Managing diabetes in preschool children. ISPAD Clinical Practice Consensus Guidelines.

Article *in* Pediatric Diabetes · May 2017

DOI: 10.1111/pedi.12554

15 authors, including:

Carmel E Smart
Hunter New England Health
94 PUBLICATIONS **2,442** CITATIONS
SEE PROFILE

Ragnar Hanas
NU Hospital Group, Sweden, Uddevalla
127 PUBLICATIONS **5,923** CITATIONS
SEE PROFILE

Katharine D Barnard-Kelly
Bournemouth University
199 PUBLICATIONS **4,171** CITATIONS
SEE PROFILE

M. Allison Cato Jackson
Cato Neuropsychology Services P.A.
32 PUBLICATIONS **1,119** CITATIONS
SEE PROFILE

Received: 6 August 2016 | Revised: 14 May 2017 | Accepted: 31 May 2017

DOI: 10.1111/pedi.12554

ISPAD GUIDELINES

WILEY ISPAD

Managing diabetes in preschool children

Frida Sundberg[1,2] | Katharine Barnard[3] | Allison Cato[4] | Carine de Beaufort[5,6] | Linda A DiMeglio[7] | Greg Dooley[8] | Tamara Hershey[9,10] | Jeff Hitchcock[11] | Vandana Jain[12] | Jill Weissberg-Benchell[13,14] | Birgit Rami-Merhar[15] | Carmel E Smart[16] | Ragnar Hanas[2,17]

[1]The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden

[2]Institute of Clinical Sciences, Department of Pediatrics, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

[3]Faculty of Health and Social Sciences, Bournemouth University, Bournemouth, UK

[4]Neurology Division, Nemours Children's Health System, Jacksonville, Florida

[5]Clinique Pediatrique, Centre Hospitalier de Luxembourg (CHL), Luxembourg, Luxembourg

[6]Department of Pediatrics, UZ Brussels, Jette, Belgium

[7]Department of Pediatrics, Section of Pediatric Endocrinology/Diabetology, Indiana University School of Medicine, Indianapolis, Indiana

[8]inspiredbyisabella.com

[9]Psychiatry Department, Washington University School of Medicine, St. Louis, Missouri

[10]Radiology Department, Washington University School of Medicine, St. Louis, Missouri

[11]childrenwithdiabetes.com

[12]Pediatric Endocrinology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

[13]Northwestern University Feinberg School of Medicine, Chicago, Illinois

[14]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois

[15]Department of Pediatric and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

[16]Department of Endocrinology, John Hunter Children's Hospital and University of Newcastle, Newcastle, Australia

[17]Department of Pediatrics, NU Hospital Group, Uddevalla, Sweden

Correspondence
Frida Sundberg, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, SE 416 85 Gothenburg, Sweden.
Email: frida.sundberg@vgregion.se

KEYWORDS: ISPAD guidelines, preschool children, type 1 diabetes

1 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- The target hemoglobin A1c (HbA1c) for all children with type 1 diabetes, including preschool children, is recommended to be <7.5% (<58 mmol/mol) (B).
- This target is chosen with the aim of minimizing hyperglycemia, severe hypoglycemia, hypoglycemic unawareness, and reducing the likelihood of development of long-term complications (B).
- Intensive insulin therapy, i.e. as close to physiological insulin replacement as possible with preprandial insulin doses and basal insulin, should be used, with frequent glucose monitoring and meal-adjusted insulin regimens. (C).
  - Insulin pump therapy is the preferred method of insulin administration for young children (aged <7 years) with type 1 diabetes (E). If pump therapy is not available, multiple daily injections (MDIs), with consideration of use of an injection port, should be used from the onset of diabetes (E).
  - For preschool children using intensive insulin therapy, preprandial administration of bolus insulin given for correction if blood glucose is high and for at least part of the meal is preferable to giving the whole dose during or after the meal (C).

Greg Dooley is parent of a child with type 1 diabetes diagnosed at age 2, co-founder of the type 1 diabetes blog Inspired by Isabella (www.inspiredbyisabella.com); Jeff Hitchcock is parent of a child with diabetes diagnosed at age 2, founder and president of Children with Diabetes (www.childrenwithdiabetes.com)

This article is a new chapter in the *ISPAD Clinical Practice Consensus Guidelines Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 in ISPAD Clinical Practice Consensus Guidelines 2014 Compendium in *Pediatric Diabetes* 2014; 15 (suppl. 20):1-3

- Carbohydrate counting is best introduced at onset of diabetes (E).
- The small insulin doses of preschool children may necessitate diluting insulin for precise dosing (E).
- Syringes with ½ unit marking and pens with at least ½ unit dosing increments should be used to facilitate more accurate insulin dosing if a pump is not used (or as a back-up to pump use) (E).
- Continuous glucose monitoring (CGM) can be helpful as an approach to adjusting insulin doses (E). Some CGM devices are approved for this use. If CGM is not available, 7 to 10 plasma glucose checks per day are usually needed for satisfactory glucose control (E).
- Injection, infusion, and CGM sites should be properly prepared and regularly rotated in order to reduce the likelihood of lipohypertrophy, scarring, infection, rashes, skin reaction, and dry skin (E).
- Injection, infusion, and CGM sites should be inspected by diabetes team members at every clinic visit to detect and treat any skin problems, such as skin reactions, lipohypertrophy, or lipohypotrophy (E).
- The use of pumps and CGM are often limited by skin reactions to the adhesive. A skin moistener that preserves water can be used to prepare the site a few days prior to insertion. Topical corticosteroid (group I or II) can be used to treat skin reactions and to manage itching after removal (E).

- Life style interventions designed to reduce the risk of subsequent cardiovascular disease in children with type 1 diabetes are needed, and should be directed toward the entire family and not just the individual child with type 1 diabetes (C).
- Family-centered meal routines with restrictions on continuous eating habits (grazing) are important to ensure dietary quality and optimize glycemic control in preschool children (C).
- Diabetes education should be provided to staff at preschools and schools where children with type 1 diabetes are enrolled, in order to ensure that equal participation in all preschool/school activities occurs and is safely managed (E).
- Optimal glycemic control, involving the minimizing of both hypoglycemia and hyperglycemia will give the child the best opportunity to concentrate, participate, and learn while at preschool and school (C).
- Weight, height (or length if <18 months), and Body Mass Index Standard Deviation Score (or percentiles) should be monitored on growth charts in all children with type 1 diabetes (E).

2 | INTRODUCTION

This chapter focuses on components of care unique to toddlers and preschool-aged children with type 1 diabetes. These guidelines are written in particular for children with type 1 diabetes aged 6 months to 6 years. Children <6 months of age at diagnosis should be suspected of having diabetes other than type 1 including monogenic diabetes, and their management is discussed in the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines on "The diagnosis and management of monogenic diabetes in children and adolescents".[1]

Preschool children are dependent on others for all aspects of their care. For the families (primarily parents) of preschool children with type 1 diabetes, their diabetes teams, and other caregivers, including school and day care staff members and babysitters, treatment is a constant challenge. Yet, despite this hurdle, it is important to strive for normoglycemia, as current knowledge about the implications of dysglycemia makes reducing the likelihood of acute and chronic complications imperative from the time of diabetes onset. Optimizing glycemic control for children in this age group often requires treatment using strategies that differ from those employed for older children and adolescents with type 1 diabetes. These strategies need to take into consideration the cognitive, motor, and social immaturity of preschool children as well as their small body size and growth pattern.

In addition to their dependence on others for insulin administration and glucose monitoring, preschool children are also dependent on others for aspects of their lifestyle related to healthy eating and engagement in physical activity. Lifestyle choices and preferences established during early childhood provide a window of opportunity for ingraining healthy habits that will be perpetuated throughout the child's life. The early establishment of positive behaviors is necessary to ameliorate the high risk of cardiovascular disease that is associated with diabetes. Providing adequate education and support of lifestyle changes requires that the multi-disciplinary diabetes team uses a family-based approach to ensure that the whole family is appropriately supported.

Supporting the family is necessary for promoting health in the preschool child with type 1 diabetes. Early childhood is important for establishing the "salutogenic" (health promoting) capacity needed for a long life with type 1 diabetes.[2] The core aspect of a person's salutogenic capacity is a good "sense of coherence", consisting of an everyday perception of comprehensibility, manageability, and meaningfulness of health promoting actions taken in everyday life. The main sources of the child's salutogenic capabilities are the parents. Supporting the parents to endure the burden of intensified insulin treatment, including their need for counseling and sleep, is essential to promote and maintain the health and well-being of the child. It is also important to support the parents to involve the child in diabetes-related tasks such as helping to select a finger for monitoring, site for injection/infusion, and to encourage age-appropriate positive problem solving strategies when diabetes-related problems occur.

Screening and promotion of optimal health-related quality of life should be regularly undertaken in preschool children with type 1 diabetes as in any child with type 1 diabetes. It is important to use validated parent and parent-proxy screening questionnaires to capture factors important to the quality of life of children and their parents as both are important and impactful on diabetes management.

Children younger than 7 years with type 1 diabetes constitute a minority of the population of all pediatric patients with type 1 diabetes. In small centers, this will make the number of very young patients small and the time needed to gain experience in care of this patient group will be longer. Close collaboration between centers is necessary in order to optimize quality of care for preschool children with type 1 diabetes.

3 | GROWTH AND DEVELOPMENT IN THE FIRST YEARS OF LIFE

Growth and development in the first years of life are characterized by an intricate interplay between genetic, metabolic, hormonal, and

environmental factors. "Growth" is an increase in size of the body and its constituent organs. "Development" is the differentiation of the form and function of the organs, and refers to not only somatic development but also neurocognitive, and psychosocial development. Rapid changes in growth and development occur in the first years of life.

In the first year of life children grow 25 to 30 cm, in the second year approximately 12 cm, (comparable to the growth spurt in puberty) and in years 3 to 6 around 6 to 8 cm/y. Weight triples in the first year of life, increases by approximately 2.5 kg in the second year, followed by an increase of around 2 kg/y in the next 3 to 4 years. A peak in subcutaneous tissue mass is observed around 9 months of age, which subsequently decreases until 6 years of age. In order for preschool children to experience normal growth and development, it is essential that they maintain near normoglycemia, aiming to increase glucose time in range, and are provided with sufficient nutrients.[3–6] Restrictive diets or lack of food make it difficult to provide essential nutrients for growth and development, and should be avoided. It is essential to monitor weight, height (or length if <18 months), and BMI-SDS (or percentiles) on growth charts in all children with type 1 diabetes at every clinic visit.

This requirement of sufficient nutrition is in part due to the brain's high metabolic expenditure in infancy and childhood (3 times higher than in adults). Body proportion at birth is characterized by a large head and prominent abdomen. After birth, the brain and the cranium continue to grow and reach 4/5 of the adult size by the end of the second year, growing much faster than many other body parts including the extremities.[7]

4 | THE BRAIN AND COGNITIVE DEVELOPMENT IN CHILDREN WITH EARLY ONSET TYPE 1 DIABETES

The brain is metabolically highly demanding, accounting for 20% of the total energy requirement in adults.[8] In the adult, the brain depends on a continuous supply of glucose as fuel. In the neonate, glucose is essential for different intracerebral pathways.[9] Brain development requires different nutrients to support the 5 key processes: (1) neuron proliferation, (2) axon and dendritic growth, (3) synapse formation, pruning, and function, (4) myelination, and (5) neuron apoptosis. Regional and temporal variation in glucose utilization suggests that glucose is essential not only for energy production in the brain, but potentially for cellular proliferation and synaptogenesis as well.[10] In the neonatal and infant brain, alternative energy sources may be identified such as ketone bodies, which are transported over the blood-brain barrier in times of glucose shortage. The ketone bodies are a substrate for lipid synthesis, although not essential.[11]

In addition to somatic growth, preschool children experience rapid cognitive development. Children start by investigating objects in their immediate environment, eventually expanding to exploring anything within reach. Mobility and thus physical activity increases with age.

Multiple risk factors have been associated with potential suboptimal cognitive and fine motor development in children and adolescents with type 1 diabetes. These factors include early onset of disease (typically defined as <5 years of age),[12] disease duration, history of moderate to severe ketoacidosis (including those at diagnosis),[13,14] severe hypoglycemia (including seizures or unconsciousness),[15] cumulative exposure to hyperglycemia, and possibly, the sex of the child.[16] A meta-analysis showed that the risk of cognitive disruption is largest for children with early-onset diabetes and that the effect is detectable after a mean diabetes duration of 6 years.[17] The mean effect size is moderate but might not be large enough to affect school performance. Clinicians should be concerned about diabetic ketoacidosis (DKA), severe hypoglycemia and hyperglycemia, all being detrimental for the health of the preschool child.

When reviewing these findings, it is important to distinguish between statistically significant group differences vs clinically significant findings. Statistically significant group differences may or may not translate into a functional impact on the daily life of a child, which has not been fully explored in children with type 1 diabetes. However, we know that early brain and cognitive development are important for later success in school and beyond.

Glucose uptake by the brain is insulin-independent and mainly driven by the concentration of glucose. This directly exposes the neuronal cells of the brain to oxidative stress and glucotoxicity in hyperglycemia, and to lack of fuel in hypoglycemia.

The maturation of gray matter in the brain is intense throughout the toddler and preschool years. Gray matter development slowly curtails over time beginning around puberty. In contrast, white matter maturation (that is necessary for processing speed and coordinated, fluid movements) continues until early adulthood.[18,19]

During toddler and preschool years, the brain is highly sensitive to metabolic disturbances, and potential abnormalities have repeatedly been identified in magnetic resonance imaging (MRI) studies of young brains exposed to glycemic extremes, as in type 1 diabetes.[20–23] The mechanisms by which early brain development is affected by type 1 diabetes are not clearly understood. Long-term exposure to hyperglycemia as well as hypoglycemia (especially with seizures) and oxidative stress caused by glycemic variability have been suggested as contributing factors. The main effects seem to occur in the early phase of the disease. It has been suggested that metabolic conditions such as hyperglycemia and ketoacidosis at diagnosis can be predisposing events that makes the brain more vulnerable to subsequent metabolic insults.[13,16]

Some, but not all, studies investigating cognition in childhood onset type 1 diabetes, report decrements in the domains of intelligence quotient (IQ) (verbal IQ in particular), executive functions (attention, working memory, and response inhibition), delayed memory (episodic recall), and processing speed (paper-pencil); however, these differences are generally not reported until the children are studied later in childhood.[24,25] One possibility is that chronic exposure to different aspects of dysglycemia is additive, and that brain and cognitive changes only become apparent over time.

Studies that specifically target the youngest children with type 1 diabetes have found only modest differences in cognitive function compared with peers. Among a large group (n = 144) of children aged 4 to 7 years, small differences in the following areas were reported: IQ, especially verbal, executive functions, and internalizing mood disorders.[26] The cognitive differences remained when

controlled for parental IQ and level of internalizing mood disorders. Longitudinal follow-up of these children is ongoing and may reveal how these differences change with time, further exposure to diabetes (including hypoglycemia and hyperglycemia), and brain development.[27]

A young child who has executive functioning difficulties, language/literacy deficits, slowed processing speed, or fine motor coordination difficulties will likely require professional attention at some point in their youth. Typically, these children are referred to a neuropsychologist or other learning specialist during the early elementary years. These children can require specialized tutoring, small group instruction, support in the classroom, or other assistance. For all children with cognitive development issues, early identification and remediation are crucial to avoid poor outcomes. Optimal glycemic control will give young children with type 1 diabetes the best opportunity to concentrate, participate, and learn while at preschool and school. By achieving good glycemic control, including mitigating prolonged exposure to hyperglycemia, and by providing early identification and intervention of academic, cognitive, or motor issues, health care professionals are best able to help children avoid any negative impact of type 1 diabetes on everyday function.

For further reading, the ISPAD guidelines on psychological care of children and adolescents with type 1 diabetes comprehensively addresses this subject.[28] See also the ISPAD Guidelines on hypoglycemia.[29]

5 | GLYCEMIC TARGETS AND CONTROL IN PRESCHOOL CHILDREN WITH TYPE 1 DIABETES

Optimizing glycemic control for preschool children with type 1 diabetes is crucial for their future, both with respect to acute and long-time diabetes complications as well as their neurocognition, brain structure, and health-related quality of life (HRQoL).

ISPAD published glycemic targets for hemoglobin A1c (HbA1c; <7.5%, (<58 mmol/mol) and for self measured blood glucoses (SMBGs) (from optimal to high risk) in the latest guidelines 2014 (Table 1).[30] The targets are applicable to all pediatric age groups, including preschool children, and the aim should be to achieve optimal glycemic control. The American Diabetes Association[31] in 2014 redefined blood glucose targets for all pediatric age groups to be at the same level as ISPAD.[32] In United Kingdom, glycemic targets for all pediatric age groups are recommended in the National Institute for Clinical Excellence (NICE) guidelines, recently updated to an even lower HbA1c level of ≤6.5% (≤48 mmol/mol; the numbers are based on the published studies).[33]

It is important that the diabetes team and family share the same target HbA1c and glucose ranges. Otherwise, there is a high risk of discrepancy that can go both ways. Sometimes parents strive for lower glucose levels than the diabetes team, who at times may articulate that the family is too strict and take too many glucose checks, especially at night. At other times, the parents have their own set of higher glucose targets that they feel fit better with their daily life, finding the targets set by the health care team unachievable.

When evaluating glycemic targets together with the family, it might be useful to express them as time spent within target and time below or above target. It is important that both the diabetes team and the families consequently use a language that tells the child that a glucose value can be high, low or normal, and that the glucose level is never "bad". The knowledge of a glucose value often calls for action, but never for blaming or punishing the child.

- Parents express that diabetes management style can make a difference. A positive, non-judgmental, attitude will likely have a positive influence on the way a young child views and manages his/her type 1 diabetes as he/she gets older. Parents should be encouraged to adopt a "matter-of-fact" approach to the routines (injections/pump site changes, finger pricks, and meal times), treating numbers as just numbers/data points, and not apologizing for aspects of care such as finger pricks, site changes, and injections that cannot be avoided.

Maximizing the amount of time glucose values are in range needs to be the target for multi-disciplinary diabetes teams, as well as the family/caregivers. Diabetes education[34,35] and a clearly set glycemic target[36] are very important.[37,38] Age-specific challenges need to be considered and age-appropriate actions taken to achieve these.

As discussed above, there are detrimental effects of hyperglycemia; yet it is an existing practice to allow glucose levels to reach the hyperglycemic range in the youngest age group in order to avoid hypoglycemia at all costs. This is unsafe, and treatment should instead aim to minimize both hyperglycemia and hypoglycemia in the effort to achieve (near) normoglycemia. If the diabetes team is inexperienced in treating preschool children with type 1 diabetes, support and advice should be sought from more experienced colleagues.

TABLE 1 Glycemic targets in preschool children with type 1 diabetes according to ISPAD, ADA and NICE guidelines

	ISPAD[30]	American Diabetes Association[31]	NICE[33]
Preprandial glucose target	4.0-8.0 mmol/L (70-145 mg/dL)	5.0-7.2 mmol/L (90-130 mg/dL)	4.0-7.0 mmol/L (72-126 mg/dL)
Postprandial glucose target (2 h post meal)	5.0-10.0 mmol/L (90-180 mg/dL)		5.0-9.0 mmol/L (90-162 mg/dL)
Bedtime	6.7-10 mmol/L (120-180 mg/dL)	5.0-8.3 mmol/L (90-150 mg/dL)	
Overnight	4.5-9.0 mmol/L (80-162 mg/dL)		
HbA1c target	<58 mmol/mol (<7.5%)	<58 mmol/mol (<7.5%), a lower target of <53 mmol/mol (<7%) can be set if it can be achieved without hypoglycemia	≤48 mmol/mol (≤6.5%)

Abbreviations: HbA1c, hemoglobin A1c; ISPAD, International Society for Pediatric and Adolescent Diabetes, NICE, National Institute for Clinical Excellence.

It might not just be the HbA1c level that is important. Glycemic variability may play a role in the development of diabetic complications,[39,40] but the long-term impact of glycemic variability remains controversial.[41,42] In adults using continuous glucose monitoring (CGM), glycemic variability was significantly lower in those without complications compared with those with complications (Standard Deviation SD 3.4 vs 4.1 mmol/L), despite comparable HbA1c values.[43]

Age-specific, family-centered diabetes education plays a key role in achieving metabolic targets, together with flexible insulin regimens, glucose monitoring, and carbohydrate (CHO) counting.[30,34,44]

Hyperglycemia is a major risk factor for (recurrent) ketoacidosis[45] and microvascular complications later in life.[46,47]

Long-term tracking of glycemic control from childhood until adulthood has been reported.[48–52] There is a correlation between the HbA1c achieved within the first few months after diabetes diagnosis, the glycemic control later in life, and the risk for cardiovascular complications. A lower HbA1c achieved at an early phase of life with diabetes is associated with a lower HbA1c later on.[48–52]

Long-term studies, for example, the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC), describe a prolonged effect of prior glycemic levels on diabetic complications, called glycemic memory. This effect is independent of more recent glycemic control. The DCCT showed a significant difference of around 2% in HbA1c between the intensive and conventional groups, but 1 year after the closeout of the study, HbA1c levels were approximately the same (around 8%).[46,47] Nevertheless, the intensive group showed fewer microvascular complications, with a risk reduction in retinopathy even 18 years after the end of the study.[53] The DCCT-EDIC results have led to the recommendation of early tight glycemic control to reduce the risk for diabetic microvascular and macrovascular complications.[47,54,55] The ISPAD guidelines on microvascular and macrovascular complications provides a more detailed discussion.[56]

Early onset of diabetes at a very young age will lead to a longer duration, which in itself is associated with a higher lifelong risk of complications, compared with persons with later onset type 1 diabetes.[57] So far, conflicting data exist to whether the prepubertal years contribute to the same degree as the pubertal years for the development of microvascular complications.[58] Suboptimal metabolic control in children with early prepubertal diabetes onset may further contribute to the risk of complications.[59–61] Persons with poor glycemic control during childhood have a high risk of long-term complications, even if substantial improvement is achieved as young adults,[62] and NICE emphasizes the need to reduce the risk of long-term complications of type 1 diabetes in a population that will have a long duration of diabetes because the condition starts before adulthood.

6 | INSULIN THERAPY IN PRESCHOOL CHILDREN

Insulin treatment guidelines for preschool children are essentially similar to older children and adolescents, but age-dependent aspects have to be taken into consideration. See the ISPAD guidelines for further reading on insulin and insulin analogs in pediatric use.[63] Worldwide, most preschool children with diabetes use insulin injections to manage their diabetes. Although insulin pump use should be considered for many of these children," injection, injection therapy is used in many centers in the following instances: early in the course of the disease in their remission period; children who were using an insulin pump but have experienced pump failures "or skin reactions", "inexperience of the diabetes team in using pumps in this young age group," and if living in limited resource settings where insulin pumps are unavailable.

Approval of insulin analogs in different age groups is regulated by authorities. Two examples are the European Medicines Agency (EMA) (www.ema.europe.eu) approvals and the US Food and Drug Administration (FDA) (www.fda.gov) as of June 2017 (Table 2).

When using injections for insulin delivery, pain can be reduced by usage of subcutaneous catheters changed every third day (Insuflon; Unomedical, Lejre, Denmark or I-port: Medtronic MiniMed, Northbridge CA, USA).[64]

6.1 | Insulin dosing

Preschool children with optimal glycemic control usually need somewhat less insulin than older children. The total insulin dose has been reported to be 0.4 to 0.8 U/kg/d (median 0.6 U/kg/d) in preschool children with well controlled type 1 diabetes after the remission phase.[65] Insulin pumps offer both greater flexibility in insulin dosing and a better means to deliver very small, precise doses of insulin than when using injections,[66] and are thus considered the preferred method for insulin delivery in infants, toddlers, and preschoolers with diabetes, although earlier randomized studies have failed to show an effect on glycemic control.[63] If pump therapy is not available due to lack of economic resources, multiple daily injections (MDIs), with consideration of use of an injection port, can be used. If the diabetes team is not experienced enough in pump treatment of preschool children, advice should be sought from a more experienced center to optimize quality of care.

6.2 | Basal insulin

When using injections for insulin treatment, the special diurnal pattern of insulin requirements in preschool children should be taken into consideration in designing an individualized basal dosing scheme. The low requirement of insulin and tendency toward low glucose

TABLE 2 Approved insulin analogs in different age groups according to EMA and FDA

	Approved by EMA from age	Approved by FDA for (studied from age)
Insulin lispro	"Adults and children" (2 y)	"Adults and children" (3 y)
Insulin aspart	≥2 y	"Adults and children" (2 y)
Insulin glulisine	≥6 y	"Adults and children" (4 y)
Insulin detemir	≥1 y	"Adults and children" (2 y)
Insulin glargine	≥2 y	Adults and pediatric patients" (6 y)
Insulin degludec	≥1 y	≥1 y

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

levels are often most obvious during the night and especially between 3 and 6 AM. Preschool children often need much more insulin late in the evening between 9 PM and 12 midnight.[67–69] This creates typical patterns when programming the basal rates of an insulin pump used by a preschool child. With MDIs, a basal insulin analog can reduce hypoglycemia, including nighttime hypoglycemia, compared with NPH insulin.[70–72]

The combination of the low body weight, and thus low total insulin dose, demands special consideration when using commercially available insulin pumps. A pump with a very high precision in delivering very small basal rates should be chosen for a preschool child. Sometimes further reduction in the dose is needed, necessitating dilution of the current U-100 insulin,[65,73,74] or an intermittent basal rate of 0 U/h for limited periods, i.e. every second hour during the night. Use of these approaches may help to meet the needs of the young child and the planning of the child's insulin treatment has to be carefully discussed (with advantages and disadvantages) with the parents so that they are well aware of the benefits and risks of the chosen strategy. The given insulin should always be prescribed and documented in normal units to avoid hazardous misunderstandings regarding insulin dosing, especially if the child is admitted to hospital. A pump containing diluted insulin should be labeled with information regarding the currently contained concentration of insulin (Table 3).

A glucose and meal-adjusted basal-bolus insulin regimen (delivered by injections or pump) requires that the basal rate can be fine-tuned by the parents in accordance with the child's current insulin sensitivity. Insulin sensitivity can be increased after very active days, such as a day at the beach or out in the snow (decreased insulin resistance). The overnight basal might then be reduced by 10% to 30% when using a pump or a similar decrease in bedtime long-acting insulin. Insulin sensitivity can be markedly reduced (increased insulin resistance) for example during fever when the basal rate might need to be increased by 20% to 100% according to glucose levels when using a pump, or a similar increase in dose of long-acting insulin. Under these circumstances, glucose levels have to be extremely carefully monitored and parents need constant access to support from the diabetes team.

6.3 | Bolus dosing

Although still often used, twice daily insulin dosing in this age group does not give the flexibility needed in adapting doses to varying situations in daily life. It is difficult to fine-tune, and difficult for the family to understand and adjust on their own, which is a necessity for a successful insulin treatment. A glucose and meal-adjusted basal-bolus insulin regimen (delivered by injections or pump) can be adapted to the preschool child's daily activities, and is the preferred type of insulin treatment.

Preschool children often need proportionally larger bolus doses than older children, often constituting 60% to 80% of the total daily insulin dose (TDD). The often used rule of 500 (500/TDD = how many grams of CHO is covered by 1 U of insulin) for bolus calculations, as detailed in the ISPAD guidelines on insulin therapy[63] rarely fits the youngest children as it often underestimates the insulin dose.[70,75,76] Different strategies can be used; either use a 330 or 250 rule (gives 50%-100% more insulin) instead of 500, or, which is preferable, to observe and calculate the correct proportion between insulin and CHO from real life meals. To calculate the insulin to CHO ratio from a given meal, divide the CHO content in the meal (in grams) by the insulin dose in units that gives an appropriate glucose profile after the meal. The need for insulin at breakfast is often very high, and one might consider using 150/TDD in the calculation, or calculate from real life meals as above.

The timing of the prandial bolus is important. As outlined in the review by Bell et al,[77] several studies show that preprandial bolus insulin is preferable to insulin administered during or after the meal and should thus be routinely advised for all toddlers and preschoolers, even the most unpredictable eaters. However, the dose can be split into 1 preprandial and 1 during the meal when eating is erratic or new foods are offered.

The dose given during the meal can be based on what the parent estimates the child will eat of the remaining meal, taking into consideration the food that has just been eaten and the child's remaining appetite. Small inaccuracies in calculation of up to 5 to 7 g CHO will usually not be problematic.[78] Larger inaccuracies may result in possible hypoglycemia or hyperglycemia 2 to 3 hours after eating, but not immediately.[79] These can be anticipated and treated with additional CHO or a small correction dose of insulin. With a pump, a combination bolus (also called combo or dual wave bolus) can be helpful, i.e. part of the bolus is given before the meal and the remainder over 20 to 40 minutes. If the child stops eating before the meal is finished, the remainder of the bolus can be suspended.

When giving these relatively large bolus doses, one must remember that they interact with the need for basal insulin in the following hours. Thus, the total basal rate can be relatively low, around 20% to 40% of TDD. In preschool children, it is often estimated that the effect of a subcutaneous bolus of rapid-acting insulin analogs (eg, as lispro, aspart, or glulisine) lasts for only 2 to 3 hours (active insulin time in pumps).[75]

At breakfast there is often some degree of insulin resistance, and it is common to experience a marked glucose peak after breakfast in spite of an adequate insulin dose taken before the meal. The nutritional content of the breakfast has to be discussed and planned by the dietitian together with the parents. Increasing the insulin dose (lower insulin-to-CHO ratio) too much can risk hypoglycemia before lunch. In this situation, it may be helpful to give the prandial insulin 10 to 20 minutes before breakfast. The need for a large bolus dose of insulin to cover breakfast might necessitate a very low or suspended basal rate during the following 3 hours. For some children, a small amount of fruit (5-10 g of CHO) may be given 2 hours after breakfast (without insulin) to avoid hypoglycemia, but it is preferable not to establish a practice that necessitates skipping a bolus as this may continue as the child gets older.

When using MDIs with frequent glucose checking and meal-adjusted insulin dosing, one possible strategy is to give a rapid-acting insulin analog for all meals, with the exception of the last meal of the day when short-acting regular insulin can be used to meet the increase in glucose before midnight. Part of the dose can be given as rapid-acting analog insulin to avoid needing to give the dose 30 minutes before the meal; the insulins can be mixed in a syringe or given as separate injections (if an injection aid is used).

TABLE 3 Different strategies for delivering minute basal rates. No pumps that are available today can be adjusted to the insulin concentration. Thus, if using diluted insulin, recommended doses from the bolus calculator must be recalculated to the diluted concentration

	Advantages	Disadvantages
Diluted insulin (i.e. 10 or 50 U/mL)	• Fine tuning of basal rates is possible. • All technical features of the pump can be used, such as temporary basal rate changes and bolus calculations. • Possible to set extremely low basal rates and make changes in small increments.	• Risk of mistakes due to the delivered insulin dose not being the same as that displayed on the screen. • Pain can occur when large volumes are given as bolus doses. • Impractical to prescribe doses with diluted insulin • More expensive insulin.
"Empty" hours without basal rate	• The pump gives exactly the doses displayed on the screen, decreased risk of mistakes in dosing for instance when insulin is given temporarily with pen. • Use of more stable commercially available insulins is possible.	• Increased risk of occlusion in tubing due to low flow rate. • Increased risk of ketosis due to planned hours without insulin. • Some of the pumps' technical features (as temporary basal dose changes) cannot be used.

7 | NUTRITIONAL NEEDS OF THE PRESCHOOL CHILD WITH TYPE 1 DIABETES

Breastfeeding should be encouraged for all infants, including infants with diabetes (World Health Organization [WHO] recommendation, www.who.int). Complementary foods, preferably iron-rich, should be commenced from 4 to around 6 months of age.[80] If breastfeeding is not possible, an iron-fortified infant formula should be given as the main milk drink until 12 months of age.

A routine regarding breast- or formula-feeding is important for infants with diabetes as this enables appropriate interpretation of glucose levels and basal and bolus insulin adjustments. This may involve 3 to 4 hourly feeds (of approximately 150-240 mL) during the day with complementary solids. Continuous or hourly breastfeeding is discouraged as this makes insulin dosing difficult. Breast milk has approximately 7.4 g CHO per 100 mL; so for infants 6 months and older it is possible to bolus before the feed for at least 5 to 7 g CHO and 15 g CHO in older babies (>9 months).

Optimal nutrition is required to provide sufficient energy and nutrients to meet the rapidly changing needs of children at this stage of life. Dietary recommendations are based on healthy eating principles suitable for all preschool children, with the aim of establishing family based meal-time routines that promote glycemic control and reduce cardiovascular risk factors. CHO counting is important to permit the matching of insulin dose to CHO intake on intensive insulin regimens,[44] and should be taught to the family at the onset of diabetes. Nutritional advice must be individualized and adapted to cultural and family traditions. A pediatric diabetes dietitian should provide education, monitoring, and support at regular intervals throughout the preschool years, as parents of preschool children with diabetes report meal-times as one of the most difficult components of their child's care.[81] Preschoolers require more frequent review than older children,[44] with a suggestion for reassessment twice annually until the age of 6.

There is international agreement that CHO should not be restricted in children with type 1 diabetes as it may result in deleterious effects on growth. Care should be taken when giving dietary education, so that methods of quantifying CHO do not increase total fat and/or saturated fat intake.[44] Although caregivers may prefer high-fat snacks to avoid affecting glucose levels, this should be discouraged as they will provide unnecessary calories, an unhealthy fat intake, and negatively impact dietary quality.

Preschool children with type 1 diabetes should consume a diet that emphasizes fruit, vegetables, whole grain bread and cereals, dairy foods and appropriate types and amounts of fats. Low fat diets are not suitable for children under 2 years of age. Lower glycemic index (GI) choices, such as wholegrain bread and cereals can be introduced as substitutes for higher GI food choices from 2 years of age. Iron deficiency can be a concern in this age group; adequate consumption of lean meat or alternatives is important and should not be overlooked because of the increased focus on CHO.

A guide to the macronutrient distribution of the total daily energy intake in preschool children is as below. However, this should be based on an individualized assessment.

- Carbohydrates: 45 to 55 Energy (E) %.[44,82] Average intakes 150 g/d in children aged 1½ to 3 years; 200 g/d in children 4 to 10 years.[83]
- Protein: 15 to 20 E % (decreasing with age from approximately 1.5 g/kg body weight/day in 6-month-old infants to 1 g/kg body weight/day in preschoolers)[84]
- Fat: 30 to 35 E % (less than 10 E% saturated fat, less than 10 E% polyunsaturated fat, and more than 10 E% mono-unsaturated fat). Infants less than 12 months may consume up to 40% energy from fat.

It is important to encourage all children, including children with type 1 diabetes, to eat plenty of fruit and vegetables. Examples of recommendations from Australia,[85] United States,[86] and the Nordic countries[87] are expressed in different ways but consistent in content, and state 180 g vegetables (2½ servings) and 150 g fruit (1 serving) daily from 2 years of age[85]; or 1½ serving of fruit and vegetables daily between 1 and 3 years.[86] 400 g of fruits/vegetables are recommended each day from 4 years of age.[87]

Research has shown the dietary quality of preschool children with diabetes is poorer than their healthy peers.[88]Studies have shown that preschool children with type 1 diabetes consume less fruit and vegetables and have higher saturated fat intakes than peers[89] and than recommendations would advise.[90,91] Poor food intake may increase the risk of cardiovascular disease. Eating habits in young children can influence food choices later in life,[92] so early intervention with increased attention to an increase in fruit and vegetable intake and decrease in saturated fat is needed. Just like healthy children, children with diabetes may require up to 10 exposures to a new food before it is accepted.[93]

Several studies show that children with type 1 diabetes are more overweight compared with children in the general population,[91,94] with the youngest children (<6 years) being the most overweight.[95,96] It is important to plot the growth chart including assessments of weight for length or height regularly to identify excessive weight gain, in order to commence interventions that involve the whole family. Encouraging participation in family meals has been recommended to promote dietary quality[97] and social interaction.

Age-appropriate finger foods should be encouraged for self-feeding, and the reintroduction of a bottle as an easy method of CHO intake discouraged. Bottles can lead to overconsumption of fluids, increasing CHO intake and placing other nutrients at risk.

8 | ESTABLISHING POSITIVE FOOD BEHAVIORS AND MEAL-TIME ROUTINES

Establishing positive food behaviors and meal-time routines are important for preschool children with type 1 diabetes, as these behaviors impact glycemic control[81,98] and encourage life-long nutrition practices.[92] Normal early childhood development, including seeking independence, transient food preferences, variable appetite, food refusal, and behavioral resistance often make meal times challenging for parents and carers. Parents of children with type 1 diabetes report more disruptive meal behaviors, including longer meal duration and more frequent food refusal compared with controls[99,100]; even for children using insulin pump therapy.[101] Research has demonstrated positive correlations between suboptimal dietary adherence and higher glucose levels.[81,89,101,102] Caregivers' fear of hypoglycemia associated with food refusal or unpredictable dietary patterns can result in force feeding, grazing continually over the day, and postprandial insulin administration, causing prolonged periods of hyperglycemia.

Family-centered meals are important to model eating practices and to encourage new foods. For small children, meal times should be limited to approximately 20 minutes per meal.[103] Conventional insulin regimens require adherence to a structured plan of CHO intake, and parents frequently report problems with this approach.[81] Intensive insulin management offers greater flexibility in meal timing and CHO quantities.

To assist the reliable intake of CHO at meal-times and to minimize food refusal, the following strategies should be adviced:

- structured meal-times
- avoidance of continuous eating habits
- small snacks including limits on low CHO foods as these fill the child up
- limits on the time spent at the table
- avoidance of force feeding
- reassurance by all team members regarding the usual non-severity of hypoglycemic episodes related to inadequate CHO consumption.

Parents should be adviced that postprandial bolus insulin is problematic as it can become an established habit and also reinforces anxiety about the child under-eating. Fear of hypoglycemia can lead to under-bolusing for meals, resulting in inadequate bolus doses given over the day and subsequent hyperglycemia. Continuous eating (grazing) makes interpretation of glucose levels and insulin dose adjustments difficult. A regular meal pattern with 1 small snacking episode between meals (7-15g CHO preceded by an appropriate insulin dose) will assist with preventing food refusal as the child will be hungrier at main meals. A dietitian should advise regarding age appropriate CHO amounts as it is necessary to ensure the anticipated CHO intake is reasonable based on age, growth, and the child's previous intake. Unreasonable expectations of a child's intake may result in food refusal and subsequent hypoglycemia. Food refusal should generally be dealt with effectively and similarly to toddlers without diabetes. Preschool children becoming increasingly independent can recognize parental stress and quickly learn to use their diabetes as a way of getting their favorite foods. It is important to emphasize parental patience and to encourage parents not to use food bribes.

All diabetes team members should provide the family with clear and consistent messages regarding food and meal-time behaviors. Distractions such as the television and toys should be removed at mealtimes. Research has demonstrated that disruptive child behaviors can be reduced by establishing specific rules and consequences for mealtimes and teaching parents behavioral strategies for meals.[104]

There is consensus that continuation of support by a pediatric dietitian throughout childhood and adolescence is essential for optimal care.

- In parental experience, it can be difficult at times to give preprandial bolus doses of insulin due to the fear of food refusal and resultant hypoglycemia. Strategies to handle this need to be discussed with the parents (as above) and all aspects of the risk of dysglycemia following postprandial bolus doses need to be explored.
- Should a child have a high plasma glucose because of eating something unplanned, a calm explanation of the need to cover food with insulin is necessary.

9 | LIFESTYLE FACTORS IN PRESCHOOL CHILDREN

The American Heart Association (AHA) has identified certain childhood conditions (including type 1 diabetes) associated with extremely high risk of cardiovascular disease, calling for treatments to minimize this risk.[105]

Lifestyle habits, such as nutritional preferences,[92] physical activity,[106] and time spent sedentary,[107] that are established in childhood have a great propensity to follow into adulthood. Thus, lifestyle factors in early childhood have a dual impact on later cardiovascular risk, observable both as early markers of atherosclerosis during adolescence[108] and also as a set of behaviors that influences the child's risk of cardiovascular disease as an adult and even into senescence.

Children tend to follow the lifestyle habits of their parents and entire family regarding physical activity,[109] TV watching[110] and food

choices,[97,111,112] and this has been found to influence children´s food habits throughout their lives.[92] Lifestyle supporting interventions should thus be directed toward the parents and entire family and not the individual child with type 1 diabetes mellitus (T1DM).

There is no contradiction between population-based interventions to promote increased physical activity or healthier food choices in all children and interventions that are routinely part of the diabetes care delivered by the diabetes team. Preschool children with type 1 diabetes can benefit from both efforts, but targeted interventions are necessary to meet the specific needs of children with type 1 diabetes.

10 | PHYSICAL ACTIVITY

Physical activity confers many health benefits for all children. A strong graded inverse cross-sectional association has been observed between physical activity, insulin resistance,[113,114] and body fat.[115] Spending more time in moderate and vigorous physical activity is associated with decreased cardiometabolic risk factors in children.[116] When designing physical activity interventions to reduce the risk of cardiovascular disease in children, including children with type 1 diabetes, it is important to focus on high-intensity physical activity to be most effective.[116] Engaging in regular physical activity is also necessary in order to acquire and improve gross motor skills.[117]

Many countries recommend at least 60 min/d of moderate and vigorous physical activity for all children,[118] and WHO recommends this at least from 5 years of age.[119] Some countries have changed their recommendations for physical activity in preschool children from 60 minutes of moderate and vigorous physical activity to 180 minutes of any intensity of physical activity per day.[120,121] This change of recommendation has been questioned because the reduction in the risk of cardiovascular and metabolic problems might be too low with lower intensity of physical activity.[115,116]

It has been shown that outdoor playing and especially spacious outdoor playing environments are associated with increased physical activity in preschool children.[122] Asking families about the amount of time spent playing outdoors can be a useful way to quantify the physical activity of a preschool child with type 1 diabetes.

Physical activity should be promoted in all children with type 1 diabetes. Both having diabetes and being a girl has been reported to be associated with lower levels of physical activity in preschool children with type 1 diabetes, indicating that particularly young girls with type 1 diabetes are at high risk of being too physically inactive.[123]

11 | PRACTICAL MONITORING OF GLYCEMIC CONTROL

In this section, "blood glucose" values refer to glucose values measured by capillary blood check ("finger prick" and "blood glucose monitoring") although meters generally display plasma glucose. Since plasma glucose is 11% higher than whole blood glucose, this term is used when exact numbers are mentioned.

11.1 | Blood glucose checking

Glycemic control is often evaluated with blood glucose monitoring (SMBG). All families with a child with diabetes should be taught how to measure and interpret plasma glucose values. A high precision glucometer (error less than 10%) should be used in preschool children, both when relying on SMBG for glycemic monitoring and when using the glucometer for calibration of CGM. Accuracy in everyday monitoring situations should be ensured by follow-up with the diabetes team. This shall include education on the importance of ensuring that the fingertips are clean and dry before monitoring blood glucose, as sugar on the fingertips is a common reason for erroneously high blood glucose levels. The child should be introduced to checks glucose monitoring and interpretation according to age appropriate and individual capabilities, as the development of the mathematical understanding of numbers and time is gradual.

Most children with type 1 diabetes can by the age of 7 be capable of taking blood glucose checks and performing some basic interpretation of glucose levels under supervision. However, this should always be overseen by a parent or other caregiver, as independent self-care is not expected from any preschool child with type 1 diabetes.

General advice on SMBG monitoring is available in the ISPAD guidelines on Assessment and monitoring of glycemic control.[29] In children younger than 7 years of age, the recommended checking frequency of 4 to 6 times per day is rarely sufficient when striving for target glucose and HbA1c levels. Even with a higher monitoring frequency of 7 or 10 checks per day, the number of undetected hypoglycemia and hyperglycemic events in insulin treated preschool children are high.[124,125]

Observational studies from different countries show that a common frequency of SMBG in preschool children with type 1 diabetes is 7 to 10 checks per day.[125,126] Nighttime SMBG is recommended by many diabetes teams, and performed by most families with preschool children.[127] Preschool children with diabetes can spend a long time in the hypoglycemic range without detection, despite nighttime monitoring of SMBG.[125]

Many parents are sleep-deprived due to nighttime checking of plasma glucose.[127,128] The normal activities of the child have to be interrupted in order to measure a blood glucose value during daytime. Thus, SMBG has several limitations as a method of monitoring glycemic control.

11.2 | Continuous glucose monitoring

CGM can provide an effective mode of monitoring for low and high glucose levels, allowing for efficacious insulin adjustment. When available, CGM with alarms is generally the preferred method for monitoring of glucose levels in children younger than 7 years of age with type 1 diabetes. CGM should be available and utilized as a tool for adjusting insulin doses.

- Parent experience from Children with diabetes (CWD) conferences: "I have seen many young children in the age group of 5 to 6 who understand both the numbers and trend arrows on their CGM". We also know from personal experience that children

who are diagnosed young sometimes grasp 'the numbers' of diabetes very quickly.

- Data on CGM use in preschool children are limited, but suggest low overall rates of use,[126,129] often due to financial constraints.
- Parental satisfaction with CGM use is high, in large part because the technology can decrease the likelihood of severe hypolycemia.[130]
- When parents/caregivers share their thoughts and interpretations, real-time CGM information, including a color-coded screen with arrows, and alarms can often be understood by preschool children from around age 5 to 6 years. Talking with the child in an age-appropriate way about actual CGM information gradually increases the child´s understanding and participation in their insulin treatment.
- Even if children can have some understanding of this, interpretation and necessary steps of action are always the responsibility of the parent/caregiver.
- Use of CGM devices in preschool children can be hampered by issues of adhesion and skin irritation.[131,132]
- The ability of some CGM devices to remotely transmit glucose values to a phone can be of benefit for parents/caregivers who rely on others for part-time care of their child with diabetes, for example, while at day care or preschool.
- CGM enables deepened analysis and understanding of glycemic patterns (such as postprandial glycemic excursions), and downloading data from the device is a pedagogic tool for the team when discussing solutions to various problems with the parents of a child with diabetes.
- Downloading at home by parents should be encouraged, and can form a basis for self-adjustment of insulin doses for experienced families.

12 | USE OF INSULIN PUMPS WITH AND WITHOUT CGM IN PRESCHOOL CHILDREN

Preschool children are unique consumers of novel insulin delivery and device technologies, as they are dependent on caregivers for all aspects of device use. Recent technologies, such as pumps and CGM, can be particularly helpful to parents and caregivers of preschool children who are extremely dependent on fine-tuning of small insulin doses, both with regard to size and timing of insulin doses.

An insulin pump system is available that can suspend insulin delivery when glucose levels, as measured by CGM, are predicted to become low, and thus reduce the risk and duration of hypoglycemia.[133] On the other hand, insulin pumps and CGM are associated with increased cost and may increase the provider burden; insulin pumps may also carry additional risks associated with pump and infusion set malfunctions.

- Insulin doses in preschool children need to be modified frequently as children of this age are growing rapidly and have changing patterns of eating and sleeping.
- The decrease in size of insulin pumps and CGM devices (including the infusion sets/sensors) over the past few years make these therapies more acceptable for preschool children.
- The safety of insulin pump and CGM use in this population appears to be similar to that seen in other age groups.[130,134]
- It is essential for the family to have access to blood ketone checking to detect problems with the supply of insulin from the pump. See the section on ketone monitoring below and the ISPAD guidelines on sick days.[135]
- Regular downloading of data from the pump (and CGM if used), both at home and in clinic, allows patterns of dosing[136] and glucose levels to be recognizable.
- Always give extra insulin with a pen or syringe in case of suspicion of problems with insulin delivery from the pump.
- If the child is prone to ketosis, replacing part of the overnight basal (30%-40%) with a small dose of long-acting insulin (detemir, glargine or degludec) may help, but might also reduce the flexibility in basal insulin administration by temporary basal rates.
- Parents of preschool children who switch from MDI to insulin pumps report more flexibility and freedom, as well as less stress and anxiety related to their child's care.[137]
- Data suggest a decrease in HbA1c[129,134] and reductions in rates of severe hypoglycemia[95,134] after implementation of insulin pumps in preschool children.
- Insulin pump features that enable automatic bolus calculations based on insulin sensitivity factors and insulin to CHO ratios can aid caregivers in insulin administration.
- Insulin pump therapy may be effective in helping to manage toddlers' eating behaviors by facilitating split bolus dosing.
- The pump calculates "insulin on board", i.e. how many units from a previous dose of insulin that still exerts a glucose-lowering effect. A phone app that can calculate "insulin on board" can be used for calculation of bolus doses of insulin when on injection therapy.
- Although CGM provides an overwhelming amount of data, it is important to look for daily patterns (eg, the "modal day" when downloading data), and adjust insulin-to-CHO ratios and correction factors only after a repeated pattern has been identified.
- The frequency of insulin pump and CGM use varies between centers. Barriers to the use of these treatment options in preschool children need to be explored.

13 | SKIN CARE

There are very few data on special considerations regarding skin care in preschool children with type 1 diabetes but CGM-related skin problems seem to be most common in very young users.[132] CGM-related skin problems are not associated with atopy.[138] In general, recommendations for site use (including site selection, site preparation, and site rotation) are similar as for older children. Many preschool children receive insulin injections and insert infusion sets and CGM sensors in their buttocks, an area often covered by a diaper. The abdomen, upper arm, and upper thigh regions are also commonly used. For children under the age of 6 using insulin pumps, data suggest that rates of scarring and lipohypertrophy are high (50% and 45%, respectively) but not different than in older children.[139]

- Injection, infusion, and CGM sites should be properly prepared and regularly rotated in order to reduce the likelihood of

lipohypertrophy, superficial scarring, infection, rashes, skin reactions, and dry skin.

- Injection, infusion, and CGM sites should be inspected by diabetes team members at every visit to the clinic to detect any skin problem or lipo-hyper/hypotrophy early, in order to treat promptly.
- The use of pumps and CGM are often limited by skin reactions to the adhesive. Prepare the site a few days prior to insertion by the use of a skin moistener that preserves water. Topical corticosteroid (group I or II) can be used to treat skin reactions and break the vicious circle of itching after removal.

14 | KETONE MONITORING

Measuring ketone bodies in blood (betahydroxybutyrate, BOHB) should be recommended as the primary method of detecting and monitoring ketosis in preschool children with type 1 diabetes; see the ISPAD Guidelines on Sick days.[135] Measurement of acetoacetate in urine can be used as an alternative, but gives less precise information. As preschool children do not urinate on command, especially when sick, results from blood ketone monitoring will be more easily available both for the child and parent. Blood ketone checking also gives the health care professional much better information to provide advice over the phone or in the emergency room.

Ketones should be monitored when there is a suspicion of lack of insulin raised either by high blood glucose (2 values above 14 mmol/L within 2 hours that do not decline on a correction insulin dose) or when the child shows symptoms suggestive of ketosis (vomiting, nausea, stomach pain, fever, or unclear illness).

Elevated glucose levels and ketone levels suggest lack of insulin and should promptly be treated with injection of insulin 0.1 U/kg (or 10% of TDD) every second hour until BOHB is below 0.5 mmol/L. If levels are above 3.0 mmol/L, the family should seek guidance by phone or in person immediately, possibly in an emergency room, due to the high risk of ketoacidosis. Slightly elevated BOHB (usually <1.0 mmol/mol) in combination with normal or low glucose levels indicates combined lack of CHO and insulin, commonly associated with gastroenteritis in preschool children. This can most often be treated at home with ingestion of sugary fluids and administration of extra insulin subcutaneously. See the ISPAD Guidelines on Sick days for further advice.[135]

Ketoacidosis is a life-threatening acute complication of diabetes that demands care at a skilled hospital unit. Six percent of children younger than 6 years in the United States and 4% of children in Germany/Austria (from data from the Type 1 Diabetes Exchange clinic registry and the Prospective Diabetes Follow-up Registry: DPV) have suffered from ketoacidosis during the past year.[45] Education of families on prevention of ketoacidosis is an essential part of diabetes care.[140] See the ISPAD Guidelines on Diabetic Ketoacidosis for further advice.[140]

15 | HYPOGLYCEMIA

Hypoglycemia, including fear of hypoglycemia, is a limitation to striving for normoglycemia. The risk of hypoglycemia presents a major physiological and psychological barrier to achieving optimal glycemic control, and may result in significant emotional morbidity for patients and caregivers.[29,141,142] Young age is traditionally regarded as a marker of high risk of severe hypoglycemia during insulin treatment.[29]The frequency of severe hypoglycemia has decreased over time in all children.[29,35,143,144] In Germany and Austria, fewer than 2% of children younger than 6 years with type 1 diabetes have experienced a severe hypoglycemic event with seizures/unconsciousness during the previous year; in the United States this figure is less than 3%.[126]

The erratic daily life of a preschool child (food intake, activity, sleep, and sick days) has been regarded as the explanation for the historically high risk of severe hypoglycemia in preschool children with type 1 diabetes. Preschool children are not yet able to identify and articulate their symptoms and it can be very difficult for caregivers to detect these symptoms. Prolonged nocturnal hypoglycemia is not uncommon in children younger than 7 years with type 1 diabetes as detected in CGM studies,[125,145–147]which is associated with a higher risk of severe hypoglycemia.[146]

The fear of an hypoglycemic event, rather than the frequency of hypoglycemic events, is associated with higher HbA1c and poorer HRQoL.[141] The role of fear of hypoglycemia cannot be underestimated for parents of children with type 1 diabetes.[142] Asking about frequency and severity of hypoglycemia is typical in a clinic visit, and it may also be helpful to ask about thoughts and feelings during and after the hypoglycemic event. Fear of nocturnal hypoglycemia is a particular challenge.[142] Fear is not correlated with the numbers of hypoglycemic episodes, but is related to their severity, especially in mothers of children who have experienced a hypoglycemic seizure.

The use of insulin pumps and CGM has been reported to decrease the risk of hypoglycemia.[148,149] Insulin pumps with low glucose suspend features appear to further reduce the time spent in hypoglycemia.[150,151]

The comparison of data between the United States T1D Exchange and German/Austrian DPV registries showed that an HbA1c of <7.5% (<58 mmol/mol) can frequently be achieved in children younger than 6 years with type 1 diabetes without an increased risk of severe hypoglycemia.[126] In many countries, children younger than 7 years most frequently have the lowest HbA1c. In Sweden, 74% of insulin-treated children younger than 7 years have HbA1c < 7.4% (<57 mmol/mol), and the overall frequency of severe hypoglycemia (seizures/unconsciousness) in the pediatric age (0-18 years) is 2.5%.[152]

For definitions and further information see the ISPAD Guidelines on Hypoglycemia.[29]

15.1 | Treatment of mild hypoglycemia in infants and preschool children

Oral glucose as tablets, gel, or a drink (0.3 g glucose/kg bodyweight) is the preferred method of hypoglycemia treatment.[29,153] This dose will raise plasma glucose approximately 2.5 to 3.6 mmol/L (45-64 mg/dL).[29] It is important not to give too much CHO when treating hypoglycemia, in order to avoid subsequent hyperglycemia. Giving something that contains fat (ie, milk and chocolate) will slow down the gastric emptying, and cause a slower rise in plasma glucose.[154] Sucrose sweetened confectionary should not be routinely used to treat hypoglycemia, as it can lead to increased risk of dental caries and food refusal if the child learns that sweets are substituted for

unconsumed food. It is important that hypoglycemia is not over-treated, as 5 to 7 g CHO is usually adequate in raising the plasma glucose to normal levels for small children using intensive therapy.

To treat hypoglycemia in breast- or formula-fed infants, CHO gel, diluted juice, or a glucose polymer from a spoon or bottle can be offered. Honey should not be given to infants younger than 1 year due to risk of botulism.

16 | SCREENING FOR ASSOCIATED DISEASES

Early onset of type 1 diabetes is associated with a higher frequency of celiac disease compared with older children, which affects the treatment situation of the child,[155–157] and may influence the risk of complications and quality of life. Repeated screening for celiac disease, thyroid disease, and other autoimmune disorders is essential.[158]

17 | LIVING WITH DIABETES IN THE FAMILY

For people living with type 1 diabetes and their families, the management of the condition is complex and individual. Daily challenges imposed by type 1 diabetes include cognitive and emotional burdens that can take the form of increased vigilance to dietary intake, symptom monitoring, and frustrations with glucose excursions. For caregivers of preschool children with type 1 diabetes, additional complexities are encountered, including the necessity to adapt to developmental changes to ensure adequate psychological adjustments for the child and themselves, and to facilitate care in the context of other care providers such as preschool staff.[159] Clinicians need to be aware of the overwhelming sense of responsibility and worry which parents of preschool children with type 1 diabetes can feel. Parents who have access to a supportive network (relatives and/or friends) have lower risk of diabetes-related stress and burnout.[128] It is important to educate secondary caregivers about type 1 diabetes and insulin treatment. Attention should be given to the needs of the siblings of a child with type 1 diabetes.

As children grow, they understand more about health and illness. When appropriate, it needs to be explained that diabetes is not caused by eating too much sugar, and that you cannot catch diabetes from another person. This needs to be actively taught to friends and relatives as well to avoid common misconceptions about diabetes.

Parents are an integral part of the diabetes team and have the most important supportive role to play over the years as their children eventually learn to self-manage their diabetes. Providing this support can be difficult when parents have their own stressors to deal with, and struggle with the constant vigilance needed to ensure the safety of their child. Dashiff et al[160] report that parents of older children with type 1 diabetes experience an ongoing struggle, worry, and frustration about their parenting role. During young childhood, parents take responsibility for all diabetes-related tasks such as insulin administration, dosing calculations, blood glucose checking, and so on. It is important that they do this in a way that is neither threatening nor frightening for their child. Involving the child in aspects of diabetes management as soon as possible (eg, finger pricks and CHO counting) is recommended, so the child can begin to develop a sense of ownership/management of their own health. A supportive and emotionally warm parenting style is important for promoting improved quality of life for children with type 1 diabetes.[161]

Establishing good habits in the early years will form the basis for optimal diabetes self-management during adolescence and into adulthood.[2,92,106,107] In order to create an environment in which parents feel confident and comfortable, it is crucial that they are appropriately supported by all members of their multi-disciplinary team and that they have adequate access to appropriate support when they need it. The way that parents model diabetes-related tasks will have a direct impact on the way their children learn. Supporting parents toward a positive adjustment to living with diabetes will help them to effectively model those tasks and assignments involved in daily life with diabetes. It is important to engage both fathers and mothers in diabetes care from the onset, and to keep them both involved in everyday diabetes care throughout the childhood years.

- Parents express that it is important to explain to their child in very simple and clear terms what type 1 diabetes involves. There are certain aspects of diabetes management that are not negotiable (glucose checking, insulin injections/pump site changes, CGM use, etc), and the child needs to begin to understand that as early as possible. It is important to involve the child in diabetes management as soon as possible so they can begin to develop a sense of ownership/management of their own disease. Reinforcing such an attitude early on will help to shape the child's attitude and approach to diabetes in the future.
- Parents report that diabetes will often initially disrupt the normal parent-child relationship, as diabetes frequently comes first in the mind of the parent in response to a child's requests. It is important for parents to ask themselves, “If my child didn't have type 1 diabetes, would I say no to this request?”, and thus strive to re-establish the normal parent-child relationship.

18 | SCREENING CHILDREN FOR PSYCHOSOCIAL DISTRESS

Regular screening of children for psychosocial distress is important to ensure that difficulties are identified early, and appropriate support and treatment plans established as soon as possible. Most children are not able to complete questionnaires or report on their own level of emotional distress in a reliable manner until they are approximately 7 to 8 years of age. Therefore, either talking with them directly about how they feel, or asking their parents to report on their children's psychosocial well-being is recommended. For children who are older, there are several pediatric measures of depressive symptoms that are validated and reliable for use with children as young as 7 years of age, varying in length and depth of detail. These include the Children's Depression Inventory (CDI)[162] and the Center for Epidemiologic Studies – Depression (CES-D) scale.[163] Both measures are self-reported questionnaires containing items on types of symptoms

(eg, sadness and low self-esteem) and functional areas (eg, not having friends, schoolwork is not as good as it was before, and arguing with others). Pediatric quality of life can be addressed by specific questionnaires such as the Pediatric Quality of Life Inventory (PedsQL) generic and Type 1 Diabetes modules.[164] These measures offer a child self-report for youth ages 5 to 7 and also for youth ages 8 to 18. There are also PedsQL parent proxy reports for children ages 2 to 18.[164] Diabetes-specific emotional distress can be assessed in children ages 8 to 11 Problem Areas in Diabetes Survey-Children (PAID-C) and teens Problem Areas in Diabetes Survey-Teens (PAID-T) and parent's diabetes-specific emotional distress can also be assessed (P-PAID-C and P-PAID-T) in measures developed by Weissberg-Benchell and colleagues. Similarly, diabetes-specific emotional distress from age 8 can be assessed by the PAID-Parent (PAID-PR) scale and from age 8 in youth with the PAID-Peds scale, both developed by Markowitz et al.[165,166]

Parental anxiety can have a direct and negative effect on diabetes management and health outcomes. There can often be a comorbidity of depression; however, they are 2 separate conditions and should be treated separately. They may act in opposite directions with regard to diabetes management and control, so we recommend assessing anxiety separately from depression. The Center for Epidemiological Studies-Depression Scale (CESD) is often used as a measure of depressive symptoms in adults, and the Beck Depression as well as the Beck Anxiety scales are also often used. Worries about diabetes impact on glycemic control in children, should be acknowledged and addressed.

19 | PRESCHOOL CARE

Many preschools provide excellent care for children with type 1 diabetes. Parents and health care professionals should work together to overcome any difficulties and ensure the safety and well-being of the child with type 1 diabetes when cared for outside the home setting. It is crucial that every child is supported effectively to achieve their full potential. Legislation protects children with type 1 diabetes in many countries. One example is the Equality Act 2010 (England, Scotland, and Wales) which dictates that schools must make reasonable adjustments to ensure that children with disabilities are not put at a substantial disadvantage compared with their peers. For diabetes, this means schools ensuring they have enough staff trained so that the child with diabetes can take part in all aspects of preschool and school life. Contingency plans must be in place to train replacement staff quickly. The Kids and Diabetes in Schools (KiDS) program of the International Diabetes Federation (IDF) offers education and guidance for families and school staff on ways to help children with type 1 diabetes manage in school. KiDS information is available in 10 languages (as of June 2017) and can be accessed online at http://www.idf.org/education/kids.

In addition to ensuring the rights of the child with diabetes, it is important to create trust and cooperation between the preschool, the family, and the diabetes team. An individually written diabetes management plan is helpful in this cooperation to help the child with type 1 diabetes,[167] and should include information about and practical training for the use of diabetes-related technologies.[168] Both the parents and the diabetes team need to share the responsibility for educating the preschool institution, especially when the child is newly diagnosed with diabetes or when additional diagnosis such as celiac disease occurs. Preschool staff often find CHO counting helpful as it gives them a tool to assess the dose of insulin to be given in relation to the food intake and current glucose level. In countries where there are no regulations to support the child with diabetes, the diabetes team together with the parent organizations should advocate for improved regulations.

- Parents express that while regulations certainly help to ensure documentation and agreements on daily care, maintaining a close relationship with the school (staff, teachers, etc) is equally if not more important to ensure effective daily management of their child's diabetes. Parents can be in very close contact with the school, including offering training sessions, educational materials for other parents etc, which will lead to better and more effective diabetes management. This helps them to feel more comfortable/less stressed when sending their child to preschool.

20 | ALTERNATIVE AND COMPLEMENTARY THERAPIES

At times families try alternative indigenous remedies and even discontinue insulin. This can be avoided if parents are counseled regarding the absolute necessity of insulin for the child's survival. Alternative therapies may be tolerated if important for the family as long as they do not interfere with the regular diabetes care, including insulin doses, glucose monitoring and healthy food choices, or impact the child's growth or development or deplete economic resources needed for insulin treatment.

21 | CARE FOR THE PRESCHOOL CHILD WITH TYPE 1 DIABETES IN LIMITED RESOURCES SETTINGS

Whenever possible, the guidelines described above in the preceding sections should be followed.

It is important to remember that building a good rapport with the family and providing comprehensive diabetes education are inexpensive, and remain the most effective strategies to improve diabetes management by the family.[37] Knowledge about the effects of insulin, food, and physical activity on glucose levels are essential to protect the child from acute and chronic complications of diabetes under all circumstances. The first few visits of the family are the most crucial in this regard. Initial approach to diagnosis and treatment is based upon staffing and facilities at specialized centers for the care of young children with diabetes, with many centers recommending hospitalization. Parents should be counseled and educated in detail.

The challenges in managing type 1 diabetes in the preschool child are several-fold higher in resource limited settings. Awareness, health infrastructure, and number of medical professionals trained in the

management of childhood diabetes are inadequate for a significant proportion of the population in many countries in South East Asia and sub-Saharan Africa. The diagnosis is often delayed, and may even be missed in some cases, resulting in death before diagnosis. Common misdiagnoses are gastroenteritis, pneumonia, asthma, urinary tract infection, genital tract infection (candidiasis), enuresis, and malaria. Parents may take longer to come to terms with the diagnosis and the need for life-long insulin therapy. The financial implications of the condition add to the psychological distress brought about by the diagnosis. Risk of acute and chronic complications, as well as mortality, is higher in these children due to suboptimal management.[169] In the United States, young people of African descent have increased risk of short-term complications (ketoacidosis and severe hypoglycemia) when adjusted for socioeconomic status,[170] and higher HbA1c even when adjusted for mean glucose levels.[171] HbA1c was higher even when fasting glucose is <7 mmol/L in black individuals both with and without diabetes compared with white, but the prognostic value of HbA1c for predicting cardiovascular disease, nephropathy and retinopathy were similar.[172]

The financial issues need to be addressed upfront by the treating team. The challenge of finding ways to support the families lies chiefly with the care providers. The team should be familiar with the governmental and non-governmental agencies in the area that may provide financial assistance for procuring insulin and glucose strips, and ensure that parents have access to these before the child is discharged home.

Most preschool children in resource-limited settings remain on regular and NPH insulin administered by insulin syringes. With only regular and NPH available (as in the DCCT study), a multiple injection therapy with regular insulin for meals and NPH insulin at bedtime can be effective in teaching the family the relationship between insulin dose and CHO content of the meal. CHO counting can be used in this situation. The challenge to overcome will be the lunchtime injection at school. It is very important to motivate and explain this to the school staff as the alternative of giving a twice daily mixture of regular and NPH does not result in a physiological insulin profile. In a situation where food availability is unpredictable, a child on twice daily injections will experience hypoglycemia, while the child on multiple injections can adjust mealtime doses accordingly.

Few patients are able to afford analog insulin and pen devices. The use of insulin pumps is only affordable by a low percentage of the population. Administration of small doses is therefore a practical challenge. In young infants, parents may be taught to dilute insulin with normal saline (available in 10 mL vials). The use of 0.3 mL insulin syringes (100U/ml, 30 U in total) allows an accurate administration of half units, appropriate for most preschool children. Similarly, use of CGM remains unavailable for most children with type 1 diabetes in the resource-limited scenario, and frequent self-monitoring of blood glucose is the only method for monitoring glycemia. However, even this may not be feasible for some families due to the high cost of blood glucose strips. If possible, the child can be recommended a meal plan with a relatively consistent CHO intake at meal and snack times during the day to match the insulin regimen. The family can be taught to have a high index of suspicion for hypoglycemia and treating it on suspicion, relying mostly on urinary glucose monitoring for insulin dosing, and to use SMBG at least on sick days if available.[173] With limited number of strips, the family can, for example, measure before and 2 hours after lunch 1 week, and before and after dinner the next to get a more stringent picture of the day compared with random checks. Urine strips should be available for ketone monitoring during sick days.

Another issue that may compound the challenge in resource-limited settings is that some parents may have low levels of literacy and health literacy, meaning thereby that they cannot read the numbers on the insulin syringe and on the glucometer. For example, in India, literacy rate is 74.04% according to the 15th official census in 2011 (http://www.census2011.co.in/literacy.php). In such cases, it is helpful to identify a suitably literate relative, friend or neighbour who can undergo diabetes education along with the parents and assist them in the domiciliary management. The parents should also be encouraged to learn the basics of reading and writing. In the case of low literacy, a simpler insulin regime such as twice daily dosing with premixed insulin can be given. Hearing the number of clicks from an insulin pen can obviate the need to read the number of units. Teaching the parents to recognize “Hi” and “Lo” on glucometer, to treat hypoglycemia based on symptoms alone, and to recognize hyperglycemia and ketonuria by urinary strips is also useful to prevent life-threatening episodes.

Vomiting in a child with diabetes should always be regarded as imminent ketoacidosis, and appropriate treatment should be sought immediately in the absence of knowledge and diagnostic measurements. If the child is not feeling well with other symptoms, the first line of treatment should be something containing sugar to treat impending hypoglycemia. This should be well known by all the older children and adults who are close to the child with diabetes, and they should know where to readily find a source of sugar.

To conclude, the goals of management of type 1 diabetes in resource-limited settings must be situated in the context of the resource-limited environment and based on the family's educational and financial status. Avoidance of acute life-threatening complications and continuation of regular treatment and follow-up are the immediate goals.

22 | FUTURE NEEDS OF PRESCHOOL CHILDREN WITH TYPE 1 DIABETES

> “Diabetes during early childhood creates a psychosocial challenge to the families of these children. Successful management of infants and toddlers with diabetes depends on a well functioning and educated family, the availability of a diabetes health care team experienced in the treatment of these youngsters, and the involvement of the extended family, child care personnel and others who play a role in their daily care” (Daneman).[174]

The addition of new tools should enable families living with type 1 diabetes to provide increasingly effective therapy and support for preschool children with diabetes. The cognitive, motor and social

immaturity, as well as the small body size of preschool children must be considered when designing new equipment, including sensors, insulin pumps, and (hybrid) closed-loop solutions for insulin delivery.

It is important to include children younger than 7 years in both epidemiological and clinical studies regarding treatment strategies and tools (both technical equipment and pharmacological) and outcomes; moreover, when the youngest children with type 1 diabetes are included in these studies, data regarding children with early-onset diabetes must be presented separately to enable subgroup analysis. Children younger than 7 years with type 1 diabetes constitute only approximately 10% of the population of all children and adolescents with type 1 diabetes,[126,152] but in many countries the incidence in this subgroup is increasing most quickly. Collaboration between centers is thus necessary in order to conduct studies that are sufficiently powered.

REFERENCES

1. Rubio-Cabezas O, Hattersley AT, Njolstad PR, et al.ISPAD Clinical Practice Consensus Guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2014;15(suppl 20):47-64.
2. Antonovsky A. *Unraveling the Mystery of Health*. Jossery-Bass Inc. Publishers: San Francisco, CA; 1987.
3. Gruszfeld D, Socha P. Early nutrition and health: short- and long-term outcomes. *World Rev Nutr Diet*. 2013;108:32-39.
4. Khadilkar VV, Parthasarathy LS, Mallade BB, Khadilkar AV, Chiplonkar SA, Borade AB. Growth status of children and adolescents with type 1 diabetes mellitus. *Indian J Endocrinol Metab*. 2013;17:1057-1060.
5. Kim MS, Quintos JB. Mauriac syndrome: growth failure and type 1 diabetes mellitus. *Pediatr Endocrinol Rev*. 2008;5(suppl 4):989-993.
6. Prado EL, Dewey KG. Nutrition and brain development in early life. *Nutr Rev*. 2014;72:267-284.
7. Kuzawa CW, Chugani HT, Grossman LI, et al. Metabolic costs and evolutionary implications of human brain development. *Proc Natl Acad Sci U S A*. 2014;111:13010-13015.
8. Leonard WR, Snodgrass JJ, Robertson ML. Effects of brain evolution on human nutrition and metabolism. *Annu Rev Nutr*. 2007;27:311-327.
9. Brekke E, Morken TS, Sonnewald U. Glucose metabolism and astrocyte-neuron interactions in the neonatal brain. *Neurochem Int*. 2015;82:33-41.
10. Caravas J, Wildman DE. A genetic perspective on glucose consumption in the cerebral cortex during human development. *Diabetes Obes Metab*. 2014;16(suppl 1):21-25.
11. Morris AA. Cerebral ketone body metabolism. *J Inherit Metab Dis*. 2005;28:109-121.
12. Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. *Diabetes Care*. 2001;24:1541-1546.
13. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. *Pediatr Diabetes*. 2006;7:289-297.
14. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *Lancet*. 2012;379:2291-2299.
15. Asvold BO, Sand T, Hestad K, Bjorgaas MR. Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. *Diabetes Care*. 2010;33:1945-1947.
16. Schoenle EJ, Schoenle D, Molinari L, Largo RH. Impaired intellectual development in children with type I diabetes: association with HbA (1c), age at diagnosis and sex. *Diabetologia*. 2002;45:108-114.
17. Gaudieri PA, Chen R, Greer TF, Holmes CS. Cognitive function in children with type 1 diabetes: a meta-analysis. *Diabetes Care*. 2008;31:1892-1897.
18. Bullmore E, Sporns O. The economy of brain network organization. *Nat Rev Neurosci*. 2012;13:336-349.
19. Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron*. 2010;67:728-734.
20. Bjorgaas MR. Cerebral effects of severe hypoglycemia in young people with type 1 diabetes. *Pediatr Diabetes*. 2012;13:100-107.
21. Perantie DC, Koller JM, Weaver PM, et al. Prospectively determined impact of type 1 diabetes on brain volume during development. *Diabetes*. 2011;60:3006-3014.
22. Ferguson SC, Blane A, Wardlaw J, et al. Influence of an early-onset age of type 1 diabetes on cerebral structure and cognitive function. *Diabetes Care*. 2005;28:1431-1437.
23. Mauras N, Mazaika P, Buckingham B, et al. Longitudinal assessment of neuroanatomical and cognitive differences in young children with type 1 diabetes: association with hyperglycemia. *Diabetes*. 2015;64:1770-1779.
24. Lin A, Northam EA, Rankins D, Werther GA, Cameron FJ. Neuropsychological profiles of young people with type 1 diabetes 12 yr after disease onset. *Pediatr Diabetes*. 2010;11:235-243.
25. Perantie DC, Lim A, Wu J, et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. *Pediatr Diabetes*. 2008;9:87-95.
26. Cato MA, Mauras N, Ambrosino J, et al. Cognitive functioning in young children with type 1 diabetes. *J Int Neuropsychol Soc*. 2014;20:238-247.
27. Cato MA, Mauras N, Mazaika P, et al. Longitudinal evaluation of cognitive functioning in young children with type 1 diabetes over 18 months. *J Int Neuropsychol Soc*. 2016;22:293-302.
28. Delamater AM, de Wit M, McDarby V, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Psychological care of children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):232-244.
29. Ly TT, Maahs DM, Rewers A, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15-(suppl 20):180-192.
30. Rewers MJ, Pillay K, de Beaufort C, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):102-114.
31. American Diabetes Association. Children and Adolescents. *Diabetes Care*. 2016;39(suppl 1):S86-S93.
32. Chiang JL, Kirkman MS, Laffel LM, Peters AL, Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care*. 2014;37:2034-2054.
33. NICE (National Institute for Clinical Excellence). Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. National Institute for Clinical Excellence, 2015. http://www.nice.org.uk/guidance/ng18. Accessed 18 June 2017
34. Lange K, Swift P, Pankowska E, Danne T, International Society for Pediatric and Adolescent DiabetesISPAD Clinical Practice Consensus Guidelines 2014. Diabetes education in children and adolescents. *Pediatr Diabetes*. 2014;15(suppl 20):77-85.
35. Rosenbauer J, Dost A, Karges B, et al. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. *Diabetes Care*. 2012;35:80-86.
36. Swift PG, Skinner TC, de Beaufort CE, et al. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere childhood diabetes study group centre differences study 2005. *Pediatr Diabetes*. 2010;11:271-278.
37. Cameron FJ, de Beaufort C, Aanstoot HJ, et al. Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach. *Pediatr Diabetes*. 2013;14:473-480.
38. de Beaufort CE, Lange K, Swift PG, et al. Metabolic outcomes in young children with type 1 diabetes differ between treatment centers: the Hvidoere Study in Young Children 2009. *Pediatr Diabetes*. 2013;14:422-428.

39. Ceriello A, Ihnat MA. 'Glycaemic variability': a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med*. 2010;27:862-867.
40. Virk SA, Donaghue KC, Cho YH, et al. Association between HbA1c variability and risk of microvascular complications in adolescents with type 1 diabetes. *J Clin Endocrinol Metab*. 2016;101:3257-3263.
41. McNeilly AD, McCrimmon RJ. The Scylla and Charybdis of glucose control in childhood type 1 diabetes? *Pediatr Diabetes*. 2015; 16:235-241.
42. Shalitin S, Phillip M. Which factors predict glycemic control in children diagnosed with type 1 diabetes before 6.5 years of age? *Acta Diabetol*. 2012;49:355-362.
43. Soupal J, Skrha J Jr, Fajmon M, et al. Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control. *Diabetes Technol Ther*. 2014;16:198-203.
44. Smart CE, Annan F, Bruno LP, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Nutritional management in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):135-153.
45. Maahs DM, Hermann JM, Holman N, et al. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. *Diabetes Care*. 2015;38:1876-1882.
46. DCCT Research Group (Diabetes Control and Complications Trial Research Group). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329: 977-986.
47. Nathan DM, Group DER. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care*. 2014;37:9-16.
48. Edge JA, James T, Shine B. Persistent individual tracking within overall improvement in HbA1c in a UK paediatric diabetes clinic over 15 years. *Diabet Med*. 2010;27:1284-1288.
49. Hofer SE, Raile K, Frohlich-Reiterer E, et al. Tracking of metabolic control from childhood to young adulthood in type 1 diabetes. *J Pediatr*. 2014;165:956-961 e1-e2.
50. Danne T, Mortensen HB, Hougaard P, Lynggaard H, Aanstoot HJ, Chiarelli F. Persistent differences among centers over 3 years in glycemic control and hypoglycemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidore Study Group. *Diabetes Care*. 2001;24:1342-1347.
51. Lawes T, Franklin V, Farmer G. HbA1c tracking and bio-psychosocial determinants of glycaemic control in children and adolescents with type 1 diabetes: retrospective cohort study and multilevel analysis. *Pediatr Diabetes*. 2014;15:372-383.
52. Samuelsson U, Steineck I, Gubbjornsdottir S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood – a pilot study using two nation-wide population based quality registries. *Pediatr Diabetes*. 2014;15:229-235.
53. Diabetes Control and Complications Trial /Epidemiology of Diabetes I, Complications Research Group, Lachin JM, White NH, Hainsworth DP, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. *Diabetes*. 2015; 64:631-642.
54. Lind M, Oden A, Fahlen M, Eliasson B. The shape of the metabolic memory of HbA1c: re-analysing the DCCT with respect to time-dependent effects. *Diabetologia*. 2010;53:1093-1098.
55. Bailey C, Day C. Glycaemic memory. *Br J Diabetes Vasc Dis*. 2008;8:242-247.
56. Donaghue KC, Wadwa RP, Dimeglio LA, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Microvascular and macrovascular complications in children and adolescents. *Pediatr Diabetes*. 2014;15-(suppl 20):257-269.
57. Olsen BS, Sjolie AK, Hougaard P, et al. The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes. *J Diabetes Complications*. 2004;18:160-164.
58. Cho YH, Craig ME, Donaghue KC. Puberty as an accelerator for diabetes complications. *Pediatr Diabetes*. 2014;15:18-26.
59. Salardi S, Porta M, Maltoni G, et al. Infant and toddler type 1 diabetes: complications after 20 years' duration. *Diabetes Care*. 2012;35:829-833.
60. Donaghue KC, Fung AT, Hing S, et al. The effect of prepubertal diabetes duration on diabetes. Microvascular complications in early and late adolescence. *Diabetes Care*. 1997;20:77-80.
61. Holl RW, Lang GE, Grabert M, Heinze E, Lang GK, Debatin KM. Diabetic retinopathy in pediatric patients with type-1 diabetes: effect of diabetes duration, prepubertal and pubertal onset of diabetes, and metabolic control. *J Pediatr*. 1998;132:790-794.
62. Anderzen J, Samuelsson U, Gudbjornsdottir S, Hanberger L, Akesson K. Teenagers with poor metabolic control already have a higher risk of microvascular complications as young adults. *J Diabetes Complications*. 2016;30:533-536.
63. Danne T, Bangstad HJ, Deeb L, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):115-134.
64. Hanas R. Reducing injection pain in children and adolescents with diabetes: a review of indwelling catheters. *Pediatr Diabetes*. 2004;5:102-111.
65. Danne T, Battelino T, Jarosz-Chobot P, et al. Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. *Diabetologia*. 2008;51:1594-1601.
66. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2007;30:1653-1662.
67. DiMeglio LA, Boyd SR, Pottorff TM, Cleveland JL, Fineberg N, Eugster EA. Preschoolers are not miniature adolescents: a comparison of insulin pump doses in two groups of children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2004;17:865-870.
68. Holterhus PM, Bokelmann J, Riepe F, et al. Predicting the optimal basal insulin infusion pattern in children and adolescents on insulin pumps. *Diabetes Care*. 2013;36:1507-1511.
69. Nicolajsen T, Samuelsson A, Hanas R. Insulin doses before and one year after pump start: children have a reversed dawn phenomenon. *J Diabetes Sci Technol*. 2012;6:589-594.
70. Alemzadeh R, Hoffmann RG, Dasgupta M, Parton E. Development of optimal kids insulin dosing system formulas for young children with type 1 diabetes mellitus. *Diabetes Technol Ther*. 2012;14:418-422.
71. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. *Pediatr Diabetes*. 2011;12:632-641.
72. Hathout EH, Fujishige L, Geach J, Ischandar M, Maruo S, Mace JW. Effect of therapy with insulin glargine (lantus) on glycemic control in toddlers, children, and adolescents with diabetes. *Diabetes Technol Ther*. 2003;5:801-806.
73. Mianowska B, Fendler W, Tomasik B, Mlynarski W, Szadkowska A. Effect of insulin dilution on lowering glycemic variability in pump-treated young children with inadequately controlled type 1 diabetes. *Diabetes Technol Ther*. 2015;17:605-610.
74. Elleri D, Allen JM, Tauschmann M, et al. Feasibility of overnight closed-loop therapy in young children with type 1 diabetes aged 3-6 years: comparison between diluted and standard insulin strength. *BMJ Open Diabetes Res Care*. 2014;2:e000040.
75. Hanas R, Adolfsson P. Bolus calculator settings in well-controlled prepubertal children using insulin pumps are characterized by low insulin to carbohydrate ratios and short duration of insulin action time. *J Diabetes Sci Technol*. 2017;11(2):247-252.
76. Andersen AJ, Ostenfeld A, Pipper CB, et al. Optimum bolus wizard settings in insulin pumps in children with Type 1 diabetes. *Diabet Med*. 2016;33:1360-1365.
77. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care*. 2015;38:1008-1015.

78. Smart CE, Ross K, Edge JA, Collins CE, Colyvas K, King BR. Children and adolescents on intensive insulin therapy maintain postprandial glycaemic control without precise carbohydrate counting. *Diabet Med*. 2009;26:279-285.
79. Smart CE, King BR, McElduff P, Collins CE. In children using intensive insulin therapy, a 20-g variation in carbohydrate amount significantly impacts on postprandial glycaemia. *Diabet Med*. 2012;29:e21-e24.
80. Infant Feeding Guidelines. Australian Government; National Health and Medical Research Council, Canberra, 2012. https://www.nhmrc.gov.au/guidelines-publications/n56. Accessed 18 June 2017
81. Patton SR, Dolan LM, Powers SW. Mealtime interactions relate to dietary adherence and glycemic control in young children with type 1 diabetes. *Diabetes Care*. 2006;29:1002-1006.
82. Mann J, Cummings JH, Englyst HN, et al. FAO/WHO scientific update on carbohydrates in human nutrition: conclusions. *Eur J Clin Nutr*. 2007;61(suppl 1):S132-S137.
83. Carbohydrates and Health Scientific Advisory Committee on Nutrition, TSO, London 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf. Accessed 18 June 2017
84. Joint FAO/WHO/UNU expert consultation on protein and amino acid requirements in human nutrition. WHO Technical Report Series, No. 935, Geneva, 2002
85. Australian Dietary Guidelines Australian Government; National Health and Medical Research Council, Canberra, 2013. https://www.nhmrc.gov.au/guidelines-publications/n55. Accessed 18 June 2017.
86. 2015–2020 Dietary Guidelines for Americans. 8th ed. U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015. http://health.gov/dietaryguidelines/2015/guidelines/. Accessed 18 June 2017
87. Integrating nutrition and physical activity. Nordic Nutrition Recommendations 2012. 5th ed, 2014. http://www.livsmedelsverket.se. Accessed 18 June 2017
88. Sundberg F, Augustsson M, Forsander G, Cederholm U, Axelsen M. Children under the age of seven with diabetes are increasing their cardiovascular risk by their food choices. *Acta Paediatr*. 2014;103:404-410.
89. Patton SR, Dolan LM, Chen M, Powers SW. Dietary adherence and mealtime behaviors in young children with type 1 diabetes on intensive insulin therapy. *J Acad Nutr Diet*. 2013;113:258-262.
90. Patton SR, Dolan LM, Powers SW. Does eating during television viewing affect mealtimes in young children with type 1 diabetes mellitus? *J Pediatr Nurs*. 2013;28:364-368.
91. Mehta SN, Volkening LK, Quinn N, Laffel LM. Intensively managed young children with type 1 diabetes consume high-fat, low-fiber diets similar to age-matched controls. *Nutr Res*. 2014;34:428-435.
92. Kaikkonen JE, Mikkila V, Magnussen CG, Juonala M, Viikari JS, Raitakari OT. Does childhood nutrition influence adult cardiovascular disease risk? – insights from the Young Finns Study. *Ann Med*. 2013;45:120-128.
93. Cooke L. The importance of exposure for healthy eating in childhood: a review. *J Hum Nutr Diet*. 2007;20:294-301.
94. DuBose SN, Hermann JM, Tamborlane WV, et al. Obesity in youth with type 1 diabetes in Germany, Austria, and the United States. *J Pediatr*. 2015;167:627-632 e1-e4.
95. Kapellen TM, Heidtmann B, Bachmann J, Ziegler R, Grabert M, Holl RW. Indications for insulin pump therapy in different age groups: an analysis of 1,567 children and adolescents. *Diabet Med*. 2007;24:836-842.
96. Islam ST, Abraham A, Donaghue KC, et al. Plateau of adiposity in Australian children diagnosed with type 1 diabetes: a 20-year study. *Diabet Med*. 2014;31:686-690.
97. Christian MS, Evans CE, Hancock N, Nykjaer C, Cade JE. Family meals can help children reach their 5 a day: a cross-sectional survey of children's dietary intake from London primary schools. *J Epidemiol Community Health*. 2013;67:332-338.
98. Overby NC, Margeirsdottir HD, Brunborg C, Andersen LF, Dahl-Jorgensen K. The influence of dietary intake and meal pattern on blood glucose control in children and adolescents using intensive insulin treatment. *Diabetologia*. 2007;50:2044-2051.
99. Powers SW, Byars KC, Mitchell MJ, Patton SR, Standiford DA, Dolan LM. Parent report of mealtime behavior and parenting stress in young children with type 1 diabetes and in healthy control subjects. *Diabetes Care*. 2002;25:313-318.
100. Patton SR, Dolan LM, Powers SW. Differences in family mealtime interactions between young children with type 1 diabetes and controls: implications for behavioral intervention. *J Pediatr Psychol*. 2008;33:885-893.
101. Patton SR, Piazza-Waggoner C, Modi AC, Dolan LM, Powers SW. Family functioning at meals relates to adherence in young children with type 1 diabetes. *J Paediatr Child Health*. 2009;45:736-741.
102. Patton SR, Dolan LM, Powers SW. Dietary adherence and associated glycemic control in families of young children with type 1 diabetes. *J Am Diet Assoc*. 2007;107:46-52.
103. Adamson M, Morawska A, Wigginton B. Mealtime duration in problem and non-problem eaters. *Appetite*. 2015;84:228-234.
104. Kuhl ES, Clifford LM, Stark LJ. Obesity in preschoolers: behavioral correlates and directions for treatment. *Obesity*. 2012;20:3-29.
105. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114:2710-2738.
106. Telama R, Yang X, Leskinen E, et al. Tracking of physical activity from early childhood through youth into adulthood. *Med Sci Sports Exerc*. 2014;46:955-962.
107. Biddle SJ, Pearson N, Ross GM, Braithwaite R. Tracking of sedentary behaviours of young people: a systematic review. *Prev Med*. 2010;51:345-351.
108. Trigona B, Aggoun Y, Maggio A, et al. Preclinical noninvasive markers of atherosclerosis in children and adolescents with type 1 diabetes are influenced by physical activity. *J Pediatr*. 2010;157:533-539.
109. Hesketh KR, Goodfellow L, Ekelund U, et al. Activity levels in mothers and their preschool children. *Pediatrics*. 2014;133:e973-e980.
110. Jago R, Sebire SJ, Edwards MJ, Thompson JL. Parental TV viewing, parental self-efficacy, media equipment and TV viewing among preschool children. *Eur J Pediatr*. 2013;172:1543-1545.
111. Fisk CM, Crozier SR, Inskip HM, et al. Influences on the quality of young children's diets: the importance of maternal food choices. *Br J Nutr*. 2011;105:287-296.
112. Raynor HA, Van Walleghen EL, Osterholt KM, et al. The relationship between child and parent food hedonics and parent and child food group intake in children with overweight/obesity. *J Am Diet Assoc*. 2011;111:425-430.
113. Brage S, Wedderkopp N, Ekelund U, et al. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). *Diabetes Care*. 2004;27:2141-2148.
114. Andersen LB, Harro M, Sardinha LB, et al. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). *Lancet*. 2006;368:299-304.
115. Steele RM, van Sluijs EM, Cassidy A, Griffin SJ, Ekelund U. Targeting sedentary time or moderate- and vigorous-intensity activity: independent relations with adiposity in a population-based sample of 10-y-old British children. *Am J Clin Nutr*. 2009;90:1185-1192.
116. Ekelund U, Luan J, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *JAMA*. 2012;307:704-712.
117. O'Neill JR, Williams HG, Pfeiffer KA, et al. Young children's motor skill performance: relationships with activity types and parent perception of athletic competence. *J Sci Med Sport*. 2014;17:607-610.

118. Beets MW, Bornstein D, Dowda M, Pate RR. Compliance with national guidelines for physical activity in U.S. preschoolers: measurement and interpretation. *Pediatrics*. 2011;127:658-664.
119. WHO. Global Recommendations on Physical Activity for Health, Geneva, 2010. http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/. Accessed 18 June 2017
120. Tremblay MS, Leblanc AG, Carson V, et al. Canadian Physical Activity Guidelines for the early years (aged 0-4 years). *Appl Physiol Nutr Metab*. 2012;37:345-369.
121. Australian Government, Department of Health. National Physical Activity Recommendations for Children (0-5 years). 2014. http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines#npa05. Accessed 18 June 2017
122. Boldemann C, Blennow M, Dal H, et al. Impact of preschool environment upon children's physical activity and sun exposure. *Prev Med*. 2006;42:301-308.
123. Sundberg F, Forsander G, Fasth A, Ekelund U. Children younger than 7 years with type 1 diabetes are less physically active than healthy controls. *Acta Paediatr*. 2012;101:1164-1169.
124. Jeha GS, Karaviti LP, Anderson B, et al. Continuous glucose monitoring and the reality of metabolic control in preschool children with type 1 diabetes. *Diabetes Care*. 2004;27:2881-2886.
125. Sundberg F, Forsander G. Detection and treatment efficacy of hypoglycemic events in the everyday life of children younger than 7 yr. *Pediatr Diabetes*. 2014;15:34-40.
126. Maahs DM, Hermann JM, DuBose SN, et al. Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries. *Diabetologia*. 2014;57:1578-1585.
127. Barnard KD, Oliver N, Adolfsson P, Aldred C, Kerr D. Is iatrogenic sleep disturbance worth the effort in Type 1 diabetes? *Diabet Med*. 2015;32:984-986.
128. Lindstrom C, Aman J, Norberg AL. Parental burnout in relation to sociodemographic, psychosocial and personality factors as well as disease duration and glycaemic control in children with Type 1 diabetes mellitus. *Acta Paediatr*. 2011;100:1011-1017.
129. Blackman SM, Raghinaru D, Adi S, et al. Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. *Pediatr Diabetes*. 2014;15:564-572.
130. Tsalikian E, Fox L, Weinzimer S, et al. Feasibility of prolonged continuous glucose monitoring in toddlers with type 1 diabetes. *Pediatr Diabetes*. 2012;13:301-307.
131. Englert K, Ruedy K, Coffey J, et al. Skin and adhesive issues with continuous glucose monitors: a sticky situation. *J Diabetes Sci Technol*. 2014;8:745-751.
132. Heinemann L, Kamann S. Adhesives used for diabetes medical devices: a neglected risk with serious consequences? *J Diabetes Sci Technol*. 2016;10:1211-1215.
133. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of Hypoglycemia With Predictive Low Glucose Insulin Suspension in Children With Type 1 Diabetes: A Randomized Controlled Trial. *Diabetes Care*. 2017;40:764-770.
134. Mack-Fogg JE, Orlowski CC, Jospe N. Continuous subcutaneous insulin infusion in toddlers and children with type 1 diabetes mellitus is safe and effective. *Pediatr Diabetes*. 2005;6:17-21.
135. Brink S, Joel D, Laffel L, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Sick day management in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15(suppl 20):193-202.
136. Pankowska E, Skorka A, Szypowska A, Lipka M. Memory of insulin pumps and their record as a source of information about insulin therapy in children and adolescents with type 1 diabetes. *Diabetes Technol Ther*. 2005;7:308-314.
137. Sullivan-Bolyai S, Knafl K, Tamborlane W, Grey M. Parents' reflections on managing their children's diabetes with insulin pumps. *J Nurs Scholarsh*. 2004;36:316-323.
138. Sundberg F, Viberg C, Soderlund T, Forsander G. CGM related skin problems are most common in very young users but not associated with atopy. *Pediatr Diabetes*. 2015;16:112 (suppl 21 abstract P157).
139. Schober E, Rami B. Dermatological side effects and complications of continuous subcutaneous insulin infusion in preschool-age and school-age children. *Pediatr Diabetes*. 2009;10:198-201.
140. Wolfsdorf JI, Allgrove J, Craig ME, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2014;15(suppl 20):154-179.
141. Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with type 1 diabetes and their parents. *Diabet Med*. 2013;30:1126-1131.
142. Barnard K, Thomas S, Royle P, Noyes K, Waugh N. Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review. *BMC Pediatr*. 2010;10:50.
143. O'Connell SM, Cooper MN, Bulsara MK, Davis EA, Jones TW. Reducing rates of severe hypoglycemia in a population-based cohort of children and adolescents with type 1 diabetes over the decade 2000-2009. *Diabetes Care*. 2011;34:2379-2380.
144. Cengiz E, Xing D, Wong JC, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. *Pediatr Diabetes*. 2013;14:447-454.
145. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. *Diabetes Care*. 2010;33:1004-1008.
146. Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. *Diabetes Care*. 2008;31:2110-2112.
147. Golicki DT, Golicka D, Groele L, Pankowska E. Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetologia*. 2008;51:233-240.
148. Phillip M, Danne T, Shalitin S, et al. Use of continuous glucose monitoring in children and adolescents. *Pediatr Diabetes*. 2012;13:215-228.
149. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med*. 2008;25:765-774.
150. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med*. 2013;369:224-232.
151. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA*. 2013;310:1240-1247.
152. Åkesson K, Eriksson E, Fureman A, Gudbjornsdottir S, Hanberger L, Pundziute-Lycka A, et al. Data from the Swedish National Paediatric Diabetes Registry (SWEDIABKIDS). 2015.
153. McTavish L, Wiltshire E. Effective treatment of hypoglycemia in children with type 1 diabetes: a randomized controlled clinical trial. *Pediatr Diabetes*. 2011;12:381-387.
154. Brodows RG, Williams C, Amatruda JM. Treatment of insulin reactions in diabetics. *JAMA*. 1984;252:3378-3381.
155. Pham-Short A, Donaghue KC, Ambler G, Chan AK, Craig ME. Coeliac disease in type 1 diabetes from 1990 to 2009: higher incidence in young children after longer diabetes duration. *Diabet Med*. 2012;29:e286-e289.
156. Cerutti F, Chiarelli F, Lorini R, Meschi F, Sacchetti C. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes. *Diabetes Care*. 2004;27:1294-1298.
157. Frohlich-Reiterer EE, Kaspers S, Hofer S, et al. Anthropometry, metabolic control, and follow-up in children and adolescents with type 1 diabetes mellitus and biopsy-proven celiac disease. *J Pediatr*. 2011;158:589.e2-593.e2.
158. Kordonouri O, Klingensmith G, Knip M, et al.ISPAD Clinical Practice Consensus Guidelines 2014. Other complications and diabetes-associated conditions in children and adolescents. *Pediatr Diabetes*. 2014;15(suppl 20):270-278.

159. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28:186-212.
160. Dashiff C, Riley BH, Abdullatif H, Moreland E. Parents' experiences supporting self-management of middle adolescents with type 1 diabetes mellitus. *Pediatr Nurs*. 2011;37:304-310.
161. Botello-Harbaum M, Nansel T, Haynie DL, Iannotti RJ, Simons-Morton B. Responsive parenting is associated with improved type 1 - diabetes-related quality of life. *Child Care Health Dev*. 2008;34:675-681.
162. Kovacs M. *Children's Depression Inventory*. North Tonawanda, NY: Multi-Health Systems, Inc.; 1992.
163. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measur*. 1977;1:385-401.
164. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL. The PedsQL in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and type 1 Diabetes Module. *Diabetes Care*. 2003;26:631-637.
165. Markowitz JT, Volkening LK, Butler DA, Antisdel-Lomaglio J, Anderson BJ, Laffel LM. Re-examining a measure of diabetes-related burden in parents of young people with type 1 diabetes: the Problem Areas in Diabetes Survey - Parent Revised version (PAID-PR). *Diabet Med*. 2012;29:526-530.
166. Markowitz JT, Volkening LK, Butler DA, Laffel LM. Youth-perceived burden of type 1 diabetes: problem areas in diabetes survey-pediatric version (PAID-Peds). *J Diabetes Sci Technol*. 2015;9:1080-1085.
167. Siminerio LM, Albanese-O'Neill A, Chiang JL, et al. Care of young children with diabetes in the child care setting: a position statement of the American Diabetes Association. *Diabetes Care*. 2014;37:2834-2842.
168. Bratina N, Battelino T. Insulin pumps and continuous glucose monitoring (CGM) in preschool and school-age children: how schools can integrate technology. *Pediatr Endocrinol Rev*. 2010;7(suppl 3):417-421.
169. Kumar KM, Saboo B, Rao PV, et al. Type 1 diabetes: awareness, management and challenges: current scenario in India. *Indian J Endocrinol Metab*. 2015;19:S6-S8.
170. Willi SM, Miller KM, DiMeglio LA, et al. Racial-ethnic disparities in management and outcomes among children with type 1 diabetes. *Pediatrics*. 2015;135:424-434.
171. Kamps JL, Hempe JM, Chalew SA. Racial disparity in A1C independent of mean blood glucose in children with type 1 diabetes. *Diabetes Care*. 2010;33:1025-1027.
172. Parrinello CM, Sharrett AR, Maruthur NM, et al. Racial differences in and prognostic value of biomarkers of hyperglycemia. *Diabetes Care*. 2016;39:589-595.
173. Rotchford AP, Rotchford KM, Machattie T, Gill GV. Assessing diabetic control – reliability of methods available in resource poor settings. *Diabet Med*. 2002;19:195-200.
174. Daneman D, Frank M, Perlman K, Wittenberg J. The infant and toddler with diabetes: challenges of diagnosis and management. *Pediatr Child Health*. 1999;4:57-63.

How to cite this article: Sundberg F, Barnard K, Cato A, de Beaufort C, DiMeglio LA, Dooley G, Hershey T, Hitchcock J, Jain V, Weissberg-Benchell J, Rami-Merhar B, Smart CE, Hanas R. Managing diabetes in preschool children. *Pediatr Diabetes*. 2017;0:1–19. https://doi.org/10.1111/pedi.12554