is associated with significant morbidity and mortality with outcomes ranging from mild cognitive impairment to coma, seizure, and sudden death.[11] Also of importance, hypoglycemia can be a limiting factor in people with T1D obtaining tight glycemic control.[13]

Symptoms of hypoglycemia in general include tremor, palpitations, anxiety, sweating, hunger, and paresthesias.[13] The American Diabetes Association (ADA) defines level 3 hypoglycemia as a severe event that involves altered mental and/or physical function during which an individual requires assistance to recover.[14] Level 3 hypoglycemia may progress to unseriousness, seizure, coma, or death.[14]

Counterregulatory responses to hypoglycemia are impaired in people with T1D.[11] The first 2 physiologic protections against hypoglycemia (decrease in insulin secretion and increase in glucagon secretion) are lost and the third physiologic defense, release of epinephrine, is often attenuated.[13] The attenuated epinephrine response to declining glucose levels is responsible for defective glucose counterregulation. While the mechanism behind the attenuated sympathoadrenal response to hypoglycemia in those with T1D is not known, the loss of its sympathetic neural component causes hypoglycemia unawareness.[13] Hypoglycemia-associated autonomic failure is the concept that recent episodes of hypoglycemia or prior exercise or sleep causes defective glucose counterregulation as well as hypoglycemia unawareness, leading to recurrent hypoglycemia.[13]

Causes of hypoglycemia include missed meals, insulin dosing errors, and rapid insulin absorption due to intramuscular injection or taking a hot shower or bath soon after injection.[11] In addition, patients may overdose on insulin intentionally for secondary gain or suicide attempt.[11] In these situations, insulin overdose causes decreased hepatic glucose output.[11] Physical activity can also lead to hypoglycemia due to increased glucose utilization.[11]

Alcohol consumption suppresses gluconeogenesis and glycogenolysis and improves insulin sensitivity, therefore alcohol consumption is another risk factor for hypoglycemia.[11] Frequent hypoglycemia can lead to hypoglycemia unawareness, which can increase the risk for even lower blood sugars without detection and severe hypoglycemia.[11]

Since the DCCT, there have been several studies investigating the incidence rates of severe hypoglycemia in youth with T1D. In 1 study of children aged 0 to 19 years, where severe hypoglycemia was defined as a hypoglycemic episode causing loss

of consciousness or seizure or resulting in an emergency department (ED) visit or admission, an incidence rate of 19 per 100 patient-years was reported.[15]

Exercise, which lowers blood glucose levels via skeletal muscle uptake, can also result in hypoglycemia.[11] Numerous studies in both adults and children have shown severe hypoglycemia events are more common at night, particularly following days with increased physical activity.[16] One study on adolescents with T1D participating in moderate-intensity exercise in the afternoon showed that glucose requirements to maintain euglycemia increased in a biphasic manner, with increased requirements during and shortly after exercise as well as between 24:00 and 04:00 hours.[17]

The use of insulin pumps has the benefit of lowering HbA1c levels without increasing the risk of hypoglycemia in pediatric patients. Adding continuous glucose monitors (CGM) to insulin pump therapy further decreases the rates of hypoglycemia.[11] Results of a systematic review of commercial hybrid closed-loop (HCL) automated insulin delivery (AID) systems showed that these technologies improve glycemic control without increasing the incidence of severe hypoglycemia.[18] In adults, use of CGM has also been shown to decrease time with glucose less than 70 mg/dL.[19] HCL systems also decrease hypoglycemia in this population.[20]

Most episodes of asymptomatic or symptomatic hypoglycemia can be effectively treated with glucose tablets or carbohydrate-containing food or drink.[13] Glucose gel is another option, particularly when a person is conscious but not oriented.[21] Glucagon injections have been used for decades to manage severe hypoglycemia.[11] More recently, glucagon nasal powder has been approved for management of severe hypoglycemia.[22] In the hospital setting, dextrose infusion is another option for treatment.[11]

CHRONIC COMPLICATIONS

Microvascular Complications

Diabetic retinopathy

Diabetic retinopathy (DR) is a microvascular complication that causes progressive vision loss in people with T1D. Its prevalence is highly correlated with the individual's duration of diabetes, and it is the most frequent cause of new cases of blindness in adults aged 20 to 74 years.[2] DR is characterized by abnormalities of the retina and is divided into 2 main categories: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).[23] The global prevalence for any DR is 27%. There is a 25% prevalence of NPDR, 1.4% PDR, and 4.6% diabetic macular edema.[24]

In addition to duration of diabetes, chronic hyperglycemia is a major risk factor for the development of DR.[2] The development of DR is also strongly correlated with hypertension.[25] Higher Hb A1C levels are associated with the progression of DR, while intensive glycemic control decreases the incidence and deterioration of retinopathy.[25] Other risk factors include nephropathy, dyslipidemia, smoking, and higher body mass axis (BMI).[25] Interestingly, worsening of DR is also associated with initiation of effective treatment and large and rapid reductions in blood glucose levels.[26]

The ADA currently recommends that adults with T1D have an initial dilated and comprehensive eye examination within 5 years after onset of diabetes.[27] Following initial examination, if there is no retinopathy for 1 or more annual examinations and glycemia is well controlled, screening every 1 to 2 years can be considered.[27] However, if retinopathy is present, eye examinations should be repeated at least annually, and if progressing or sight-threatening, eye examinations will need to be more frequent.[27] For children and adolescents, the first dilated and comprehensive eye examination is recommended 3 to 5 years after diagnosis, provided the child is $\geq$ 11 year old or puberty has started, whichever is earlier.[28] Following the initial examination, repeated

dilated and comprehensive eye examinations should occur every 2 years; however, less frequent examinations may be appropriate based on risk factor assessment.[28]

Treating diabetic retinopathy depends on treating both the underlying metabolic conditions that lead to the development of retinopathy as well as treating the particular abnormalities identified.[2] Therefore, intensive diabetes management aimed at achieving near normoglycemia is 1 goal of treatment. Improved glycemic control has been shown to prevent DR as well as delay its progression.[2] In addition to optimizing blood glucose management, high blood pressure and dyslipidemia should also be addressed to avoid progression of retinopathy.[2,25]

In addition to the medical management discussed previously, there are several intraocular therapies for DR.[25] For those with diabetic macular edema, anti-vascular endothelial growth factor (VEGF) therapy (such as ranibizumab, bevacizumab, and aflibercept) has been shown to reduce diabetic macular edema and improve vision.[25] Laser photocoagulation is another well-established treatment for those with diabetic retinopathy.[2] Panretinal laser photocoagulation is the preferred treatment for all patients with PDR as well as those with severe NPDR.[25] In addition, recent studies have shown that intravitreous injection of anti-VEGF may be an alternative treatment to panretinal laser photocoagulation for those with PDR.[25]

Nephropathy

Diabetic nephropathy (DN) is one of the most frequent and severe complications of diabetes.[29] DN most commonly presents 5 to 15 years after diagnosis of T1D.[30] DN is estimated to occur in 20% to 40% of people with diabetes, is the most common cause of end-stage renal disease (ESRD), and is associated with an increased risk of death, primarily from cardiovascular causes.[2]

Albuminuria is a marker of many of the pathologic findings associated with DN, including elevated glomerular pressure, glomerular basement membrane abnormalities, and injury to endothelial cells and kidney tubules.[31] The earliest stage of DN is microalbuminuria, which is defined as albumin excretion of 30 to 299 mg/24 hours.[2] Macroalbuminuria, a more advanced stage of DN, represents albuminuria $\geq$ 300 mg/24 hours.[2] People with T1D who progress from microalbuminuria to macroalbuminuria are likely to develop ESRD.[32] While, classically, DN has been characterized by persistent albuminuria followed by a decline in glomerular filtration rate (GFR), there are several alternative phenotypes including albuminuria regression, rapid decline in GFR, and non-proteinuric or non-albuminuric DKA, which are characterized by a decreased GFR without proteinuria.[33]

A longer duration of diabetes has been found to be associated with a higher prevalence of DN.[31] Persistent hyperglycemia is also directly associated with DN.[31] It is well established that the main risk factors for DN are hyperglycemia, hypertension, and genetic predisposition.[2] Other risk factors include elevated serum lipids, obesity, smoking, and a family history of DN.[31]

Screening for DN is important as people with T1D are often asymptomatic until their GFR has significantly declined.[31] The main method of screening for DN is by urine albumin excretion, measured by an albumin-to- creatinine ratio in random spot urine.[2] For those with T1D, the ADA recommends considering annual screening for albuminuria with annual urine albumin at puberty or age greater than 10 year old or puberty (whichever is earlier) and have had diabetes for $\geq$5 years.[28] The ADA currently recommends that all adults with T1D for $\geq$5 years also obtain an annual estimated GFR.[30] In patients who have a diagnosis of DN, urinary albumin should be assessed more frequently, anywhere from 1 to 4 times per year depending on the stage of the disease.[30]

Prevention of DN involves effective treatment for the known risk factors, including hypertension, hyperglycemia, smoking, and dyslipidemia.[2] In individuals who have evidence of nephropathy, the goal of treatment is to prevent the progression from microalbuminuria to macroalbuminuria which helps to prevent decline in renal function and reduces the risk of cardiovascular events.[2] Intensive diabetes management, specifically targeting an HbA1c $\leq$ 7%, has been shown to prevent progression from microalbuminuria to macroalbuminuria.[31] In people with T1D who have hypertension, angiotensin converting enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs) are the first-line treatment.[31] These agents have been shown to prevent or forestall progression to albuminuria and decreased renal function in people with T1D and hypertension.[31]

Neuropathy

Microvascular complications of the nervous system also occur in those with T1D. The diabetic neuropathies represent a heterogenous group of different disorders that can present with diverse clinical symptoms and may be focal or diffuse in presentation.[2] Distal symmetric polyneuropathy, also referred to as peripheral neuropathy, is the most common neuropathy in people with diabetes.[31] Diabetic peripheral neuropathy (DPN) occurs in a "stocking and glove" distribution, affecting the hands and lower limbs.[34] Diabetic autonomic neuropathies (DAN) are also common in those with T1D.[2] Various types of autonomic neuropathies can occur, including cardiac autonomic neuropathy, gastrointestinal dysmotility, diabetic cytopathy, and erectile dysfunction.[34]

It is estimated that at least 20% of adults with diabetes have at least 1 manifestation of DPN.[2] In youth with T1D, the prevalence of peripheral neuropathy has been estimated to be anywhere from 7% to 90%, the large range likely reflecting both symptomatic and asymptomatic patients as well as various measures used in different studies.[31] The prevalence of DAN is reported to range from 1.6% to 90%, depending on the test used for assessment.[2] When looking specifically at cardiac autonomic neuropathy (CAN) in young people with T1D, the prevalence was found to be 12%.[34]

Poor glycemic control is the main risk factor in the development and progression of DPN in both youth and adults with diabetes.[31] Near-normal glycemic control has been shown to delay or prevent the development of DPN and CAN in those with T1D.[27] DPN has also been associated with other risk factors, including lipid and blood pressure indexes and duration of diabetes.[35] Risk factors for DAN include diabetes duration, age, poor glycemic control, hypertension, and dyslipidemia.[2]

Up to half of people with DPN may be asymptomatic and therefore at high risk of injury, emphasizing the importance of screening for peripheral neuropathy to prevent further loss of sensory function and improve quality of life.[2] Clinical screening for peripheral neuropathy by physical examination can be via pinprick of the foot, ankle reflexes, vibratory sensation via tuning fork, and examination of proprioception.[31] Screening for autonomic neuropathy can include asking patients about symptoms of orthostatic dizziness, syncope, or dry, cracked skin in the extremities.[27] In adults, screening for DPN and DAN should begin 5 years after diagnosis of T1D and should occur annually thereafter.[27] For children and adolescents, the ADA recommends screening for DPN with a yearly comprehensive foot examination beginning at the start of puberty or at age $\geq$10 years, whichever is earlier once the patient has had a diabetes duration of 5 years.[28]

It is recommended that control of glucose, blood pressure, and serum lipids be optimized to prevent or delay the development of neuropathy.[27] Furthermore, while treatments aimed at reversing underlying nerve damage in diabetic neuropathy are currently not available, both pharmacologic and non-pharmacologic strategies for

pain relief in DPN and for relief of symptoms in DAN are available.[27] For neuropathic pain in diabetes, pregabalin or duloxetine are the recommended initial treatments.[36] Treatments for autonomic neuropathy are aimed at the specific organ affected.[2] In CAN, treatment is aimed at alleviating symptoms specific to the patient's clinical manifestation.[36] For example, postural hypotension and dizziness may be treated with mechanical measures or pharmacologic agents.[2] Gastroparesis may be treated by eating small frequent meals.[2] Metoclopramide, a prokinetic agent, is the only FDA- approved treatment for gastroparesis at the present time.[27] Lastly, potential treatments for erectile dysfunction include phosphodiesterase type 5 inhibitors.[2] Other treatment options include intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses.[27] The ADA does not currently have recommendations for treatment of neuropathy in children or adolescents.[28]

As a result of multiple factors, including peripheral neuropathy, foot ulcerations and amputations are associated with diabetes.[27] Therefore, the ADA recommends a comprehensive foot examination for adults at least annually to identify those at risk for ulceration and amputation.[27] Those with evidence of sensory loss or a history of ulceration or amputation should have foot inspections more frequently.[27]

Macrovascular Complications

Cardiovascular disease (CVD) is a broad term that encompasses numerous conditions that affect the heart and the major blood vessels, including coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD).[37] There is significant overlap in the disease processes involved in all 3 subtypes of cardiovascular disease.[37] Prior studies have revealed that patients with T1D have an increased incidence of cardiovascular events as well as increased cardiovascular disease mortality.[38]

CVD is characterized by vascular dysfunction and in diabetes this is a result of endothelial dysfunction and chronic vascular inflammation which cause atherosclerosis and vascular obstruction.[37] In the macrovasculature, these pathologic changes lead to CAD, PVD, and cerebrovascular disease.[37] It is theorized that hyperglycemia itself may cause both endothelial dysfunction and vascular inflammation through numerous metabolic processes that involve oxidative stress.[37]

The long-term cumulative incidence of CVD in those with T1D from the DCCT/EDIC study was 14% after 30 years of diabetes duration.[39] The risk of mortality from CVD in those with T1D is 3 to 10 fold higher than those without T1D.[40] In youth with T1D, subclinical signs of CVD are evident based on assessment of carotid intima-media thickness and arterial stiffness.[41,42] Youth with T1D also have higher rates of CVD risk factors with anywhere from 14% to 45% having 2 or more risk factors.[43,44]

The increased cardiovascular risk in patients with T1D is multifactorial with risk factors of chronic hyperglycemia, diabetic nephropathy, and cardiac autonomic neuropathy, as well as the usual cardiovascular risk factors of tobacco smoking, elevated LDL cholesterol, and hypertension.[38] Several other factors are also suspected to play a role in the increased cardiovascular risk in T1D, including hypoglycemia, increased glycemic variability, insulin resistance in overweight/obese patients, other lipid disorders, and potentially a dysfunctional immune system response.[38]

The ADA provides recommendations for the screening of cardiovascular risk factors in people with T1D. For both children and adults with T1D, blood pressure should be monitored at every visit.[28,45] In children (age $\geq$2 years) and adolescents, dyslipidemia should be screened with an initial lipid profile soon after diagnosis, once glycemia has improved .[28] If initial LDL is $\leq$ 100 mg/dL, testing should be repeated at 9 to 11 years of age.[28] If repeated LDL is <100 mg/dL, then lipid panel should be repeated every

3 years.[28] For adults not taking statins or other lipid-lowering therapy, the ADA recommends obtaining a lipid profile at the time of diabetes diagnosis and at least every 5 years thereafter if under the age of 40 years.[45] Screening for signs and symptoms of CV autonomic neuropathy should begin 5 years after diagnosis of T1D.[46] Currently, in asymptomatic adults with T1D, the ADA does not recommend routine screening for CAD, as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated.[45]

Treatment for CVD depends on the specific condition and can include lifestyle modifications, lipid-lowering medications, and anti-hypertensives. Recent studies have also suggested the potential of metformin to improve cardiovascular and cerebrovascular risk factors.[47]

SUMMARY

T1D is associated with acute and chronic complications in youth and adults. Chronically elevated HbA1c levels are the most common risk factor associated with complications. Following the DCCT, HbA1c became the gold standard for the assessment of glycemic control.[48] While there is a substantial body of data that links increasingly high HbA1c levels to increased rate of complications, people with the same HbA1c sometimes have significantly different rates of complications.[48] HbA1c does not capture fluctuations in glucose levels between different days or throughout any given day and is affected by non–diabetes-related conditions, including hemoglobinopathies, liver disease, pregnancy, and chronic kidney disease.[49] Limitations in the utility of HbA1c measurements have led to a desire to find other methods of assessment of glycemic control.

Usage of continuous glucose monitors (CGMs) has become more widespread in recent years, providing data that can complement monitoring of HbA1c in the clinical setting.[48] The ADA recommends that a CGM should be offered to adults and children using multiple daily injections or continuous subcutaneous insulin.[50] CGM has resulted in the development of core metrics for comprehensive understanding of glycemic status, including time in range (TIR), which is defined as 70 to 180 mg/dL.[49] A TIR of 70% correlated with an HbA1c of 7.0%, while a TIR of 80% approximates a HbA1c of 6.5%.[49] As TIR becomes a more prominent method for assessing glycemic control, numerous studies have evaluated the impact of TIR on diabetes complications.[49] Various studies have associated TIR with DR, albuminuria, and diabetic polyneuropathy.[49] Recent evidence has shown that AID systems increase TIR and improve A1C in those with diabetes.[50]

Improvements have been made to decrease the risk of complications, including the expansion of types of insulin available and advancement of technologies. Early identification of autoantibodies before diabetes diagnosis may help decrease the high rates of DKA at T1D diagnosis. However, despite recent advancements, there is still a significant burden from complications. Continued efforts and interventions are needed to decrease complication rates further, including earlier identification of diabetes and interventions to improve diabetes management as early as possible.

CLINICS CARE POINTS

- DKA is still prevalent at diagnosis in youth, occurring with ~30% of new-onset diagnoses in children. The risk of cerebral edema, and its associated morbidity and mortality, remains a severe potential consequence of DKA.

- Elevated HbA1c levels are associated with the development of acute and chronic complications. Greater percent TIR has been associated with less DR, albuminuria, and polyneuropathy.
- Use of insulin pumps has the benefit of lowering HbA1c levels without increasing the risk of hypoglycemia in pediatric patients. Adding CGM to insulin pump therapy further decreases the rates of hypoglycemia.
- Use of CGM in adults using both multiple daily insulin injections and insulin pump therapy not only lowers HbA1c but also increases TIR and reduces hypoglycemia.
- HCL AID systems further improve glycemic control in both children and adults.
- Attention to improving glycemic, blood pressure, and lipid control can reduce chronic diabetes complications. A rapid decrease in HbA1c has been associated with transient worsening of DR.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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