Assessment and monitoring of glycemic control in children and adolescents with diabetes

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Assessment of glycemic control

Aims

• To assess with accuracy and precision the level of glycemic control achieved by each individual so that they may benefit from attaining their most realistic glycemic targets (1, 2) (A).
• To help in preventing both the acute complication of hypoglycemia and the chronic complications of microvascular and macrovascular diseases (A).
• To minimize the effect of hypoglycemia (A) and hyperglycemia (B/C) on cognitive function and mood.
• To collect data on glycemic control from each diabetes center for comparison with stated local, national, and international standards so that the performance and standards of the interdisciplinary Diabetes Care Teams may be improved (3).

General principles determining glycemic targets

Measurement of immediate glycemic control is best determined by self-monitoring of blood glucose (SMBG) as this provides immediate documentation of hyperglycemia and hypoglycemia, allowing implementation of strategies to optimally treat, as well as to avoid, out of range glucose values.

Hemoglobin A1c (HbA1c) is the only measure of glycemic control for which robust outcome data are available. Elevated HbA1c predicts long-term microvascular and macrovascular outcomes (1, 2) (A). However, HbA1c has limitations as a measure of glycemic control, i.e., average blood glucose (BG). In the Diabetes Control and Complications Trial (DCCT), the same average HbA1c conferred significantly higher risk of microvascular complications (4) and hypoglycemia (5) in the conventionally treated patients vs. intensively treated patients. HbA1c of 7.0% corresponded also to a higher average BG (measured seven times a day) of 192 mg/dL in the conventionally treated patients vs. 163 mg/dL in the intensively treated patients (6).

HbA1c can only be one of the several measures of optimal glycemic control, along with documented hypoglycemia, type of treatment, patient’s age, and quality of life.

The DCCT, and similar studies, provides clear evidence in adults and adolescents that better metabolic control, as measured by a lower HbA1c level, is associated with fewer and delayed microvascular complications (1, 2, 7–15). The DCCT also showed that patients in the intensive treatment group had less risk of retinopathy than the conventional group even when having the same HbA1c (4). Additional studies have shown that frequent and accurate BG monitoring and
concomitant optimal adjustment of insulin to carbohydrate intake and exercise (16, 17) are required to attain and to maintain optimal metabolic control. Finally, follow-up data from the DCCT indicate that 5–7 yr of poor glycemic control, even during adolescence and young adulthood, results in an increased risk for microvascular and macrovascular complications in the subsequent 6–10 yr (7, 9, 13, 14, 18). These data support trying to achieve for each individual an HbA1c as close to the normal range as possible.

Both hypoglycemia and hyperglycemia may result in central nervous system (CNS) alterations, both acutely and chronically. Lower HbA1c levels may be associated with an increase in episodes of severe hypoglycemia (1, 2) (A). Severe hypoglycemia is a significant cause for morbidity and occasional mortality in young people with type 1 diabetes (19–22). Most, but not all, studies have shown that repeated episodes of hypoglycemic seizures in young children may cause permanent CNS changes and/or cognitive dysfunction (23–30). Additionally, the long-term follow-up of the DCCT participants has been reassuring that there was no evidence for permanent neurocognitive changes related to hypoglycemia in adolescent and young adult individuals, suggesting that the effect of severe hypoglycemia on long-term neuropsychological functioning may be age dependent (31, 32). Regardless of the long-term sequelae of hypoglycemia, the fear of hypoglycemia has been shown to cause intentional decreases in insulin dosing, resulting in elevated glucose levels and increased HbA1c (33).

Conversely, there is evidence that chronic hyperglycemia (particularly in young boys) might be related to poorer neurocognitive outcomes (34) (B). Acute hyperglycemia (BG > 15 mmol/L) is associated with reduced motor cognitive performance in a field study of adults with type 1 diabetes (35) (B), confirming findings using clamp studies in children of reduced performance when BG was >20 mmol/L compared with 5–10 mmol/L (36) (B). Families report effects of hyperglycemia (15–18 mmol/L) on mood and coordination (37) (C). Long-term studies on hyperglycemia and cognitive functioning are not available.

Brain imaging studies show that both hypoglycemia and hyperglycemia cause changes in the white and gray matter of developing brains (38). There is evidence for CNS changes in children with diabetes associated with hyperglycemia as well as hypoglycemia, although the cognitive functioning and brain imaging findings in children with diabetes as a whole are not significantly different from healthy control children (38, 39). The CNS changes in association with hyperglycemia are relatively new findings but are consistent with reported neurocognitive findings (34).

Experts agree that at present, safest recommendation for improving glycemic control generally in all children is to achieve the lowest HbA1c that can be sustained without disabling or severe hypoglycemia while avoiding prolonged periods of significant hyperglycemia (BG levels >15–20 mmol/L) (35–37) and episodes of diabetic ketoacidosis (DKA) and that these goals can only be achieved by some form of frequent glucose monitoring.

**Monitoring of glycemic control**

**Self-monitoring of blood glucose**

**SMBG**

- helps to monitor immediate and daily levels of control;
- helps to determine immediate and daily insulin requirements;
- helps guide insulin adjustments to decrease fluctuations in BG levels;
- detects hypoglycemia and assists in its management; and
- assists in the safe management of hyperglycemia.

The frequency of SMBG is associated with improved HbA1c in patients with type 1 diabetes (40) (A) (16, 17, 41–45) (B). This is thought to be because of both better insulin adjustment for food consumed and an improved ability to quickly correct out-of-target glucose values. In addition, early detection of lower glucose values prior to symptomatic hypoglycemia may allow correction with a decreased risk of overcorrection and resultant hyperglycemia. The use of SMBG during exercise may also allow improved insulin management and a decreased risk for hypoglycemia during and following exercise (46).

Patient acceptance of SMBG may be enhanced by including the opportunity for testing alternative sites in addition to the fingertips, e.g., the palm of the hand or the forearm. In the fasting state, glucose readings from the forearm are similar to the fingertip (47) (B). These alternative sites may be slower to reflect falling BG levels, so it is advised that fingertips are used when symptoms of hypoglycemia are present and to recheck the glucose using the fingertip if the alternative site test is in a low range (48) (B).

**Equipment.** There are many types of excellent monitors for SMBG; however, significant inaccuracies may arise from operator-related errors (49).

Health care professionals should choose and advise on a type that is robust, precise, accurate, and familiar to them as well as affordable to the patient.

**Timing of SMBG.** BG is best measured

- at different times in the day to show levels of BG after the overnight fast, during the night to detect unnoticed hypoglycemia and hyperglycemia, in response to the action profiles of insulin (at anticipated peaks and troughs of insulin action), and after food intake
Rewers et al. (1.5–2 h after a meal), and in association with vigorous sport or exercise (during and several hours after) so that changes may be made in management to improve BG profiles (44, 50, 51) (B); to confirm hypoglycemia and to monitor recovery; and during intercurrent illness to prevent hyperglycemic crises.

The number and regularity of SMBG should be individualized depending on
- availability of equipment;
- type of insulin regimen; and
- ability of the child to identify hypoglycemia.

Note: successful application of intensified diabetes management with multiple injection therapy or insulin infusion therapy requires frequent SMBG (four to six times a day) and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan.

Targets. The targets are intended as guidelines. There is little age-related scientific evidence for strict glucose targets (Table 1).

However, each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia as well as frequent mild to moderate hypoglycemia (E).

Recommendations for BG monitoring
- SMBG is an essential tool in the optimal management of childhood and adolescent diabetes (16, 40) (A) and, when financially possible, should be made available for all children with diabetes (E).
- SMBG should be prescribed at a frequency to optimize each child’s diabetes control because frequency of SMBG correlates with glycemic control (16) (A) (16, 17, 41–45) (B).
- In many countries, the cost of BG monitoring is very expensive relative to the cost of living. However, all centers caring for young people with diabetes should urge nations, states, and health care providers to ensure that children and adolescents with diabetes have adequate glucose monitoring equipment available to them. It must be recognized that without accurate monitoring, the risks of acute crises and long-term vascular and other damaging complications are greatly increased leading to high levels of health care costs and personal disability (E).

Monitoring of urine glucose

It is recognized that in many countries, urine glucose monitoring is the only monitoring method available and that it provides useful but different information from SMBG (52) (B). Urinary glucose reflects glycemic levels over the preceding several hours and is affected by the renal threshold for glucose, which in children is approximately 10–11 mmol/L (180–200 mg/dL) (53). Periodic, quantitative, timed urine glucose determinations to include different times of the day, e.g., from dinner until bed, overnight until arising, etc., can allow determination of grams of glucose excreted during these times and may increase the usefulness of urine glucose determinations (E).

Limitations of urine glucose monitoring include
- uncertain correlation with BG levels;
- inability to detect hypoglycemia or monitor response to treatment of hypoglycemia;
- less valuable as an educational tool to identify glycemic patterns; and
- unhelpful in hyperglycemic crises because of the lag phase between recovery and changes in urine glucose.

Target.
- As many urine tests as possible should show no glycosuria without the occurrence of frequent or severe hypoglycemia (E).

Equipment.
- Glucose oxidase strips that are relatively inexpensive, convenient, and safe.
- Some non-specific reducing agent methods are used such as Clinitest tablets or Benedict’s test. These are less convenient to use and are also potentially dangerous if the chemical reagents come into contact with the skin, esophagus, or gastrointestinal tract.

Monitoring of urinary or blood ketones
- Urine or blood ketone measurement should be monitored during episodes of uncontrolled hyperglycemia, insulin deficiency, intercurrent illness (sick days), and impending ketoacidosis (E).
- Blood ketone determination has been shown to be more helpful in avoiding emergency room visits than urine ketone determinations (54, 55) (B).

Equipment for urinary ketone determination.
- Tablets or urine testing strips for ketone testing are available, which detect increased levels of urinary acetoacetate (present in lower concentrations than β-OH-butyrate).

A urinary ketone reading of
- 0.5 mmol/L corresponds to ‘trace’ ketones;
- 1.5 mmol/L corresponds to ‘small’ ketones;
Table 1. Target indicators of glycemic control

| Level of control | Ideal (non-diabetic) | Optimal | Suboptimal (action suggested) | High risk (action required) |
|------------------|----------------------|---------|------------------------------|-----------------------------|
| **Clinical assessment** | | | | |
| Raised BG | Not raised | No symptoms | Polyuria, polydipsia, and enuresis | Blurred vision, poor weight gain, poor growth, delayed puberty, poor school attendance, skin or genital infections, and signs of vascular complications |
| Low BG | Not low | Few mild and no severe hypoglycemas | Episodes of severe hypoglycemia (unconscious and/or convulsions) | |
| **Biochemical assessment*** | | | | |
| SBGM values | | | | |
| AM fasting or preprandial PG† in mmol/L (mg/dL) | 3.6–5.6 (65–100) | 5–8 (90–145) | >8 (>145) | >9 (>162) |
| Postprandial PG† | 4.5–7.0 (80–126) | 5–10 (90–180) | 10–14 (180–250) | >14 (>250) |
| Bedtime PG† | 4.0–5.6 (80–100) | 6.7–10 (120–180) | <6.7 or 10–11 (<120 or 180–200) | <4.4 or >11 (<80 or >200) |
| Nocturnal PG† | 3.6–5.6 (65–100) | 4.5–9 (80–162) | <4.2 or >9 (<75 or >162) | <4.0 or >11 (<70 or >200) |
| HbA1c (%) (DCCT standardized) | <6.05 | <7.5† | 7.5–9.0† | >9.0‡ |

BG, blood glucose; DCCT, Diabetes Control and Complications Trial; HbA1c, hemoglobin A1c; PG, plasma glucose.

These targets are intended as guidelines, and each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia as well as frequent mild to moderate hypoglycemia.

*These population-based target indicators must be adjusted according to individual circumstances. Different targets will be appropriate for various individuals such as those who have experienced severe hypoglycemia or those with hypoglycemic unawareness.

†These figures are based on clinical studies and expert opinion, but no strict evidence-based recommendations are available. PG levels are given because BG meters are internally calibrated to reflect the plasma glucose level.

‡DCCT conventional adult cohort had a mean HbA1c value of 8.9%, and both DCCT and EDIC have shown poor outcomes with this level; therefore, it seems prudent to recommend levels below this value.
\* 4 mmol/L corresponds to ‘moderate’ ketones; and
\* ≥8 mmol/L corresponds to ‘large’ ketones.

**Interpretation of urine ketone testing.** Moderate or large urinary ketone levels in the presence of hyperglycemia indicate insulin deficiency and risk for metabolic decompensation leading to ketoacidosis. The presence of vomiting with hyperglycemia and large urinary ketones must be assumed to be because of systemic decompensation leading to ketoacidosis. The presence of vomiting and hyperglycemia indicate insulin deficiency and risk for metabolic decompensation leading to ketoacidosis. The presence of vomiting with hyperglycemia and large urinary ketone levels in the presence of hyperglycemia indicate insulin deficiency and risk for metabolic decompensation leading to ketoacidosis. The presence of vomiting with hyperglycemia and large urinary ketone levels in the presence of hyperglycemia indicate insulin deficiency and risk for metabolic decompensation leading to ketoacidosis.

**Equipment for blood ketone determination.**
- Meters are available for blood β-OH-butyrate testing and can also be used for capillary BG testing (two different strips). Because the β-OH-butyrate strips are expensive, many centers advise using the blood ketone testing for young children, in whom it is often more difficult to obtain a urine specimen, or for any age individual if the urine ketone measurement is large – i.e., >4–8 mmol/L. Blood ketone testing is especially important for pump patients as they have a much smaller subcutaneous (s.c.) insulin depot.
- Determination of blood ketone levels can guide management, e.g., if oral therapy can be safely continued or if more intensive treatment is required to avert severe ketoacidosis (54, 55).

- <0.6 mmol/L is normal, and no action is needed.
- 0.6–1.5 mmol/L is somewhat elevated, but usually responds quickly to oral fluids containing carbohydrate if BG is <10 mmol/L. Give additional s.c. injection of a rapid-acting insulin if BG is elevated to 10 mmol/L (180 mg/dL) or above.
- 1.5–3.0 mmol/L marks high risk of ketoacidosis, but usually can be managed with oral fluids and s.c. injection of a rapid-acting insulin if BG is elevated to 10 mmol/L (180 mg/dL) or above.
- >3.0 mmol/L is usually accompanied by acidosis. Urgent contact with diabetes provider or Emergency Department (E.D.) is needed.
- See ISPAD guidelines for Sick Day Management for more detailed advice.

**Note:** BG levels must be checked before administering insulin in patients with ketonuria or ketosis. Urine or blood ketones may be elevated in diabetic patients as a physiological metabolic response to fasting, low carbohydrate diets (e.g., Atkins diet), during prolonged exercise, or pregnancy as well as in gastroenteritis and in alcohol intoxication. BG levels are normal or low in these situations, and supplemental insulin is not indicated. To correct the metabolic ‘starvation’, electrolyte-containing fluids with low glucose content (e.g., Gatorade, Pedialyte, and Poweraid) may be used when BG levels are 150–250 mg/dL (8.5–14 mmol/L). The sugar content of the fluid should be increased further when BG is <150 mg/dL (8.5 mmol/L). However, if β-OH-butyrate is >1.0 mmol/L, extra insulin is needed, once the BG level has risen after giving extra carbohydrate. See ISPAD guidelines for sick days (ref) for more detailed advice.

**Recommendations for ketone testing**
- Illness with fever and/or vomiting.
- BG value above 14 mmol/L (250 mg/dL) in an unwell child (to be in accordance with the sick day guidelines).
- Persistent BG levels above 14 mmol/L (250 mg/dL), especially in a young child, insulin pump user, or a patient with a history of prior episodes of DKA.
- Persistent polyuria with elevated BG or urine glucose.
- Episodes of drowsiness.
- Abdominal pains or rapid breathing.

**Record keeping of glycemic control**
- It is common practice for a monitoring diary, logbook, or some type of electronic memory device to be used to record patterns of glycemic control and adjustments to treatment.
- The record book is useful at the time of consultation and should contain time and date of
  - BG levels;
  - insulin dosage;
  - note of special events affecting glycemic control (e.g., illness, parties, exercise, menses, etc.);
  - hypoglycemic episodes, description of severity, and potential alterations in the usual routine to help explain the cause for the event; and
  - episodes of ketonuria/ketonemia.

**Recommendations for record keeping**
- Monitoring records should not be used as a judgment but as a vehicle for discussing the causes of variability and strategies for improving glycemic control (E).
- Frequent home review of records to identify patterns in glycemic levels and subsequent adjustment in diabetes management are required for successful intensified diabetes management (E).
- In some instances, especially among teenagers, maintaining written monitoring records is difficult. If the family has access to a computer and can upload the BG monitoring data for review, this may substitute for a manual record, although details of management may be lost with this method (E).
Glycated hemoglobin

- Glucose becomes irreversibly attached to the molecule of hemoglobin during the life cycle of the circulating red cell (which is approximately 120 d) forming glycated hemoglobin (HbA1 or HbA1c).
- HbA1c reflects levels of glycemia over the preceding 4–12 wk, weighted toward the most recent 4 wk. However, the most recent week is not included because the most recent glycation is reversible (58). HbA1c monitoring has been shown to be the most useful measure in evaluating metabolic control and is the only measure for which good data are available in terms of its relationship with later microvascular and macrovascular complications (1, 2) (A).

Equipment and facilities.

- A normal reference range for non-diabetic children should be available.
- There should be regular quality control comparisons with national and DCCT standards. It is recommended that scientific papers also provide HbA1c in DCCT numbers if the local analysis is not calibrated to display these numbers (E).
- It is preferable that a capillary method for collection of the child’s blood is available and that the HbA1c result is available at the time of the medical visit so that immediate adjustments in management can be based on the HbA1c level. A rapid method using a prepared kit has been shown to provide comparable results to chromatographic methods (59) (E).

Recommendations for HbA1c testing

- Facilities for the measurement of HbA1c should be available to all centers caring for young people with diabetes (E).
- Frequency of measurement will depend on local facilities and availability, but every child should have a minimum of one measurement per year. Ideally, there should be four to six measurements per year in younger children and three to four measurements per year in older children (E).
- Adolescents with stable type 2 diabetes should have two to four measurements per year because adolescents may become insulin requiring more rapidly than adults (E).

HbA1c targets. A target range for all age-groups of <7.5% is recommended (Table 1).

These targets are intended as guidelines.

Each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia as well as frequent mild to moderate hypoglycemia.

The goal is to avoid the long-term microvascular and macrovascular complications of diabetes while also avoiding sequelae of acute hypoglycemia and the CNS changes associated with both hypoglycemia and hyperglycemia.

Evidence from the DCCT is available for adolescents, and recommendations for younger children can only be determined using these data and expert opinion. The intensively treated adolescent cohort of the DCCT achieved a mean HbA1c of 8.1%, while subjects in the corresponding adult cohort achieved a mean HbA1c of 7.1%. Subjects in the follow-up observational study, Epidemiology of Diabetes Interventions and Comlications (EDIC), maintained an average HbA1c of 7.8–8.2% (regardless of DCCT randomization) during the 12 yr of follow-up reported to date. In addition, a proportion of children should expect to achieve an HbA1c within the normal reference range at some time in the first year after diagnosis (during the partial remission phase), generally between 1 and 6 months after diagnosis.

In many studies, there is evidence of an increased risk for hypoglycemia as the HbA1c decreases (1, 2) (A) (60, 61) (C), but this is not always the case (3, 17, 42, 62) (C). Glycemic control and the risk of hypoglycemia may be decreased by the choice of insulin regimens and the frequency of BG monitoring.

Targets for HbA1c are given with the expectation that careful attention will be taken to avoid severe hypoglycemia. Because severe hypoglycemia is more common when hypoglycemia unawareness is present, HbA1c targets must be increased when hypoglycemia unawareness occurs.

- In non-diabetic individuals, counter-regulatory systems are normally activated at a plasma glucose (PG) level of 3.6–3.9 mmol/L (65–70 mg/dL), while symptoms of hypoglycemia occur at a PG of ~3.0 mmol/L (54 mg/dL) and cognitive dysfunction at ~2.7 mmol/L (49 mg/dL) (63, 64) (C, B).
- Asymptomatic hypoglycemia in persons with diabetes is defined as the occurrence of a plasma glucose value <4 mmol/L (70 mg/dL) without signs or symptoms of adrenergic release (ADA working group 2005). PG below this level reduces sympathoadrenal responses to subsequent hypoglycemia (65) (B).
- Hypoglycemia unawareness is defined as neuroglycopenia occurring before autonomic activation and can be associated with reduced awareness of the onset of hypoglycemia (66).
- It occurs when a single, or multiple, hypoglycemic episode(s) lead to a significant decrease in neuro–hormonal counter-regulatory responses causing unawareness of hypoglycemia (67).
- Hypoglycemia unawareness is more common in those who maintain generally lower BG levels (68, 69).
- Continuous monitoring devices are becoming available that may particularly benefit those with hypoglycemic unawareness, as the devices will alarm when glucose is below a specified range or with rapid rate of fall of glucose.
- There is evidence that loss of awareness of hypoglycemia can be reversed by avoiding hypoglycemia for 2–3 wk (70, 71), although this is difficult for very young patients.
- Individuals and families should be instructed in the signs and symptoms of hypoglycemia unawareness, and a history for hypoglycemia unawareness should be taken at every diabetes care visit (E).

The youngest children (<6 yr) are at increased risk for adverse neurologic outcomes from severe hypoglycemia, and because they are unable to self-identify hypoglycemia, caution in achieving lower targets for younger children is appropriate (72, 73). In reality, many pediatric centers find that the average HbA1c is in fact lowest in this youngest age-group, reflecting the more complete caregiver involvement at younger ages.

As teens approach adulthood, targets similar to those of the adult population should be approached (<7%), recognizing that the hormonal alterations and psychological adjustments of adolescence make achieving these targets difficult. Of all age-groups, adolescents are currently the farthest from achieving HbA1c <7.5%, reflecting the diabetes mismanagement that frequently accompanies the increased independence in diabetes care during the adolescent years, as well as the effect of psychological and hormonal challenges of adolescence. However, results from the DCCT and the follow-up EDIC studies document that poor control for 5–7 yr that is similar to the duration of puberty may have prolonged adverse effects (7, 9, 13, 14, 18) (A). While better insulins, insulin pumps, and glucose monitors are available today, compared with the DCCT era, adolescents at large may still be unable to achieve a lower HbA1c levels than the DCCT adolescent average without novel approaches to care in this age-group. Too ambitious goals may lead to an unwarranted sense of failure and alienation on part of many teenage patients (E).

As diabetes technology improves, especially continuous glucose monitoring, recommended target indicators for glycemic control will likely decrease to reflect a new balance of benefits and risks.

Health care priorities: care providers should be aware that achieving an HbA1c consistently below the target range without extensive personal and national health care resources and outside of a clinical trial structure may be very difficult. As a benchmark, the most recent mean HbA1c is 7.8% in a well-educated EDIC cohort that has excellent access to the newest diabetes technology and a mean age of 45 ± 7 yr (9).

### Recommendations for HbA1c targets

- Target HbA1c for all age-groups is recommended to be 7.5% (E).
- There is evidence that for a given HbA1c level, intensive treatment as in the DCCT study results in less long-term complications (A).
- Targets for all age-groups include the requirement for minimal levels of severe hypoglycemia and absence of hypoglycemia unawareness (E).
- When hypoglycemia unawareness is present, glycemic targets must be increased until hypoglycemia awareness is restored (68, 69) (B).
- In the youngest children, <6 yr, particular vigilance for unrecognized hypoglycemia should be undertaken (E).

### Fructosamine and other glycated products.

Fructosamine measures the glycation of serum proteins such as albumin and reflects glycemia over the preceding 3–4 wk. It is therefore used for the assessment of shorter periods of control than HbA1c. Fructosamine or glycated albumin may be useful in monitoring glucose control over time in individuals with abnormal red cell survival time. Fructosamine and other glycated products have not been evaluated in terms of later vascular risk.

### Continuous glucose monitoring

Intermittent BG monitoring, SMBG, determines the capillary glucose level at the moment when the test is performed, generally two to six times a day. Devices are available, and others are in development that measure interstitial fluid glucose every 1–20 min, i.e., ‘continuous’ measurement. Both non-invasive and minimally invasive devices are available. Currently, these devices are expensive and may not be available in many countries. Insurance coverage is also limited. Over time, it is anticipated that these devices will become more widely available and covered by both national and private insurance.

Minimally invasive sensors use a catheter or a small plastic chip containing a sensor inserted into the subcutaneous space to measure the interstitial glucose. They are replaced every 3–7 d and require calibration two to three times daily using SMBG devices. These sensors transmit glucose levels to a pager-like receiver box or to an insulin infusion pump for readout by the user. The continuous glucose results are available to the wearer during the monitoring time and are stored in the receiver device or pump for downloading to a computer at a later time. The download allows the patient and/or the physician to review the results and make insulin dose adjustments. The review of the continuous glucose monitoring results is a very helpful teaching tool for the
effects of food, insulin timing, and exercise on glucose levels.

Continuous sensor devices may guide real-time adjustments of insulin dosing and can identify times of consistent hyperglycemia and times of increased risk for hypoglycemia presenting a much more sophisticated approach to home SMBG (74, 75) (A). Both ‘real-time’ and delayed readout devices have been helpful in adjusting management following initiation of insulin infusion pumps and identification of asymptomatic hypoglycemia and unrecognized postprandial hyperglycemia (74, 76, 77) (B). These devices have been used in research settings to evaluate frequency of hypoglycemia and develop strategies to decrease its occurrence, especially during and following exercise, and to provide information that will allow improved recommendations for insulin management for all individuals with diabetes (78–81).

Devices may allow targets to be determined so that an alarm will alert the wearer to a glucose value projected to fall below or above the preset target in 10–30 min, based on the rate of change of the interstitial glucose (82).

As continuous glucose monitoring becomes more widely available, decreased BG targets may be more safely achieved, allowing further decreases in target HbA1c levels and improved outlooks for children with diabetes (83, 84).

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Appendix

International standardization of HbA1c assays developed from publications of the American Diabetes Association and from minutes of the The American Diabetes Association/European Association for the Study of Diabetes/International Diabetes Federation (ADA/EASD/IDF) Working Group (85). Standardization of HbA1c assays and a better understanding of the relationship of HbA1c measurements to average BG are a necessary next step in improving diabetes care. Current efforts are in progress to standardize HbA1c measurements and relate them better to prevailing BG levels (86, 87).

The development of the HbA1c assay revolutionized diabetes management and provided an objective, long-term measure of glycemia. However, there are disparities between the relationship of HbA1c and average BG with different diabetes treatment intensities and between HbA1c assays (85). Standardization of HbA1c assays and a better understanding of the relationship of HbA1c measurements to average BG are a necessary next step in improving diabetes care. Current efforts are in progress to standardize HbA1c measurements and relate them better to prevailing BG levels (86, 87).

The International Federation of Clinical Chemistry (IFCC) (the organization that establishes worldwide clinical chemistry standards and procedures) developed a new reference method that precisely measures the concentration of glycated HbA1c only (88, 89). The new reference method was also compared with the results obtained by the current methodology (90). The reference measurement procedure has been defined as bN1-deoxyfructosyl-hemoglobin, and the recommended measurement units are mmol/mol. The IFCC Working Group – HbA1c recommends maintaining the use of the name HbA1c in clinical practice to decrease provider and patient confusion.

In addition to the IFCC Working Group, an IFCC/ADA/EASD/IDF Working Group was formed, now with representation from Juvenile Diabetes Research Foundation International. This group has been focused on implementing an international study to document what the clinical world has always thought to be true but never proven: that the A1c assay does indeed reflect an average BG over many months. If the direct relationship can be documented, then the reporting of the assay would include an ‘estimated average blood glucose’, or ‘A1c-derived average glucose (ADAG)’, and the units would be in mmol/L (or mg/dL) (3, 91) (this ref is not correct).

IFCC/ADA/EASD/IDF has issued a Consensus statement (91), with which the Guideline editors agree, stating (i) A1c test results should be standardized worldwide, including the reference system and results reporting; (ii) the new IFCC reference system for A1c represents the only valid anchor to implement standardization of the measurement; (iii) A1c results are to be reported worldwide in derived National Glycohemoglobin Standardization Program (NGSP) units (%) using the NGSP-IFCC master equation and IFCC units (mmol/mol) (Note: this transaction will most likely occur over several years.); (iv) if the ongoing ‘average plasma glucose study’ fulfills its a priori specified criteria, an ADAG value calculated from the A1c result will also be reported as an interpretation of the A1c results; and (v) glycemic goals appearing in clinical guidelines should be expressed in IFCC units, derived NGSP units, and ADAG. Preliminary data presented at EASD 2007 show that there is a distinct relationship between HbA1c and PG, and thereby ADAG will be included in the reporting of HbA1c.

When the anticipated new terminology is standardized and begins to be used, the ISPAD Monitoring Guidelines will be updated to include the new terminology.