Managing diabetes in preschool children

ISPAD Clinical Practice Consensus Guidelines

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Recommendations

- The target 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 hypoglycaemia, 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 (MDI), 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).

❖ 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, 7-10 plasma glucose tests/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 cortisone (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 towards the entire family and not just the individual child with type 1 diabetes (C).

- Family-centred 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 minimising of both hypo- and hyperglycemia will give the child the best opportunity to concentrate, participate and learn whilst at preschool and school (C).
- Weight, height (or length if < 18 months) and BMI SDS (or percentiles) should be monitored on growth charts in all children with type 1 diabetes (E).

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 diabetes, including monogenic diabetes, and their management is discussed in the ISPAD guideline 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 behaviours 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 counselling 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 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 seven years of age with type 1 diabetes constitute a minority of the population of all pediatric patients with type 1 diabetes. In small centres 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 centres is necessary in order to optimize quality of care for preschool children with type 1 diabetes.

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 neuro-cognitive, and psychosocial development. Rapid changes in growth and development occur in the first years of life.

In the first year of life children grow 25-30 cm, in the second year approximately 12 cm, (comparable to the growth spurt in puberty) and in years 3-6 around 6-8 cm per year. Weight triples in the first year of life, increases by approximately 2.5 kg in the second year, followed by an increase of around 2kg per year in the next 3-4 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 (three 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).

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 five key processes: 1) neuron proliferation, 2) axon and dendritic growth, 3) synapse formation, pruning and function, 4) myelination, 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 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 six years (17). The mean effect size is moderate but might not be large enough to affect school performance. Clinicians should be concerned about DKA, severe hypo- 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 versus 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 grey matter in the brain is intense throughout the toddler and preschool years. Grey 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 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 IQ (Verbal IQ in particular), executive functions (attention, working memory, 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 to peers. Among a large group (n=144) of children aged 4 to 7 yrs, 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 hypo- 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 whilst at preschool and school. By achieving good glycemic control, including mitigating prolonged exposure to hyperglycemia, and by providing early identification and intervention for 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 guideline on psychological care of children and adolescents with type 1 diabetes comprehensively addresses this subject (28). See also the ISPAD Guideline on hypoglycaemia (29).

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 neuro-cognition, brain structure and health-related quality of life (HRQoL).

ISPAD published glycemic targets for HbA1c (<7.5%; <58mmol/mol) and for SMBGs (from optimal to high risk) in the latest guidelines 2014 (30). See Table 1. 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 UK, glycemic targets for all pediatric age groups are recommended in the NICE guidelines, recently updated to an even lower HbA1c level of ≤6.5% (≤48 mmol/mol) (33). (The numbers are based on the published guidelines).

	ISPAD (30)	**ADA** (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 (two hours 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	≤48 mmol/mol (≤6.5%)

	mmol/mol (<7%) can be set if it can be achieved without hypoglycemia

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 tests, 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, nonjudgmental, 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, 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.

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 CGM, glycemic variability was significantly lower in those without complications compared to those with complications (SD 3.4 mmol/l versus 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 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, e.g. the 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 guideline 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 to 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). Sub-optimal 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.

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 for many of these children insulin pump use should be considered, injection therapy is used in many centres 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; 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 U.S. Food and drug administration (FDA) (www.fda.gov) as of January 2016 (Table 2).

	Approved by EMA from age	**Approved by FDA for (studied from age)**
Insulin lispro	"adults and children"	"adults and children" (3 years)
Insulin aspart	≥ 2 years	"adults and children" (2 years)

Insulin glulisine	≥ 6 years	"adults and children" (4 years)
Insulin detemir	≥ 1 year	"adults and children" (2 years)
Insulin glargine	≥ 2 years	"adults and pediatric patients" (6 years)
Insulin degludec	≥ 1 year	≥ 1 year

When using injections for insulin delivery, pain can be reduced by usage of subcutaneous catheters changed every third day (Insuflon® or I-port®) (64).

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 0.4-0.8 U/kg/day (median 0.6 U/kg/day) 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 not is available due to lack of economic resources, multiple daily injections (MDI), 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.

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 levels are often most obvious during the night and especially between 3-6 am. Preschool children often need much more insulin late in the evening between 9 pm-12 midnight (67-69). This creates typical patterns when programming the basal rates of an insulin pump used by a preschool child. With MDI (multiple daily injections), a basal insulin analog can reduce hypoglycemia, including night-time hypoglycemia, compared to 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 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 labelled with information regarding the currently contained concentration of insulin. (See table 3).

	Advantages	**Disadvantages**
Diluted insulin (ie 10 U/ml or 50U/ml)	• Fine tuning of basal rates is possible. • All technical features of 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.

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

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 with 10-30% 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 20-100% 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.

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 60-80 % of the total daily insulin dose (TDD). The often used rule of 500 (500/TDD = how many grams of carbohydrate is covered by one U of insulin) for bolus calculations, as detailed in the ISPAD guideline 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 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 carbohydrates from real life meals. To calculate the insulin to carbohydrate ratio from a given meal, divide the carbohydrate 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 pre-schoolers, even the most unpredictable eaters. However, the dose can be split into one pre-prandial and one 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 5-7g carbohydrate will usually not be problematic (78). Larger inaccuracies may result in possible hypo- or hyperglycemia 2-3 hours after eating, but not immediately (79). These can be anticipated and treated with additional carbohydrate 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 20-40 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 20-40% of TDD. In preschool children, it is often estimated that the effect of a subcutaneous given bolus of rapid acting insulin analogues (e.g. as lispro, aspart, or glulisine) lasts for only 2-3 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-carbohydrate ratio) too much can risk hypoglycemia before lunch. In this situation, it may be helpful to give the prandial insulin 10-20 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 (5-10g of carbohydrates) 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 multiple daily injections (MDI) with frequent glucose testing 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 min. before the meal; the insulins can be mixed in a syringe or given as separate injections (if injection aid is used).

Nutritional needs of the preschool child with type 1 diabetes

Breastfeeding should be encouraged for all infants, including infants with diabetes (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 3-4 hourly feeds (of approximately 150-240ml) 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 carbohydrate (CHO) per 100ml; so for infants 6 months and older it is possible to bolus before the feed for at least 5-7g CHO and 15g 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. Carbohydrate counting is important to permit the matching of insulin dose to carbohydrate intake on intensive insulin regimens (44), and should be taught to the family at the onset of diabetes. Nutritional advice must be individualised 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 age 6 years.

There is international agreement that carbohydrate 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 that methods of quantifying carbohydrate 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 two 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 two 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 over-looked because of the increased focus on carbohydrate.

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: 45-55 Energy (E) % (44, 82). Average intakes 150g/day in children aged 1½- 3 years. 200g/day in children 4-10 years (83).

- Protein: 15-20 E % (decreasing with age from approximately 1.5g/kg body weight/day in six month old infants to 1g/kg body weight/day in preschoolers) (84)

- Fat: 30–35 E % (less than10 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), USA (86) and the Nordic Countries (87) are expressed in different ways but consistent in content, and state 180g vegetables (2 ½ servings) and 150g fruit (1 serving) daily from 2 years of age (85); or 1 ½ serving of fruit and vegetables daily between 1 and 3 years (86). 400g fruit/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) 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 carbohydrate intake discouraged. Bottles can lead to overconsumption of fluids, increasing carbohydrate intake and placing other nutrients at risk.

Establishing positive food behaviours and meal-time routines

Establishing positive food behaviours and meal-time routines are important for preschool children with type 1 diabetes, as these behaviours 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 behavioural resistance often make meal times challenging for parents and carers. Parents of

children with type 1 diabetes report more disruptive meal behaviours, including longer meal duration and more frequent food refusal compared to 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-centred 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 carbohydrate intake, and parents frequently report problems with this approach (81). Intensive insulin management offers greater flexibility in meal timing and carbohydrate quantities.

To assist the reliable intake of carbohydrate at meal-times and to minimise food refusal, the following strategies should be advised:

- structured meal-times
- avoidance of continuous eating habits
- small snacks including limits on low carbohydrate 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 carbohydrate consumption.

Parents should be advised 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 one small snacking episode between meals (7 to15g CHO) will assist with preventing food refusal as the child will be hungrier at main meals. A dietitian should advise regarding age appropriate carbohydrate amounts as it is necessary to ensure the anticipated carbohydrate 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 recognise parental stress and quickly learn to use their diabetes as a way of getting their favourite foods. It is important to emphasise 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 behaviours. Distractions such as the television and toys should be removed at mealtimes. Research has demonstrated that disruptive child behaviours can be reduced by establishing specific rules and consequences for mealtimes and teaching parents behavioural strategies for meals (104).

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

- In parental experience, it can be difficult at times to give pre-prandial 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 the risk of all aspects 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.

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 minimise 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 behaviours 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 towards the parents and entire family and not the individual child with 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 could benefit from both efforts, but targeted interventions are necessary to meet the specific needs of children with type 1 diabetes.

Physical activity

Physical activity confers many health benefits for healthy children. A strong graded inverse cross-sectional association has been observed between physical activity and 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 minutes per day of moderate and vigorous physical activity for all children (118), and WHO recommends this at least from five 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).

Practical monitoring of glycemic control

In this chapter, "plasma glucose" values refer to glucose values measured by capillary blood test ("finger prick", "blood glucose monitoring").

Plasma glucose (SMBG)

Glycemic control is often evaluated with plasma 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 plasma glucose, as sugar on the fingertips is a common reason for erroneously high glucose levels. The child should be introduced to 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 seven years be capable of taking plasma glucose tests and performing some basic interpretation of glucose levels under supervision. However, this should always be overseen by a parent or other caregiver, since 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 seven years of age, the recommended testing frequency of 4-6 times per day is rarely sufficient when striving for target glucose and HbA1c. Even with a higher testing frequency of 7 or 10 tests per day, the number of undetected hypo- 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 7-10 tests per day (125, 126). Nighttime SMBG is recommend 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 night-time monitoring of SMBG (125).

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

- ❖ Parent experience from Children with diabetes (CWD) conferences: “I have seen many young children in the age group of 5-6 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.

Continuous glucose monitoring (CGM)

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 seven years of age with type 1 diabetes. CGM should be available and utilized as a tool for adjusting insulin doses.

- 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 5-6 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, interpretetaion 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 daycare 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.

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 testing to detect problems with the supply of insulin from the pump. See the section on ketone monitoring below and the ISPAD guideline 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 or glargine) may help, but might also reduce the flexibility in basal insulin administration by temporary basal rates.
- Parents of preschool children who switch from multiple daily injections 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 hypoglycaemia (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 carbohydrate ratios can aid caregivers in insulin administration.
- Insulin pump therapy may be effective in helping to manage toddler-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 (for example the "modal day" when downloading data), and adjust insulin-to-carbohydrate ratios and correction factors only after a repeated pattern has been found.
- The frequency of insulin pump and CGM use varies between centres. Barriers to the use of these treatment options in preschool children need to be explored.

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, 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 cortisone (group I or II) can be used to treat skin reactions and break the vicious circle of itching after removal.

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 testing will be more easily available both for the child and parent. Blood ketone testing also gives the healthcare 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 (two values above 14 mmol/l within two hours that does not decline on a correction insulin dose) or when the child shows symptoms suggestive of ketosis (vomiting, nausea, stomach pain, fever, “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 carbohydrate 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 six years in the US 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).

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 six years with type 1 diabetes have experienced a severe hypoglycemic event with seizures/unconsciousness during the previous year; in US this figure is less than 3% (126).

The erratic daily life of a preschool child (food intake, activity, sleep, 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 seven 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, but 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% (<58mmol/mol) can frequently be achieved in children younger than six years with type 1 diabetes without an increased risk of severe hypoglycemia (126). In many countries, children younger than seven years most frequently have the lowest HbA1c. In Sweden, 74% of insulin treated children younger than seven years have HbA1c < 7.4% (< 57mmol/mol), and the overall frequency of severe hypoglycemia (seizures/unconsciousness) in the pediatric age (0-18 y.) is 2.5% (152).

For definitions and further information see the ISPAD Guidelines on Hypoglycemia (29).

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 2.5-3.6 mmol/l (45-64 mg/dl) (29). It is important not to give too much carbohydrate when treating hypoglycemia, in order to avoid subsequent hyperglycemia. Giving something that contains fat (i.e. milk, 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 5-7 g carbohydrate 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, carbohydrate 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.

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).

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 burn-out (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 actively to be 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 testing, 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 (for example finger pricks and carbohydrate 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 towards 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.

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 7-8 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 that are older, there are several paediatric 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 (e.g. sadness, low self-esteem) and functional areas (e.g. not having friends, schoolwork is not as good as it was before, 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 5-7 and also for youth ages 8-18 years. There are also PedsQL parent proxy reports for children ages 2-18 years (164). Diabetes-specific emotional distress can be assessed in children ages 8-11 (PAID-C) and 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 years 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 co-morbidity of depression; however they are two 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 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 glycaemic control in children and should be acknowledged and addressed.

Preschool care

Many preschools provide excellent care for children with type 1 diabetes. Parents and healthcare 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 eight languages (as of September 2015) 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 carbohydrate 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 organisations 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.

Alternative and complementary therapies

At times families try alternative indigenous remedies and even discontinue insulin. This can be avoided if parents are counselled 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.

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 counselled 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 sub-optimal management (169). In the US, 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 to white, but the prognostic value of HbA1c for predicting cardiovascular disease, nephro- 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 carbohydrate content of the meal. Carbohydrate 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 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 syringes with 30 U in 0.3ml 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 plasma glucose is the only method for monitoring glycemia. However, even this may not be feasible for some families due to the high cost of glucose strips. If possible, the child can be recommended a meal plan with a relatively consistent carbohydrate 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, 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 one week, and before and after dinner the next to get a more stringent picture of the day compared to random checks.

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 case of low literacy, a simpler insulin regime such as twice daily dosing with pre-mixed 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 recognise ‘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 that 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.

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 1999) (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 (semi) closed-loop solutions for insulin delivery.

It is important to include children younger than seven 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 seven 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 centres is thus necessary in order to conduct studies that are sufficiently powered.

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