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Pediatric Diabetes

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Insulin treatment in children and adolescents with diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 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 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Insulin treatment must be started as soon as possible after diagnosis (usually within 6h if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis (A).
- In all age groups, as close to physiological insulin replacement as possible and optimal glycemic control must be the aim (A). If available, an intensive insulin regimen is preferable [with analogs or regular/neutral protamine Hagedorn (NPH) insulin] (B). Although no insulin injection regimen satisfactorily mimics normal physiology, premixed insulins are not recommended for pediatric use (C). When insulin is provided through a help organization, the recommendation should be to provide regular and NPH as separate insulins, not premixed (E).
- Whatever insulin regimen is chosen, it must be supported by comprehensive education appropriate for the age, maturity, and individual needs of the child and family (A).

- Aim for appropriate insulin levels throughout 24h to cover basal requirements and higher levels of insulin in an attempt to match the glycemic effect of meals (E).
- Daily insulin dosage varies greatly between individuals and changes over time. It therefore requires regular review and reassessment (E).
- The distribution of insulin dose across the day shows great individual variation. Regardless of mode of insulin therapy, doses should be adapted to the circadian variation based on the daily pattern of blood glucose (B).
- Improvements in glycemic control, particularly when provided by intensive insulin treatment with multiple daily injection (MDI) or pump therapy with dose adjustments, reduces the risks of vascular complications. There is no reason to believe that this is not the case also in younger children (A, E).
- All children should have rapid-acting or regular insulin available for crisis management (E).
- It is essential that a small supply of spare insulin should be readily available to all children and adolescents so that the supply is uninterrupted (A).
- Children and adolescents should be encouraged to inject consistently within the same site (abdomen, thigh, buttocks, and arm) at a particular time in the day, but must avoid injecting repeatedly into the same spot to prevent lipohypertrophy (B).
- Insulins need to be administered by insulin syringes (or other injection devices) calibrated to the concentration of insulin being used (E).
- Regular checking of injection sites, injection technique, and skills remains the responsibility of parents, care providers, and health professionals (E).
- The use of pumps requires special education for users, but does not need to be restricted to centers with 24h access to pump expertise. The pump user or the family should be taught how to switch to multiple injections with pens or syringes in case of emergency (E).
- Health care professionals have the responsibility to advise parents, other care providers, and young people on adjusting insulin therapy safely and effectively. This training requires regular review, reassessment, and reinforcement (E).

Introduction

Since the last guidelines were published in 2009 (1) the changes have been modest with respect to insulin treatment, but the different modes have been refined especially when it comes to insulin pump treatment (continuous subcutaneous insulin infusion, CSII). Overall there has been a paradigm shift toward MDI and CSII over the last decade. While previously therapies have focused on avoiding painful injections in children, leading to regimens with little flexibility and dietary restrictions, nowadays intensive regimens with differential substitution of basal and prandial insulin are becoming the gold standard also in pediatric diabetology. As CSII has been proven to be safe in all ages and allows exact and flexible insulin dosing in small increments, multiple bolus dosing without need for injections, different prandial bolus options, and hourly adaptation of basal insulin, this form of therapy has become the insulin regimen of choice in many places particularly for the very young. However, there is wide variation in insulin regimens, both within regions as well as between pediatric diabetologists in the same country that are not related to inadequate funding of modern insulins or devices by national health care systems or insurance companies. Much of the variation can be explained by personal preference and experience of the respective diabetes team. As outcome comparisons through benchmarking and registries are implemented more widely in pediatric diabetes hopefully more guidance of regimens associated with better long-term prognosis becomes available.

Insulin therapy started in 1922 using regular insulin before each main meal and one injection in the night, usually at 1 AM. With the development of intermediate- and long-acting insulin, most patients moved to one or two injections per day after 1935. Already in 1960 a study showed that patients who were diagnosed between 1935 and 1945 and using one or two injections per day had a much higher risk of retinopathy after 15yr of diabetes compared with those diagnosed before 1935 using MDIs (61 vs. 9%) (2).

There are no randomized controlled studies comparing the longer term outcomes of using older more traditional insulins with newer regimens when both groups receive equal educational input. But the fact that the traditional insulins have certain clinical limitations, has led to the development of new analogs, rapid- and long-acting. These insulins represent some improvement in the care of diabetes, but the extent in a clinical long-term setting is not fully established.

Adult data is not readily transferable to pediatric patients of different age groups (3), but in children and adolescents, as in adults (4), rapid-acting insulin (aspart) is rapidly absorbed and eliminated (5). Higher maximum insulin concentrations in adolescents vs. children were reported both for insulin aspart and human regular insulin (6), but not with glulisine (7). The results from reference (6) are in line with the relatively impaired insulin sensitivity and higher insulin concentrations reported in healthy adolescents (8, 9). Such findings highlight the necessity to study the effects of these new insulins in all age groups separately. The different rapid-acting analogs

have different chemical properties, but no significant clinical difference in time of action and duration has been reported (10–12). Their advantages compared with regular (soluble) insulin are still under debate. The Cochrane review from 2006 (3) stated that in patients with type 1 diabetes, the weighted mean difference (WMD) of haemoglobin A1c (HbA1c) was −0.1% in favor of insulin analog (−0.2% when using CSII). In children and adolescents, blood glucose control has not been shown to be significantly improved with these analogs (13–17).

A reduction in hypoglycemia has been reported, both for lispro (14, 15, 18, 19) and aspart (20, 21). In the Cochrane review, the WMD of the overall mean hypoglycemic episodes per patient per month was −0.2 [95% confidence interval (CI): −1.1–0.7] (3) in favor of rapid-acting insulin analogs. In adolescents, a significantly reduced rate was found with analogs (17), but in prepubertal children, no difference was found (14, 16). In the included pediatric studies, there was no difference found in prepubertal children (13, 14) or adolescents (17).

The basal insulin analogs have different modes of action. Insulin glargine is a clear insulin which precipitates *in situ* after injection whereas insulin detemir is acylated insulin bound to albumin. These analogs have reduced day-to-day variability in absorption compared with NPH-insulin, with detemir having the lowest within-subject variability (22, 23). So far the reduction in hypoglycemia and not in HbA1c is the most prominent feature (24) [A], both for glargine (25–31) and detemir (32–35). Parental fear of severe hypoglycemia, especially during night time, is an impediment to achieving morning blood glucose control. Lower body mass index (z-score) has been reported for detemir (33).

In randomized trials, better blood glucose control has been obtained using MDIs and pumps compared with a twice daily treatment (36, 37). The Diabetes Control and Complications Trial (DCCT) proved convincingly that intensive insulin therapy including a heavy multidisciplinary approach concerning insulin dose adjustment, education in adolescents with multiple injections or pumps, resulted in a lower rate of long-term complications (37). Cognitive impairment
18yr after the conclusion of the DCCT study was unrelated to the rate of hypoglycemia during intensive therapy (38, 39). Also, in a cross-sectional clinical setting HbA1c, hypoglycemia, and diabetic ketoacidosis were not associated with the number of injections per day in pediatric populations (40). A longitudinal Australian study showed a significant decrease in retinopathy and microalbuminuria and only a slight decrease in HbA1c (from 9.1 to 8.5%) during the years 1990–2009 when MDI/CSII increased from 17 to 88%. Both retinopathy and microalbuminuria were significantly associated with one to two injections per day (41).

Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a preprogrammed basal rate and boluses are added to counterbalance the intake of carbohydrates. CSII has mostly been compared with MDI with NPH as the long-acting insulin (42–52). A reduction in hypoglycemia and improved blood glucose control has been reported. One randomized study has recently confirmed these findings when glargine was the basal insulin in use (53), although in a study with people naive to CSII or insulin glargine, glycemic control was no better with CSII therapy compared with glargine-based MDI therapy (54). Several studies have compared the use of analogs and regular insulin in pumps (55, 15). Insulin pumps from the onset have been found to result in superior metabolic control when compared with one to two injections per day (36) but not to MDI (53). In this study, diabetes treatment satisfaction was higher with CSII. In children <6yr of age, pumps enabled better long-term metabolic control and lowered the risk of severe hypoglycemia better than MDI, especially when initiated at diagnosis (56). Data from a large pediatric survey showed a low incidence of acute complications at a mean HbA1c-level of 8.0% (57). An international consensus on pediatric indications and instructions for use has been published (58). The most recent meta analysis of six pediatric randomized controlled trials with 165 patients showed a reduction of HbA1c by 0.24% with CSII compared with MDI (mostly using NPH as basal insulin) (59).

Unequivocal evidence for the benefit of MDI, the analogs, and CSII-treatment in children is lacking. Carefully structured randomized studies are needed. The fact that these modalities are more expensive than conventional treatment has been an obstacle to the implementation of the use of them in many countries. However, the DCCT was performed with regular and NPH insulins, which are widely available in most countries. This implies that ISPAD's new practical recommendations have to be applicable for the total diabetes community worldwide.

The DCCT study and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed that an improvement in long-term glucose control, as obtained with intensified insulin therapy including heavy support and education, can reduce the incidence of complications and delay the progressionofexistingcomplicationsintype1diabetes,
also in pediatric patients (37, 60, 61). A rapidly increasing numbers of centers around the world are

introducing the basal/bolus concept of intensive insulin treatment already from the onset of diabetes.

Continuous glucose monitoring (CGM), both in patients using pump and MDI (age 6–70), has shown to give improved HbA1c without increasing the number of severe hypoglycemia, but the decrease in HbA1c was lower in the group that used the sensor <70% of the time (62) and the emerging results from recent studies with 'closed loop systems' are promising (63–65).

Insulin availability

- Children and adolescents with type 1 diabetes are dependent on insulin for survival and should have access to adequate amounts of at least regular and NPH-insulin.
- ISPAD and IDF are working toward making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

Insulin formulation and species

- Many formulations of insulin are available; most have some role in the management of type 1 diabetes (Table 1).
- Human insulin is worldwide in distribution and use, but in many countries these are being superseded by analogs.
- Porcine or bovine insulins may be cheaper, but are virtually unavailable and subject to minimal use across the globe. The production of zinc-containing insulins (Lente) has been stopped.

The time of action of most insulins is dose-dependent in that a smaller dose has a shorter duration of effect and earlier (66, 67) peak and there is some evidence that lispro (68) and aspart (69) have the same time of action irrespective of dose. The results of these studies are obtained from a relatively small number of adult subjects, and the results in children may result in different profiles of action.

Regular insulin (short acting)

Regular soluble insulin (usually identical to human insulin) is still used as an essential component of most daily replacement regimens in many parts of the world either combined with:

- intermediate-acting insulin in twice daily regimen; or
- as premeal bolus injections in basal-bolus regimens (given 20–30min before meals) together with intermediate-acting insulin once or twice daily or a basal analog given once or twice daily.

Rapid-acting insulin analogs

Several novel insulin analogs have been developed. Three rapid-acting types are currently available for children (aspart, glulisine, and lispro). They have a rapid onset and shorter duration of action than regular insulin (see Table

Table 1. Types of insulin preparations and suggested action profiles according to manufacturers

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogs (aspart, glulisine, and lispro)	0.15–0.35	1–3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate acting Semilente (pork)	1–2	4–10	8–16
NPH	2–4	4–12	12–24
IZS Lente type	3–4	6–15	18–24
Basal long-acting analogs			
Glargine	2–4	None	Up to 24*
Detemir	1–2	None	Up to 24*
Long-acting			
Degludec†	0.5–1.5	None	>24
Ultralente type	4–8	12–24	20–30

NPH, Neutral Protamine Hagedorn insulin; IZS, insulin zinc suspension.
All insulins used must be produced under 'Good Manufacturing Practice/Good Laboratory Practice' conditions.
*The duration varies between individuals and is dose dependent
†Not yet approved worldwide.

1). No clinical significant differences have been found between the analogs in the pediatric population (70).

The rapid-acting analogs:

- can when necessary be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycemia but nocturnal hypoglycemia may also be reduced (14, 15, 18, 19);
- can in exceptional cases be given after food when needed (e.g., infants and toddlers who are reluctant to eat) (71);
- give a quicker effect than regular insulin when treating hyperglycemia, with or without ketosis, including sick days;
- are most often used as prandial or snack boluses in combination with longer acting insulins (see basal bolus regimens); and
- are most often used in insulin pumps (57).

Ultra-rapid-acting insulin

Ultra rapid-acting insulins are intended to better match the time–action profile of prandial insulins to cover the rapid increase in insulin meals and may be particularly useful for pumps and 'closed-loop' approaches. Because human insulin and rapid-acting insulin analogs generally exist in solution as stable hexamers, the delay in absorption is largely accounted for by the time it takes for hexamers to dissociate into monomers and dimers. New formulations of excipients to modify the insulin hexamer complex resulting in more rapid dissociation into dimers and monomers after s.c. injection are currently tested in clinical studies for human regular insulin (BIOD-090 to 123, Biodel, Danbury, CT, U.S.A.) and insulin aspart (FIAsp, NovoNordisk, Bagsvaerd, Denmark) (72), but none of these are approved yet.

Safety of insulin analogs

As insulin analogs are molecules with modified structure compared with human insulin, safety concerns have been raised due to changes in mitogenicity *in vitro* (73). In previous guidelines we have commented on the issue of a potential link between insulin analogs and cancer. A series of four highly controversial epidemiological papers in Diabetologia had indicated such possibility for glargine. In a new statement published online in May 2013 the European Medicines Agency (EMA) has concluded that insulin glargine containing medicines (Lantus®, Optisulin®, Sanofi, Paris, France) for diabetes do not show an increased risk of cancer. The EMA also notes that there is no known mechanism by which insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies (74). Presently, there are no safety concerns that would preclude the use of insulin analogs in the pediatric age group.

IV insulin

Regular and rapid-acting insulins are equally suited for i.v. therapy in the following crisis situations (75):

- Diabetic ketoacidosis.
- Control of diabetes during surgical procedures.

However, regular insulin is less expensive.

Intermediate-acting insulins

The action profiles of the isophane NPH insulins make them suitable for twice daily regimens, tailored basal substitution, and for pre-bed dosage in basal bolus regimens. As they are in suspension adequate pre injection mixing has to be ensured. Nevertheless they are associated with greater inter individual and intra individual variability compared with soluble basal insulins (76).

Basal insulin analogs

The currently available basal insulin analogs are glargine, detemir, and degludec.

They show a more predictable insulin effect with less day-to-day variation, compared with NPH insulin (76) and no significant clinical difference (in adult) between detemir and glargine has been found (77). In most countries, the two basal analogs are not formally approved for children below the age of 2yr – there is a report of successful use of glargine in children from <1 to 5yr of age (78). Basal analogs are more expensive (approximately +50 to 100%). Detemir is approved from age 2 years onwards in both the US and Europe, while glargine is approved from 2 years in Europe and 6 years in the US.

Glargine

A review of pediatric studies in the past 6yr of once daily insulin glargine found a comparable or small improvement in HbA1c but a reduced rate of hypoglycemia, and a greater treatment satisfaction in adolescents compared with conventional basal insulins (79). However, in a Finnish retrospective study no difference concerning hypoglycemia and HbA1c was observed when glargine was compared to NPH as basal insulins (80). A randomized controlled trial in 125

preschool children aged 2–6yr using CGM confirmed that a single injection of glargine appears at least equally effective to NPH usually injected twice daily also in the very young age. Thus glargine received regulatory approval for this age group (81).

The effect of glargine lasted for up to 24h in adults, however, a waning effect can be seen approximately 20h after injection (82). Lack of an accumulation effect of glargine given on consecutive days has been shown in one study (83). Some children report a burning sensation when injecting glargine due to the acid pH (84). Recently the EMA issued a positive opinion recommending approval for the investigational compound LY2963016 (Abrasia (R)), a new insulin glargine biosimilar product, for the treatment of type 1 and type 2 diabetes. The new insulin glargine product from Eli Lilly and Company (Indianopolis, U.S.A.) and Boehringer (Ingelheim, Germany) is the first biosimilar insulin recommended for approval in the European Union (EU). No pediatric data is available yet. Also, U300 is a new formulation of insulin glargine that is expected to last up to 40h. Preliminary data are showing positive outcomes with U300 performing the same in controlling blood glucose as insulin glargine but with less hypoglycemia during the day and night. U300 is based on the glargine molecule but requires a smaller volume of subcutaneous injection and U300 demonstrates a flatter and longer PK/PD profile than that of insulin glargine. Again, no pediatric data is available yet.

Detemir

A study with detemir in adults found the time of action to be between 6 and 23h when doses between 0.1 and 0.8U/kg were given (85). In a pediatric study, 70% of the patients used detemir twice daily (33). In adults, studies with detemir have shown less weight gain (35), which has been observed also in children and adolescents (33).

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with type 1 diabetes (23) and in a multicentre study the risk of nocturnal, severe hypoglycemia was reduced compared with glargine (86).

Long-acting insulins

Degludec

Degludec is a novel ultra-long-acting analog developed by NovoNordisk. It forms soluble multihexamers after subcutaneous administration, which then slowly dissociate and result in a slow and stable release of degludec monomers into the circulation extending the action for more than 40 initial results in pediatric patients, indicating that the long-acting properties of degludec are preserved in this age group also (87). The ultra-long action profile of degludec should allow less stringent timing of basal insulin administration from day-to-day which may be of use in the erratic lifestyles encountered frequently in the adolescent population. Another feature of degludec is that it can be mixed with short-acting insulins without the risk of forming hybrid hexamers and erratic pharmacokinetics/dynamics. Currently it is only approved for adults in several countries as the pediatric regulatory trials are currently evaluated.

PEGylated Lispro

LY2605541 is a novel long-acting insulin analog developed by Lilly, based on the polyethyleneglycol (PEG)-ylation principle. It has not yet received regulatory approval (88).

Ultralente

Ultralente insulins were designed to have a duration of more than 24h to meet basal insulin requirements, and therefore could be used in basal bolus injection regimens. Their action profile in children appears to be extremely variable (66), with dose accumulation effect. If available, basal insulin analogs are superior to traditional long-acting insulins.

Premixed insulin preparations

Premixed insulins (fixed ratio mixtures of premeal and basal insulins) are used in some countries particularly for prepubertal children on twice daily regimens. Although they reduce potential errors in drawing up insulin, they remove the flexibility offered by separate adjustment of the two types. Such flexibility is especially useful for children with variable food intake. Recently, premixed insulins have also become available with rapid-acting analogs. Biphasic insulin aspart 30 (30% aspart and 70% aspart protamine suspension) given for three main meals combined with NPH at bedtime was equally efficient as premixed human insulin (70% NPH) given for morning and bedtime with regular insulin for lunch and dinner in adolescents (89).

- There is no clear evidence that premixed insulins in young children are less effective, but there some evidence of poorer metabolic control when used in adolescents (40).
- Premixed insulins with regular (or rapid acting):NPH in different ratios, e.g., 10:90, 15:85, 20:80, 25:75, 30:70,

40:60, and 50:50 are available in various countries from different manufacturers.

- Premixed insulins are suitable for use in pen injector devices.
- Premixed insulins may be useful to reduce the number of injections when compliance (or adherence) to the regimen is a problem.

Inhaled insulin

This new form of insulin therapy has been investigated in children above 12yr of age as part of a study in adults, but was not approved for clinical use in children. The sale of inhaled insulin was discontinued in 2007. Afrezza® (MannKind, Valencia, CA, U.S.A.) is a ultra rapid-acting mealtime insulin therapy being developed for type 1 and type 2 diabetes mellitus. It is a drug-device combination product, consisting of insulin inhalation powder and an inhaler which has received a conditional approval for adults by the Food and Drug Administration (FDA). No pediatric data is published yet.

Insulin concentrations

The most widely available insulin concentration is 100IU/mL (U100). Treatment with U40 (40IU/mL), U50, or other concentrations such as U500 is also acceptable, subject to availability and special needs. Care must be taken to ensure that the same concentration is supplied each time new supplies are received. Very young children occasionally require insulin diluted with diluent obtained from the manufacturer, but special care is needed in dilution and drawing up the insulin into the syringe. Rapid acting insulin can be diluted to U10 or U50 with sterile NPH diluent and stored for 1 month (90, 91) for use in pumps for infants or very young children. Switching children from U40 to U100 insulin may increase practical problems in drawing up insulin, but has not shown a decline in glycemic control in a large pediatric cohort (92).

Storage of insulin

Regulatory requirements state that the labeled insulin productmustretainatleast95%ofitspotencyatexpiry date (93). At room temperature (25°C, 77°F), insulin will lose <1.0% of its potency over 30d. In contrast, insulin stored in a refrigerator will lose <0.1% of its potency over 30d (93). Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency (93). The individual manufacturer's storage recommendations and expiry dates must be adhered to. These usually recommend that:

- Insulin must never be frozen.
- Direct sunlight or warming (in hot climates) damages insulin.
- Patients should not use insulin that has changed in appearance (clumping, frosting, precipitation, or discoloration).
- Unused insulin should be stored in a refrigerator (4–8°C).
- After first usage, an insulin vial should be discarded after 3 months if kept at 2–8°C or 4 wk if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10–14d of use in room temperature.
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (matka), (94) or a cool wet cloth around the insulin will help to preserve insulin activity.
- Storage requirements for unused or used pens may differ from vials, and the individual manufacturers guidelines should be observed.

In children on small doses of insulin, 3mL cartridges instead of 10mL vials should be chosen to avoid wasting of insulin.

Injection sites

The usual injection sites are:

- Abdomen (the preferred site when faster absorption is required and it may be less affected by muscle activity or exercise).
- Front of thigh/lateral thigh (the preferred site for slower absorption of longer acting insulins).
- The lateral upper quadrant of the buttocks (the whole upper quadrant is useful in small children).
- Lateral aspect of arm (in small children with little subcutaneous fat, intramuscular injection is more likely and it may cause unsightly bruising).
- Rotation of injection sites are important also within the same area of injection.
- Cleaning or disinfection of skin is not necessary unless hygiene is a real problem. Infection at injection sites is rare (95).

Problems with injections

Local hypersensitivity reactions to insulin injections are uncommon but when they do occur, formal identification of the insulin (or more rarely preservative) responsible may be possible with help from the manufacturers. A trial of an alternative insulin preparation may solve the problem. If true allergy is suspected, desensitization can be performed using

protocols available from the manufacturers. Adding a small amount of corticosteroids to the insulin may help (96). Lipohypertrophy with the accumulation of fat in lumps underneath the skin are common in children (97). Lipoatrophy was said to be uncommon since the introduction of highly purified insulins and analogs (98).But a very recent report indicates that lipoatrophy is a growing problem in patients using insulin analogs and possibly mostly in patients on pumps (99, 100).

Painful injections are a common problem in children. Check angle, length of the needle ,and depth of injection to ensure injections are not being given intramuscularly and that the needle is sharp. Reused needles can cause more pain (101). Indwelling catheters (Insuflon®, iport®) can decrease injection pain (102).

Leakage of insulin is common and cannot be totally avoided. Encourage slower withdrawal of needle from skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site.

Bruising and bleeding are more common after intramuscular injection or tight squeezing of the skin. Use of thinner needles have shown significantly less bleeding at the injection site (103).

Bubbles in insulin should be removed whenever possible. If the bubble is not big enough to alter the dose of insulin it should not cause problems. When using insulin pens, air in the cartridge can cause drops of insulin appearing on the tip of the pen needle, if withdrawn too quickly (104).

Insulin absorption

Insulin activity profiles show substantial variability both day-to-day in the same individual and between individuals, particularly in children (6, 66). The onset, peak effect, and duration of action depend upon many factors which significantly affect the speed and consistency of absorption. Young people and care providers should know the factors which influence insulin absorption such as:

- Age (young children, less subcutaneous fat→faster absorption).
- Fat mass (large subcutaneous fat thickness (105), lipohypertrophy (106), also with rapid-acting analogs (107)→slower absorption).
- Dose of injection (larger dose→slower absorption (66)
- Site and depth of s.c. injection (abdomen faster than thigh (108); no good data exist on absorption from thigh vs. buttock).
- s.c. vs. i.m. injection (i.m. injection→faster absorption in thigh (109). Accidental i.m. injections can cause variable glucose control.
- Exercise (leg injection, leg exercise→faster absorption) (110).
- Insulin concentration, type, and formulation (lower concentration→faster absorption) (111).
- Ambient and body temperature (higher temperatures→faster absorption) (105).
- In general, the absorption speed of rapid-acting analogs is less affected by the above mentioned factors (112–114).
- There is no significant difference in the absorption of glargine from abdomen or thigh (115). Exercise does not influence glargine absorption (116). There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals (117).

Note: Faster absorption usually results in shorter duration of action

Hyaluronidase may increase absorption speed, either added to insulin, or injected prior to inserting an insulin pump infusion set ('pre-administration') (118). Long-term effectivity and safety need to be established before this can be recommended for a pediatric population.

Insupad (R), (Insuline, Petach Tikva, Israel) is a device that warms an area 2×4cm^2 just prior to injection of bolus insulin. The device is resited daily. It has been shown to reduce the total daily insulin dose by 20%, and achieve a 75% reduction in hypoglycemic episode. The Insupatch (R) (Insuline, Petah Tikva, Israel) has been developed for insulin pump therapy and has an integral heating element that is activated when a bolus is delivered. The action of insulin aspart peaks at 73min without heat and at 43min with heat (119). With these new devices the insulin requirements are lower, and can achieve an earlier peak reducing area under curve (AUC) for glucose and also reduce the risk of hypoglycemia.

Administration of insulin

Devices for insulin delivery

Insulin syringes. Syringes are available in a variety of sizes in different countries, ensuring accurate dose delivery, but it is desirable to have small syringes with 1U per mark (e.g., 0.3mL, 100U/mL) available for small children.

Plastic fixed-needle syringes with small dead space are preferable to glass syringes.

Plastic fixed-needle syringes are designed for single use. However, many individuals with diabetes successfully reuse them without significant increase in risk of infection (120). Reuse should be discouraged if there is concern about hygiene or injection pain as they become blunted when reused (101).

Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U100 syringes).

Syringes must never be shared with another person because of the risk of acquiring blood-borne infection [e.g., hepatitis and human immunodeficiency virus (HIV) infections].

It is advisable that all children and adolescents with diabetes should know how to administer insulin by syringe because other injection devices may malfunction.

Appropriate disposal procedures are mandatory. Specifically designed and labeled 'sharps containers' may be available from pharmacies and diabetes centers. Special needle clippers (e.g., Safeclip®, Becton Dickinson, Franklin lakes, NJ, U.S.A.) may be available to remove the needle and make it unusable. Without a 'sharps container', syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

Pen injector devices. Pen injector devices containing insulin in prefilled cartridges have been designed to make injections easier and more flexible. They eliminate the need for drawing up from an insulin vial; the dose is dialed up on a scale and they may be particularly useful for insulin administration away from home, at school, or on holidays.

Special pen injection needles of small size (4–6mm) and diameter are available and may cause less discomfort on injection (103). Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to half unit increments. Half-unit pens are particularly useful for dosing in young children and during the remission phase when small dosing increments may help to avoid hypoglycemia. A few pens have a memory for taken doses, which can be practical especially for teenagers. Availability is a problem in some countries and although pen injectors may improve convenience and flexibility, they are a more expensive method of administering insulin.

Pen injector devices are useful in children on multiple injection regimens or fixed mixtures of insulin, but are less acceptable when free mixing of insulins is used in a two- or three-dose regimen.

Needle length. The traditional needle length of 8–13mm (27 G) has been replaced by thinner needles that are 4 – 8mm long (30–32 G). There is no longer reason for needles longer than 6mm (121). A two finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection (122).

With 4–6mm needles, the injections can be given perpendicularly without lifting a skin fold but only if there is enough subcutaneous fat, which often is the case in pubertal girls (at least 8mm as the skin layers often are compressed when injecting perpendicularly) (123). Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh (123, 124). When injecting into the buttocks, the subcutaneous fat layer is usually thick enough to inject without lifting a skinfold. There is a risk of intradermal injections if 4–6mm needles are not fully inserted into the skin.

Subcutaneous indwelling catheters. Such catheters (e.g., Insuflon®, Unomedical, Denmark, i-port®, Medtronic, Northridge, CA, U.S.A.) inserted using topical local anesthetic cream, may be useful to overcome problems with injection pain at the onset of diabetes (102). The use of indwelling catheters do not affect metabolic control negatively (125). In children with injection problems, HbA1c has been lowered by using Insuflon(126). However, the use of a basal analog and a short-or rapid-acting insulin at the same injection time in an indwelling catheter is not advisable in case of possible interaction of the two insulins. Indwelling catheters should be replaced every 2–4d to prevent scarring and a negative effect on insulin absorption (127, 128).

Automatic injection devices. Automatic injection devices are useful for children who have a fear of needles. Usually a loaded syringe is placed within the device, locked into place and inserted automatically into the skin by a spring-loaded system. The benefits of these devices are that the needle is hidden from view and the needle is inserted through the skin rapidly. Automatic injection devices for specific insulin injectors are available (129).

Jet injectors. High pressure jet injection of insulin into the s.c. tissue has been designed to avoid the use of needle injection. Jet injectors may have a role in cases of needle phobia. The use of jet injectors has resulted in metabolic control comparable both to conventional injections and CSII (130), but problems with jet injectors have included a variable depth of penetration, delayed pain, and bruising (131). In a recent study, the insulin absorption was enhanced and the duration of the glucose lowering action was reduced when using aspart insulin with a jet injector (132).

Continuous subcutaneous insulin infusion. The use of external pumps is increasing and is proving to be acceptable and successful (42–44, 46–52, 57), even in young infants (48, 133). Randomized studies in the pre-school group have failed to show better glycemic control (42, 134).

The positive effects on glycemic control and hypoglycemia in non-randomized observational studies have probably been influenced by the patient selection in these studies, such as good compliance and/or poor metabolic control. Pump therapy has also been found effective in recurrent ketoacidosis (135, 136). This highlights the importance of individualizing the decision of the modality of therapy for every situation. An insulin pump is an alternative to treatment with MDI (including basal analogs) if HbA1c is persistently above the individual goal, hypoglycemia is a major problem or quality of life needs be improved (137, 138).

Pump therapy is an option for many patients to improve treatment satisfaction. In a review of five pediatric studies comparing CSII vs. MDI, a majority of the patients and families chose to continue with CSII after the completion of the studies, even in studies where insulin pumps showed no objective benefit (139). A randomized study of CSII vs. MDI from the onset of diabetes in 7–17yr olds also found a significant improvement in treatment satisfaction in spite of no difference in HbA1c (140).

Insulin pump use is increasing particularly in the younger age group during the recent years, as clinicians become more comfortable with this form of treatment. In countries with a high pump penetration centers are starting particularly their preschool children from diabetes onset with CSII. There has been circumstantial evidence that this is associated with a more rapid recovery of mothers from depressive symptoms associated with the diagnosis of a chronic disease in their child (141).

CSII is used as a more physiological insulin replacement therapy (133). The newer generation of 'smart' pumps that automatically calculate meal or correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors have shown some benefits, i.e., reduced glucose variability (142) and a higher percentage of post-meal glucose readings within target level (143).

Insulin pump treatment may be hazardous when education and adherence to therapy is inadequate, because of the smaller depot of subcutaneous insulin and the sudden rise in ketones when insulin supply is interrupted. Pump stops for 5h in adult patients resulted in B-ketone (beta-hydroxybutyrate) levels of approximately 1−1.5mmol/L but not DKA. Results in children and adolescents seem to be similar (144). Short disconnection of the pump gives a blood glucose increment of ≈1mg/dL, i.e., 1.5mmol/L per 30min (145).

The risk of DKA when using pumps comparing with MDI is unchanged in several studies (50, 146) and even lower in a recent long-term cohort study (147).

A literature review found an increased risk of DKA in pediatric pump patients in some studies (148). Data on national levels have shown both an unchanged(149) and an increased risk of DKA (150, 147).

Patients using insulin pumps, especially younger children, will benefit from being able to measure B-ketones.

The short interruption of insulin supply when changing infusion sets did not affect short-term glucose control. However, a 30-min interruption of basal insulin infusion resulted in significant glucose elevation; approximately 1mg/dL for each minute basal insulin infusion was interrupted (i.e., 1.5mmol/L per 30min) (145). Patients must be instructed on treatment of hyperglycemia, giving insulin with a pen or syringe in case of suspected pump failure (hyperglycemia and elevated ketone levels).

Rapid-acting insulin analogs are used in most pumps, and a meta-analysis has shown a 0.26% lower HbA1c when comparing with human regular insulin (28). Regular insulin is less often used in pumps but works well if rapid-acting insulin is not available.

Longer use of the infusion site may yield a faster peak of insulin and a shorter duration of insulin effect (151, 152).

Of the three rapid-acting insulins in current use, there are considerably more trial data relating to the use of insulin aspart and insulin lispro than to the use of insulin glulisine. The more widespread use of insulins aspart and lispro is supported by CSII studies that have demonstrated higher rates of occlusion and symptomatic hypoglycemia with insulin glulisine than with either of the other rapid-acting analogs (153). Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps (57). Motivation appears to be a crucial factor for the long-term success of this form of therapy (154).

Sensor-augmented pump therapy and 'closed loop'. In the Juvenile Diabetes Research Foundation (JDRF) study a significant improvement in HbA1c using sensor-augmented pump (SAP) compared with self-monitoring of blood glucose, but only in adults in the intention-to-treat-analysis (155). However, in a *post hoc* analysis the improvement in HbA1c was seen also in the non-adults who used the CGM at least 6d/wk. Many children and adolescents find it difficult to wear the sensor continuously (156), which may have prevented an overall positive effect on metabolic control in the JDRF

study. In another randomized trial, an improvement was only seen when the device was worn for more than 60% of the time (157). In the STAR 3 1-yr study, which included both children and adolescents, they were reported to achieve treatment satisfaction (158), reduced HbA1c (159), and glycemic variability (160). Which patients are likely to profit from sensor-augmented therapy needs to be studied further.

An automatic shut-off of the pump to prevent hypoglycemia when the sensor has fallen below a preset threshold and the patient does not respond to alarms has been used successfully in children and adolescents (161). There was no evidence that this temporary shutoff may lead to a increased risk for DKA.

Short-term experiments in adolescents with a closed loop system where the sensor glucose level regulates the insulin delivery in the pump have been published (65). In 2011, a closed loop system used during the night in children and adolescents showed reduced risk of hypoglycemia compared with standard pump treatment (162). In 2013, a closed loop system used in a youth camp setting showed less nocturnal hypoglycemia and tighter glucose control than with SAP (64). Meanwhile studies have been also published using these systems safely and effectively in studies with pediatric patients in a home setting (163, 164).

Injection technique

Injections by syringe are usually given into the deep subcutaneous tissue through a two-finger pinch of skin at a 45° angle. A 90° angle can be used if the s.c. fat is thick enough. Pen injector technique requires careful education including the need to ensure that no airlock or blockage forms in the needle. A wait of 15s after pushing in the plunger helps to ensure complete expulsion of insulin through the needle (104).

Self injection. It should be emphasized that a proportion of people with diabetes have a severe long lasting dislike of injections which may influence their glycemic control. For these persons, an injection aid, i-port, Insuflon (126), or insulin pump therapy may improve compliance.

There is great individual variation in the appropriate age for children to self-inject (165). The appropriate age relates to developmental maturity rather than chronological age. Most children over the age of 10yr either give their own injections or help with them (165). Younger children sharing injection responsibility with a parent or other care provider may help to prepare the device or help push the plunger and subsequently under supervision be able to perform the whole task successfully. Self-injection is sometimes triggered by an external event such as overnight stay with a friend, school excursion, or diabetes camp. Parents or care providers should not expect that self injection will automatically continue and should accept phases of non-injection with the need for help from another person. Younger children on multiple injection regimens may need help to inject in sites difficult to reach (e.g., buttocks) to avoid lipohypertrophy.

Self-mixing of insulin. When a mixture of two insulins is drawn up (e.g., regular mixed with NPH), it is most important that there is no contamination of one insulin with the other in the vials. To prevent this, the following principles apply. There is no uniformity of advice but most often it is taught that regular (clear insulin) is drawn up into the syringe before cloudy insulin (intermediate- or long-acting). Vials of cloudy insulin must always be gently rolled (not shaken) at least 10 times, preferably 20 times (166), to mix the insulin suspension before carefully drawing it up into the clear insulin. If the cloudy insulin is of Lente type the mixture must be administered immediately, otherwise the regular component interacts with zinc which blunts the action (167, 168). Insulins from different manufacturers should be used together with caution as there may be interaction between the buffering agents. Rapid-acting insulin analogs may be mixed in the same syringe as NPH immediately before injections (169, 170). Immediate injection of a mixture of Ultralente and Humalog has been found not to diminish the Humalog effect (171). The manufacturer recommends that glargine should not be mixed with any other insulin before injection, but there is some evidence that it can be mixed with insulin lispro and aspart without affecting the blood glucose lowering effect (172) or HbA1c (173). The manufacturer recommends that detemir should not be mixed with any other insulin before injection. There are no available studies on this.

Insulin regimens

The choice of insulin regimen will depend on many factors including: age, duration of diabetes, lifestyle (dietary patterns, exercise schedules, school, work commitments, etc.), targets of metabolic control, and particularly individual patient/family preferences.

- The basal-bolus concept (i.e., a pump or intermediate-acting/long-acting insulin/basal analog once or twice daily and rapid-acting or regular boluses with meals and snacks (174) has the best possibility of imitating the physiological insulin profile with dose adjustments.
- At least two injections of insulin per day (mixing short-acting/rapid-acting and basal insulin) are advisable in most children.

- Most regimens include a proportion of short- or rapid-acting insulin and intermediate-acting insulin or long-acting basal analog, but some children may during the partial remission phase maintain satisfactory metabolic control (i.e., an HbA1c close to the normal range) on intermediate- or long-acting insulins or alternatively prandial insulin without basal alone.

Principles of insulin therapy

Frequently used regimens

Basal-bolus regimen

- Of the total daily insulin requirements, 40–60% should be basal insulin, the rest pre-prandial rapid acting or regular insulin.
- Injection of regular insulin 20–30min before each main meal (breakfast, lunch, and the main evening meal).
- Intermediate-acting insulin or basal/long-acting analog at bedtime or twice daily (mornings and evenings).
- Injection of rapid-acting insulin analog immediately before (or in exceptional cases after) (14, 71) each main meal (breakfast, lunch, and main evening meal) adjusted to glycemia, meal content, and daily activity. Rapid- acting analogs may need to be given 15–20min before the meal to have full effect, especially at breakfast (175, 176).
- Intermediate-acting insulin or basal/long-acting analog at bedtime, probably before breakfast and occasionally at lunchtime or twice daily (mornings, evenings, preferable with small doses <10–15U that do not have a 24-h duration).

Pump therapy (CSII)

- Insulin pump regimes are gaining popularity with a fixed or variable basal rate and bolus doses with meals.

Sensor-augmented therapies • CGM systems used together with CSII or MDI is well tolerated in children with diabetes, but the usage over time declined in studies (155, 177).

Less-intensive regimens

- Three injections daily using a mixture of shortor rapid- and intermediate-acting insulins before breakfast; rapid or regular insulin alone before afternoon snack or dinner/the main evening meal; intermediate-acting insulin before bed or variations of this.
- Two injections daily of a mixture of short- or rapid and intermediate-acting insulins (before breakfast and dinner/the main evening meal).

Note: None of these regimens can be optimized without frequent assessment by self-monitored blood glucose (SMBG)

Daily insulin dosage

Dosage depends on many factors such as

- Age
- Weight
- Stage of puberty
- Duration and phase of diabetes
- State of injection sites
- Nutritional intake and distribution
- Exercise patterns
- Daily routine
- Results of blood glucose monitoring and glycated hemoglobin
- Intercurrent illness

Guideline on dosage

The ‘correct’ dose of insulin is that which achieves the best attainable glycemic control for an individual child or adolescent without causing obvious hypoglycemia problems, and the harmonious growth according to weight and height in children’s charts.

- During the partial remission phase, the total daily insulin dose is often <0.5IU/kg/d.
- Prepubertal children (outside the partial remission phase) usually require 0.7–1.0IU/kg/d.
- During puberty, requirements may rise substantially above 1.2IU/kg/d and even up to 2IU/kg/d.

Distribution of insulin dose

Children on twice daily regimens often require more (around two thirds) of their total daily insulin in the morning and less (around one third) in the evening. On this regimen, approximately one third of each insulin dose may be short- or rapid-acting insulin and approximately two thirds may be intermediate-acting insulin although

these ratios change with greater age and maturity of the young person.

On basal-bolus regimens the night-time intermediate-acting insulin may represent between 30% (typical for regular insulin) and 50% (typical for rapid-acting insulin) of total daily insulin. Approximately 50% as rapid-acting or approximately 70% as regular insulin is divided up between three and four premeal boluses. When using rapid-acting insulin for premeal boluses, the proportion of basal insulin is usually higher, as short-acting regular insulin also provides some basal effect.

Glargine is often given once a day, but many children may need to be injected twice a day or combined with NPH to provide full daytime basal insulin coverage (29, 178). Glargine can be given before breakfast, before dinner, or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often after breakfast injection (82). When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia (178). After that, the dose should be individually tailored.

Detemir has been used once or twice daily in pediatric studies. Dosage must be individualized according to metabolic needs and self monitoring results (33). When transferring to detemir from NPH, the same doses can be used to start with, but be prepared to increase the detemir dose according to SMBG results.

Insulin dose adjustments

Soon after diagnosis

- Frequent advice by members of the diabetes team on how to make graduated alterations of insulin doses at this stage is of high educational value.
- Insulin adjustments should be made until target BG levels and target HbA1c are achieved.
- If frequent SMBG is not possible, urinary tests are useful, especially in the assessment of nocturnal control.

Later insulin adjustments

- On twice daily insulin regimens, insulin dosage adjustments are usually based on recognition of daily patterns of blood glucose levels over the whole day, or a number of days or in recognition of glycemic responses to food intake or energy expenditure.
- On basal-bolus regimens, flexible or dynamic adjustments of insulin are made before meals and in response to frequent SMBG. In addition, the daily blood glucose pattern should be taken into account. The rapid-acting analogs may require postprandial BG tests approximately 2h after meals to assess their efficacy. Frequently, insulin is dosed based on food consumption (carbohydrates) and the current SMBG reading. Pumps have the possibility of delivering the bolus dose in different ways in order to reduce the postprandial blood glucose excursions (179). Many newer insulin pumps allow programming algorithms (bolus guide) for these adjustments for current blood glucose and amount of carbohydrate intake.
- Downloading the blood glucose meter to a computer can help in discovering daily patterns in glucose levels.

Advice for persistent deviations of BG from target

- Elevated BG level before breakfast→increase predinner or pre-bedintermediate- or long-acting insulin (BG tests during the night are needed to ensure that this change does not result in nocturnal hypoglycemia).
- Rise in BG level after a meal→increase premeal rapid/regular insulin.
- Elevated BG level before lunch/dinner meal→increase pre-breakfast basal insulin or increase dose of pre-breakfast regular/rapid-acting insulin if on basal-bolus regimen. When using rapid-acting insulin for basal-bolus regimen, the dose or type of basal insulin may need to be adjusted in this situation as the analog has most of its effect within 2–3h after injection.
- When using carbohydrate counting, persistent elevations of post meal BG may require adjustment in the insulin to carbohydrate ratio. The '500-rule' is often used to obtain an initial ratio when starting with carbohydrate counting (divide 500 by the total daily dose – basal and bolus insulin – to find the amount of carbohydrates in grams that 1U of insulin will cover).
- The insulin to carbohydrate ratio for an individual meal, for example, breakfast, can be calculated by dividing the carbohydrate content in grams by the insulin dose in units. This method often gives the most accurate results for an individual meal, and can preferably be used for breakfast when there usually is an increased insulin resistance. If the glucose before and after the meal differ more than 2–3mmol/L (20–30mg/dL), the correction factor (see below) can be used to calculate out how much more (or less) insulin should have been ideally given for a certain meal.
- Some centers also count protein and fat for calculating insulin requirements when using a pump [fat-protein units (FPUs)] (174). One FPU equals 100kcal of fat or

protein, and requires the same amount of insulin (as an extended bolus) as 10g of carbohydrates.

- Correction doses (also called insulin sensitivity factor, correction factor) can be used according to the '1800 rule', i.e., divide 1800 by total daily insulin dose to get the mg/dL that 1U of rapid acting insulin will lower the blood glucose. For mmol/L, use the '100 rule', i.e., divide 100 by total daily insulin dose (180). For regular insulin, a '1500 rule' can be used for results in mg/dL and a '83rule' for results in mmol/L. However, correction doses should always be adjusted individually before administration, depending on other factors affecting insulin resistance like exercise.
- Rise in BG level after evening meal→increase pre-evening meal regular/rapid-acting insulin.

In addition

- Unexplained hypoglycemia requires re-evaluation of insulin therapy.
- Hyperglycemia or hypoglycemia occurring in the presence of intercurrent illness requires a knowledge of 'sick day management'.
- Day-to-day insulin adjustments may be necessary for variations in lifestyle routines, especially exercise or dietary changes.
- Various levels of exercise require adjustment of diabetes management.
- Special advice may be helpful when there are changes of routines, travel, school outings, educational holidays/diabetes camps, or other activities which may require adjustment of insulin doses.
- During periods of regular change in consumption of food (e.g., Ramadan) the total amount of insulin should not be reduced but redistributed according to the amount and timing of carbohydrate intake. However, if total calorie intake is reduced during Ramadan, the daily amount of bolus insulin for meals usually needs to be reduced, for example, to two thirds or three quarters of the usual dose.

Dawn phenomenon

Blood glucose levels tend to rise in the hours of the morning (usually after 05:00hours) prior to waking. This is called the dawn phenomenon. In non diabetic individuals the mechanisms include increased nocturnal growth hormone secretion, increased resistance to insulin action, and increased hepatic glucose production. These mechanisms are more potent in puberty.

Pump studies (181–183) have shown that younger children often need more basal insulin before midnight than after (reversed dawn phenomenon). With a basal/bolus analog regimen this can be achieved by giving regular instead of rapid-acting insulin for the last bolus of the day (night time blood glucose levels need to be checked).

In individuals with type 1 diabetes, fasting hyperglycemia is predominantly caused by waning insulin levels, thus exaggerating the dawn phenomenon. Morning hyperglycemia can in some cases be preceded by nighttime hypoglycemia (so called Somogyi phenomenon), being seen less often in pump therapy compared with MDI (184). Correction of fasting hyperglycemia is likely to require an adjustment of the insulin regimen to provide effective insulin levels throughout the night and the early morning by the use of:

- intermediate-acting insulin later in the evening or at bedtime a longer acting evening insulin/basal insulin analog, and
- change to insulin pump treatment.

Conflicts of interest

RH has received lecture honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Johnson & Johnson, and Roche. PJ-C has received lecture fees from Eli Lilly, Novo-Nordisk, Sanofi, Abbott, Bayer, Medtronic, and Roche.

TD has received honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Biodel, Bekton Dickinson, Boehringer, and Roche. TB has received honoraria from NovoNordisk, Lilly, Sanofi, and Medtronic. HJB has received honoraria and lecture fees from Novo Nordisk, Lilly, Sanofi, Medtronic, and Roche. LD has received research support from Novo Nordisk and Advisory Groups for Sanofi. The remaining authors (TU, BS, and LM) have declared no potential conflicts. Editors of the ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Carlo Acerini, Maria Craig, David Maahs, and Ragnar Hanas.

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