2018 ISPAD Clinical Practice Consensus Guidelines

Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes

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What's New?

- **Emphasis on individualizing blood glucose and glycemic targets for children, adolescents and young adults aged <25 years**
- **Discussion of the impact of increased use of continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) technology**
- **Target hemoglobin A1c (HbA1c) <53 mmol/mol (<7.0%) for children and adolescents and young adults who have access to comprehensive care**

Executive Summary and Recommendations:

Glycemic control of children and adolescents must be assessed by both quarterly HbA1c and by regular home glucose monitoring. These permit achieving optimal health by:

- determining with accuracy and precision an individual's glycemic control, including assessment of each individual's glycemic determinants **(A)**,
- reducing the risks of acute and chronic disease complications **(A)**,
- minimizing the effects of hypoglycemia **(A)** and hyperglycemia **(B)** on brain development, cognitive function, mood; and
- optimizing quality of life **(E).**

Recommendations:

- Regular self-monitoring of glucose (using accurate fingerstick BG measurements, with or without CGM or isCGM), is essential for diabetes management for all children and adolescents with diabetes **(A)**.
    - Each child should have access to technology and materials for self-monitoring of glucose measurements to test enough to optimize diabetes care **(B)**.
    - Diabetes center personnel should advocate to nations, states, and health care funders to ensure that children and adolescents with diabetes have adequate glucose monitoring supplies **(E)**.
    - When fingerstick BGs are used, testing may need to be performed 6-10 times per day to optimize intensive control. Regular review of these BG values should be performed with adjustments to medication/nutritional therapies to optimize control

(B).

- Real-time CGM data particularly benefit children who cannot articulate symptoms of hypoglycemia or hyperglycemia and those with hypoglycemic unawareness **(A)**.
- isCGM can complement fingerstick BG assessments. Although isCGM provides some similar benefits to CGM, it does not alert users to hypoglycemia or hyperglycemia in real time, nor does it require calibration. Without robust pediatric use efficacy data, it cannot fully replace BG monitoring **(B)**.

- For children, adolescents and young adults aged ≤25 years we recommend individualized targets, aiming for the lowest achievable HbA1c without undue exposure to severe hypoglycemia balanced with quality of life and burden of care **(E)**.

- For children, adolescents and young adults ≤25 years who have access to comprehensive care a target of HbA1c of <53 mmol/mol (7.0%) is recommended **(E)**.
  - A higher HbA1c goal (in most cases <58 mmol/mol (7.5%)) is appropriate in the following contexts:
    - inability to articulate symptoms of hypoglycemia
    - hypoglycemia unawareness/history of severe hypoglycemia
    - lack of access to analog insulins, advanced insulin delivery technology, ability to regularly check blood glucose (BG), and CGM **(E),** and
    - individuals who are 'high glycators,' in whom an at-target HbA1c would reflect a significantly lower mean glucose than 8.6 mmol/l (155 mg/dl) **(E)**
  - A lower goal (6.5%) or 47.5 mmol/mol may be appropriate if achievable without excessive hypoglycemia, impairment of quality of life, and undue burden of care **(E).**
  - A lower goal may be appropriate during the honeymoon phase of type 1 diabetes **(E).**
  - For patients who have elevated HbA1c, a step-wise approach to improve glycemic control is advised including individualized attention to:
    - Dose adjustments **(E)**,
    - personal factors limiting achievement of the target **(E)**,
    - assessment of the psychological effect of goal setting on the individual **(E)**, and
    - incorporation of available technology to improve glucose monitoring and insulin delivery modalities **(E)**.

- HbA1c measurement should be available in all centers caring for persons with diabetes **(B).**
    - HbA1c measurements should be performed at least every 3 months **(B)**.
    - Examining variations in HbA1c between centers can assist in evaluating the care provided by health care centers including compliance with agreed standards to improve therapies and delivery of pediatric diabetes care **(B)**.

General principles determining glycemic targets

HbA1c reflects mean BG over the prior three to four months and is currently the only long-term glycemic control measure with robust outcome data. Multiple studies in diverse populations have shown that elevated HbA1c values are associated with chronic complications of diabetes. Intensive management resulting in lower HbA1c concentrations is associated with fewer and delayed development of microvascular and macrovascular chronic complications [1-5], see Chapter 18 (ref). Additionally, lower HbA1c shortly after diagnosis is associated with a lower risk of subsequent complications [6,7]. Follow-up data from the DCCT indicate that 5 – 7 years of improved glycemic control, including during adolescence and young adulthood, decreased the risk for microvascular and macrovascular complications [8-11] and mortality [12] in subsequent years.

Chronic hyperglycemia has adverse effects on neurocognitive function and brain structure and development in children and adolescents with diabetes [13-17]. Chronic hyperglycemia and large glucose fluctuations during the years of rapid brain development affect brain structure and development, including impairment of the growth of the hippocampus. These observations call into question the prevalent practice of tolerating some hyperglycemia to minimize the risk of hypoglycemia in young children with T1D [18,19]. Hypoglycemia is also a significant risk for children and adolescents with diabetes. (For a comprehensive review of effects of hypoglycemia, see Chapter 12, Hypoglycemia [add ref]). Severe hypoglycemia, particularly in young children, is associated with adverse neurocognitive effects [20]. Historically, lower HbA1c values were associated with more frequent acute episodes of severe hypoglycemia [1,2], but more recent observational studies in the era of multiple daily injections, pumps, and more intensive glucose monitoring, including use of CGM, suggest this is not as significant a risk [21-27]. Importantly, recent data suggest that lowering HbA1c targets is associated with a decreased mean HbA1c on a population and individual level without an increased frequency of severe

hypoglycemia, even in children who achieve HbA1c levels <53 mmol/mol (7.0%) [28].

HbA1c measurements are useful both for assessing risk of long-term complications and as a real-time tool for optimizing glycemic control. HbA1c is routinely integrated clinically into decision-making about medical regimens, together with data on documented hypoglycemia and hyperglycemia and other person-specific variables such as age, caregiver knowledge, carbohydrate intake, illness/stress, and exercise patterns. Overall, prolonged periods of significant hyperglycemia and episodes of diabetic ketoacidosis (DKA) should be avoided [16,29,30].

Although HbA1c remains the best measure of long-term glycemia within and between populations, several studies have shown that HbA1c has significant limitations when used in isolation to assess an individual's glycemic control. Although for a population, mean BG is highly correlated to HbA1c [31], when examining individual-level data there are often significant differences between measured glucose values (whether by fingerstick BG or CGM) and observed HbA1c values [32]. Sometimes these differences are due to conditions that alter the life span of red blood cells or changes in hemoglobin glycation, such as sickle cell disease or anemia. In addition, genetic differences in hemoglobin glycation are also present [33-35]. In a recent report from the US that identified individuals as "black" or "white" based upon self-report, blacks had mean HbA1c values 4.4 mmol/mol (0.4%) higher than whites for the same mean glucose concentration determined using CGM [32]. As indicated below, in this study, race may be a surrogate marker for genetic factors that determine the relationship between mean BG and HbA1c.

Additionally, several studies have shown significant differences between HbA1c and observed self-monitored glucose values between individuals without obvious medical or racial/ethnic biologic differences [33,36]. Data comparing 13 weeks of Dexcom G4 Platinum CGM measurements with HbA1c (measured using nonporous ion exchange high-performance chromatography) showed wide ranges of HbA1c for similar mean interstitial glucose concentrations. For example, for a HbA1c of 64 mmol/mol (8.0%) the 95% confidence interval for mean glucose ranged from 8.6 mmol/l (155 mg/dl) to 12.1 mmol/l (218 mg/dl)[33]. These data suggest estimating average glucose concentrations for individuals from measured HbA1c values should be done cautiously. However, the relationship of HbA1c to mean glucose is consistent within an individual in the absence of changes in health[37].

It is not yet known whether, for an individual, the HbA1c or overall glycemic exposure is a

better marker for risk of complications. As glycemic control guidelines become more stringent, it is important, when possible, to establish the relationship between a patient's mean BG with their HbA1c, to know whether the individual is a "high or low glycator"[38]. Without establishing this idiosyncratic relationship, modifying treatment based on HbA1c may increase the risk of iatrogenic hypoglycemia. For high glycators consideration should be given to additional glucose metrics such as measures of hypoglycemia.

Monitoring of glycemic control

Home self-monitoring of glucose:

- tracks immediate and daily levels of glucose control [39-42];
- helps to determine immediate and ongoing basal and bolus insulin requirements;
- detects hypoglycemia and assists in its management;
- assists in the appropriate management of hyperglycemia; and
- helps guide insulin adjustments to decrease glucose fluctuations.

Fingerstick BG measurements

Greater frequency of fingerstick glucose monitoring is associated with lower HbA1c in persons with type 1 diabetes [25,39-42]. HbA1c improvements with more frequent glucose measurements are due to better insulin dosing for carbohydrate consumed and an improved ability to quickly correct out-of-target range glucose values. In addition, early detection of decreasing glucose values before symptomatic hypoglycemia occurs permits more precise correction with a decreased risk of overcorrection and resultant hyperglycemia. Self-monitoring of glucose around exercise also allows improved insulin management and a decreased risk for hypoglycemia during and following exercise [43].

Equipment. There are many types of BG meters; however, significant inaccuracy may arise from operator-related errors [44,45]. Health care professionals should choose and advise on types that are robust, precise, accurate, and familiar to them as well as affordable to the person with diabetes. Devices that do not require calibration/coding may be easier to use. Low quality devices, offered sometimes to reduce cost, may compromise safety owing to lack of accuracy.

High industry standards, including accuracy, precision and ability to download and analyze data should be upheld by regulatory agencies. Industry standards state that 95% of readings should be within ±15% of the reference value [46]. ISPAD recommends exclusive use of glucose meters that achieve this standard.

Timing of Self-Monitoring of Glucose:

BG is best measured:

- during the day, before meals and snacks;
- at other times (e.g. 2-3h after food intake) to determine appropriate meal insulin doses and show levels of BG in response to the action profiles of insulin (at anticipated peaks and troughs of insulin action).
- in association with vigorous exercise (before, during and several hours after) so that changes may be made in glycemic management [43,47];
- at bedtime, during the night and on awakening to detect and prevent nocturnal hypoglycemia and hyperglycemia as well as optimize basal insulin;
- before driving a car or operating hazardous machinery;
- to confirm hypoglycemia and to monitor recovery; and
- during intercurrent illness to prevent hyperglycemic crises.

The number and regularity of fingerstick BG measurements should be individualized depending on:

- availability of equipment;
- type of insulin regimen; and
- ability of the child to identify hypoglycemia.

Successful intensive diabetes management requires self-monitoring of glucose at least six to ten times a day and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan [42,48]. This includes review by the person with diabetes and their family in addition to consultation with the diabetes care team.

Glucose targets throughout the day should correspond with individualized HbA1c targets (Table 1). Empiric data in pediatrics on which to base glucose targets and how this relates to HbA1c are needed. In the absence of such data, we advocate personalizing the above glucose targets to achieve an HbA1c of <53 mmol/mol (7.0%). Consistent targets, communication and

teamwork are important in improving HbA1c [49-51]. See Table 1 for recommended glucose targets to achieve an HbA1c of <53 mmol/mol (7.0%), although these need to be individualized based on patient and clinic characteristics.

Continuous glucose monitoring (CGM) (See also Technology Chapter)

CGM uses minimally invasive devices that measure subcutaneous interstitial fluid glucose every 1 – 5 minutes, i.e., 'continuously'. All devices permit BG targets to be set so that an alarm will alert the wearer to a glucose value projected to fall below or rise above the target in 10 – 30 min, based on the rate of change of the interstitial glucose [52,53]. Newer devices have a mean average relative difference (MARD) of <10% and, therefore, a similar accuracy to that of capillary BG meters [54].

CGM is a much more sophisticated approach than home fingerstick BG monitoring as it can also identify times of consistent hyperglycemia and times of increased risk for hypoglycemia. Days with outlier glucose values can also be more readily identified. CGM may particularly benefit those with hypoglycemic unawareness, as the devices will alarm when glucose is below a specified level or with a rapid rate of fall of glucose [55,56]. With short-term use of sensors, mean glucose values decrease, and time spent in the hypoglycemic range also decreases [57,58]. CGM use has been associated with lower HbA1c compared to fingerstick BG measurements alone; and greater improvements in HbA1c correlate with increasing hours per week of CGM use [52,59,60].

CGM can be used in "blinded" or "real time" modes. Blinded CGM provides retrospective data and is generally only useful for clinical research or for insulin adjustment by a health care provider [61]. Real-time CGM use with immediate corrections to keep glucose levels in range has been shown to more effectively improve glycemic control than 'blinded' collection of data analyzed by a health provider at a later time [62]. Appropriately calibrated CGM devices and an isCGM device are now approved for real-time non-adjunctive (replacement of fingerstick monitoring) use in some settings, although depending on the accuracy and labeling of the technology used, some CGM values must still be confirmed by fingerstick BG monitoring [63]. However, periodic downloads allow the person with diabetes and/or their caregiver and health care provider to review a larger amount of data and make more comprehensive adjustments[64]. Review of CGM data is a very helpful tool to teach patients about the effects of food, insulin timing, and exercise on glucose levels. The intermittent, delayed readout, often using blinded modes, has been helpful as a diagnostic tool and for management of hyperglycemia in special

groups, e.g., those with pre-type 1 diabetes [65], monogenic diabetes [66] or cystic fibrosis-related diabetes [67,68]. CGM studies have informed recommendations for insulin management for all individuals with diabetes including those not using continuous sensing devices [69,70].

Current limitations of real-time CGM include economic and behavioral barriers and the still imperfect accuracy and difficulty with wearability of some sensors that may discourage routine use. Currently, these devices, while approved for pediatric use, are expensive and may not be available in many countries. Insurance coverage may also be limited. Over time, these devices will continue to become more widely available and better coverage by both national and private insurance is anticipated. ISPAD advocates for increased availability of CGM for children, adolescents and young adults with diabetes.

While real-time CGM is beneficial both in persons using multiple daily injections and insulin pumps, its use in combination with an insulin pump is generally more effective [71], particularly when the CGM is integrated into a sensor-augmented pump [72]. Early studies of longer-term CGM use (6 months) found that, despite benefiting from similar reduction in HbA1c, children and adolescents may not be willing to wear a device as often, or for as prolonged a period of time as needed to consistently improve glucose control [73]. Not surprisingly, the frequency of sensor use predicts the HbA1c lowering associated with CGM [60,74]. These observations indicate that additional work is needed to develop technology that is better tolerated and less intrusive in teenagers' lives and to identify ways to help adolescents adapt to healthcare tasks required to maintain near-normal glucose levels. Early negative experiences with inaccurate sensors, devices that were not easy to wear, and high costs, may have discouraged some individuals from long-term use [75,76]. These perceptions appear to now be changing due to major improvements in sensor technology and to re-training users [77]. With more widespread use of real-time CGM, decreased BG targets can be safely achieved, improving the long-term outlook for children with diabetes. (Note: see Chapter 22 for additional discussion of Diabetes Technology (REF).)

Other CGM glycemic metrics include percentage of time in various target glucose ranges, mean glucose, measures of hypoglycemia and glucose variability. It is possible that percent time in target range will become the future metric used to assess overall glycemic control. Glucose variability may also contribute to the risk for complications independently of HbA1c [78-80]. It has been suggested that the coefficient of variation (the standard deviation of the BG values divided by the mean) may be the most descriptive of overall excursions and that "stable" glucose values can be defined as having coefficients of variation <36% with values greater

than this being “unstable”[79]. Standardized metrics for analysis and reporting of these data have been proposed, including an ambulatory glucose profile (AGP) showing data as a modal day. Few data are yet available as to how these metrics relate to long-term outcomes for persons with diabetes, particularly for children [79].

Intermittently scanned CGM

In many settings CGM may not be available for use by children. Intermittently scanned CGM (isCGM) is another way to measure glucose that has been successfully used in children [81]. Current systems provide sensor wear up for up to 14 days and require no user calibration.

isCGM has similarities with CGM but is a simpler and more economical technology[79]. Current commercially available isCGM technology has two versions, a personal and a professional format. The former uses a sensor inserted in the back of the upper arm and a separate touchscreen reader device. When the reader is swiped over the sensor, the sensor transmits an instantaneous interstitial glucose level, trends over the last 15 minutes, and a graph showing glucose data for the preceding eight hours. However, if the system is not scanned for more than eight hours, any information more than eight hours old is lost. The ambulatory glucose profile for the last 90 days is stored in the reader and can be easily downloaded. When analyzed in real-time or retrospectively, the data generated by the isCGM system are like that of real-time CGM. The main differences are that isCGM does not provide high or low glucose alarms, require or permit calibration, or control insulin infusion rates when used with a pump.

The professional format uses the same sensor technology as the personal version. Interstitial glucose is recorded every 15 minutes for 14 days; however, the data are blinded from the user. A health professional needs to wave the reader over the sensor to retrieve the information for download. The professional format is useful as an aid to understanding disparities in HbA1c levels and BG assessments and for retrospective assessment of glycemic control.

The system has acceptable accuracy compared with capillary BG measurements [82-85], which has led to approval of both versions in more than 30 countries [86]. Regulatory agencies have accepted the use of isCGM as an aid for determining insulin dose, except in the following situations: rapid changes of glucose levels, symptoms of hypoglycemia or the reader shows a low glucose level, symptoms do not match the system reading or before driving [87]. Emerging data suggest that use of isCGM can reduce time spent in hypoglycemia in adults with well-controlled T1D [83].

Advances in pump and CGM technology have led to the development of pumps that adjust

insulin delivery based on ambient interstitial glucose using computerized algorithms. These are important steps toward “closing the loop” and an eventual true artificial pancreas system. Such devices reduce the risk of severe and moderate hypoglycemia, particularly overnight, and hold promise to reduce the burden of care and improve glucose control [56,88]. Further details are available in the chapter Diabetes Technologies [ref].

Record Keeping

- It is common practice for a monitoring diary, logbook, spreadsheet, smart meter, app, or cloud-based program to be used to record patterns of glycemic control, insulin doses and amounts of carbohydrate consumed, and adjustments to treatment. These data should be reviewed regularly by the person with diabetes and family.
- The record book or data from the electronic device/cloud is required at the time of consultation and should contain time and date of
    - glucose levels;
    - carbohydrate intake
    - insulin dosage;
    - note of special events affecting glycemic control (e.g., illness, exercise, menses, alcohol intake);
    - hypoglycemic episodes, description of severity, and potential alterations in the usual routine to help explain the cause for the event; and
    - episodes of hyperglycemia, ketonuria/ketonemia.
- Glucose monitoring records should not be used judgmentally but as a vehicle for discussing the causes of variability and strategies for improving glycemic control.
- Frequent home review of records to identify glycemic patterns is required for successful intensified diabetes management.

Hemoglobin A1c (HbA1c)

Glycated hemoglobin

• Glucose is irreversibly attached to hemoglobin while the red blood cells circulate (with a life span of approximately 120 days) forming glycated hemoglobin (HbA1 or HbA1c).

• HbA1c reflects glycemia over the preceding 4 – 12 weeks, weighted toward the most recent

4 weeks. However, the most recent week is not included because the most recent glycation is reversible [89].

The HbA1c assay provides an objective, long-term measure of glycemia and revolutionized diabetes management. There is a strong correlation between HbA1c and BG and CGM glucose [31,33]. The International Federation of Clinical Chemistry (IFCC) has developed a reference method that precisely measures glycated HbA1c only [90,91]. The reference measurement procedure has been defined as bN1-deoxyfructosyl-hemoglobin, and the recommended SI measurement units are mmol/mol [92]. IFFC/ADA/EASD/IDF has issued a consensus statement regarding this standardization process [92]. A calculator for conversion between the DCCT/NGSP % units and the IFCC/SI mmol/mol units can be found at http://www.ngsp.org/convert1.asp

Equipment and facilities.

- Facilities for HbA1c measurement should be available to all centers caring for young people with diabetes.
- Every child should have a minimum of four measurements per year (at approximately 3-month intervals) [93,94].
- Capillary blood collection is preferable. It is also preferable 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 along with available glucose data.
- A reference range for non-diabetic children should be available.
- There should be regular quality control comparisons with national and DCCT or IFCC standards. It is recommended that scientific papers provide HbA1c in both DCCT/NGSP and IFCC/SI units.

Fructosamine and other glycated products.

Fructosamine measures the glycation of serum proteins such as albumin and reflects glycemia over the preceding 3 – 4 weeks. 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 in individuals with abnormal red cell survival time. Fructosamine and other glycated products have been recently evaluated as predictors of the development of vascular

complications. In DCCT/EDIC, glycated albumin and HbA1c had similar associations with retinopathy and nephropathy, which were strengthened when both measures were considered together. Only HbA1c was significantly associated with development of cardiovascular disease [95]. The Atherosclerosis Risk in Communities (ARIC) study that included adults with type 1 and type 2 diabetes found that fructosamine and glycated albumin were associated with microvascular complications with prognostic value comparable to HbA1c [96].

HbA1c targets

Goals for children, adolescent, and young adults (aged ≤25 years) with type 1 diabetes should be individualized (Table 1). A target of 53 mmol/mol (7.0%) is recommended for persons who have access to analog insulins, advanced insulin delivery technology, and the ability to regularly check BG and/or use CGM. Higher HbA1c goals, <58 mmol/mol (7.5%), are appropriate for most persons in the following contexts: inability to articulate symptoms of hypoglycemia, hypoglycemia awareness, history of severe hypoglycemia, high glycators, and in resource-limited environments.

The HbA1c value of 7% (53 mmol/mol) is chosen with the aim of avoiding long-term microvascular and macrovascular complications of diabetes while also avoiding severe hypoglycemia and the adverse central nervous system changes associated with both hypoglycemia and hyperglycemia. Evidence from the DCCT is available for adolescents, and recommendations for younger children are extrapolated from these data and are based on expert opinion. It is important to note that the intensively treated adolescent cohort of the DCCT achieved a mean HbA1c of 65 mmol/mol (8.1%), while those in the corresponding adult cohort achieved a mean HbA1c of 54 mmol/mol (7.1%) [1]. Persons who began the follow-up observational study, Epidemiology of Diabetes Interventions and Complications (EDIC), as adolescents maintained an average HbA1c of 62-66 mmol/mol (7.8 – 8.2%), regardless of DCCT randomization, during 30 years of follow-up [97].

This HbA1c target is intended as an aspirational goal, with recognition that the vast majority of children, adolescents, and young adults currently do not meet it. For instance, in the U.S., based on 2015 T1D Exchange Clinic Registry data, only 22-23% of children below the age of 12 years and 17% of children 13-17 years of age with type 1 diabetes cared for by endocrinologists met the prior target of 58 mmol/mol (<7.5%) [77]. Recent data from young adults in Norway also show peak HbA1c levels of 9.3% (78 mol/mol) for girls at age 17 and 9.1% (76

mmol/mol) at age 19 years in males[98]. The observed differences in mean HbA1c over all pediatric age groups between eight high-income countries [varying between 59 mmol/mol (7.6%) in Sweden and 8.8% (72 mmol/mol) in Wales and between centers within countries clearly shows that well-funded and more optimally resourced health care systems can achieve better outcomes [99].

Aspirational goals are important, as adolescents who target lower goals tend to have lower HbA1c levels [100,101]. Similarly, several registries and individual clinics report reduction in mean HbA1c over time highlighting the importance of benchmarking, quality improvement, and a team approach to improving glucose control[25,102]. In the well-educated EDIC adult cohort, which has excellent access to the newest diabetes technology and a mean age of 45±7 years, the most recent mean HbA1c was 62 mmol/mol (7.8%) [97]. Acute and chronic complication rates are also decreasing with improvements in care [27,103].

Of all age-groups, adolescents are currently the farthest from achieving a HbA1c goal of <58 mmol/mol (7.0%) [6,77], reflecting the sub-optimal diabetes management that frequently accompanies the increased independence in diabetes care during the adolescent years, as well as the effects of the psychological and hormonal milieu of adolescence. However, given that results from DCCT/EDIC document that elevated HbA1c for 5 – 7 years, which is similar to the duration of puberty, may have prolonged adverse effects [8,10,104,105] caregivers should not be complacent with the care of these youth, but work to improve glycemic control as much as possible. While better insulins, glucose monitoring, and insulin delivery devices are available today, compared with the DCCT era, adolescents in general may still be unable to achieve a lower HbA1c levels than the DCCT adolescent average without novel approaches to care. Sometimes, particularly for adolescents, “aiming for lower” is needed rather than moving all the way to recommended targets to reduce burnout and loss-to-follow up. Too ambitious goals may lead to discouragement and a sense of failure and alienation for many teens. Striking a balance between the increasing autonomy of the adolescent, successful transition of care from parents to child, maintaining a healthy psychological outlook [see Chapter 16 (ref Psychology chapter)] and maintaining an optimal HbA1c are the main challenges of caring for the adolescent [see Chapter 17 (ref Adolescent chapter)].

The aspirational HbA1c goal of <53 mmol/mol (7%) is most appropriate in resource-intensive settings where access to analog insulins, advanced insulin delivery systems, and state-of-the art glucose monitoring technology are available. Goals even lower than 53 mmol/mol (7.0%) may also be appropriate for those children with significant residual beta cell function who may

be able to achieve an HbA1c within the non-diabetic reference range. This condition is most likely seen in the first year after diagnosis (during the partial remission or “honeymoon” phase), generally between 1 and 6 months after diagnosis.

Organizations such as the National Institute for Health and Care Excellence and the Swedish National guidelines have recommended uniformly lower goals for children and adolescents with type 1 diabetes [106,107]. However, these guidelines are based on the likelihood of complications in adults and admit that there is “no evidence” in children for this decrease [107]. There is no evidence that these lower goals can be achieved safely, how much of a reduction in future complications they might afford, or that they do not result in significant reductions in quality of life and in increased stress/distress. Also, it is still not yet known precisely how a HbA1c of 48 mmol/l (6.5%) compared to <53 mmol/l (7%), particularly in the years before puberty, will be associated with subsequent reductions in micro- or macro-vascular disease as data on the relationship between HbA1c in the pre-pubertal years and future vascular complications are mixed [108,109].

Careful attention must be taken to avoid severe hypoglycemia. Although older studies suggested an increased risk for hypoglycemia with lower HbA1c [1,2,110,111], in recent years this has not been the case, in part due to increased use of insulin analogs, and insulin pump therapy, with or without CGM [21,23,24,28,77,112,113]. Because severe hypoglycemia is more common in patients with hypoglycemia unawareness, glucose targets must be increased when hypoglycemia unawareness occurs[114]. CGM devices, especially when coupled with pumps equipped with low glucose suspend, may also particularly benefit those with hypoglycemia unawareness, as the devices will alarm when glucose is below a specified range or with rapid rate of fall of glucose and temporarily suspend insulin delivery [55,56,115]. Hypoglycemia unawareness is more common in those who maintain generally lower BG levels [116,117].

Health care priorities and future directions:

Persons with type 1 diabetes, their families, health care providers, and others (e.g. insurers) should be aware that achieving an HbA1c consistently at or below the target range without extensive personal and national health care resources and outside of a clinical trial structure may be very difficult. The observed differences in HbA1c and other metrics across centers and countries indicate that additional work in quality improvement (with de-anonymized center- and region-specific data) with attention to best practices in care is needed [118-120]. (Reference

EDUCATION Chapter)

Each child should have their BG and glycemic 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 and optimizing quality of life. As diabetes technology improves, especially CGM and automated insulin delivery systems, recommended target indicators for glycemic control will likely decrease to reflect a new balance of benefits and risks. ISPAD advocates that as improved diabetes technology becomes available and enables patients to achieve lower glycemic targets with less burden of care and improved quality of life, such technology should be widely available to children, adolescents and young adults with diabetes worldwide.

Table 1. Glycemia and Blood Glucose Target Recommendations

<table>
<tr><td>Target HbA1c</td><td colspan="4">HbA1c <53 mmol/mol (<7.0%)
• This target must be individualized with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia, frequent mild to moderate hypoglycemia, and excessive stress/burden for the child with diabetes and their family.
• Factors that must be considered when setting an individualized target include, but are not limited to:
○ Access to technology, including pumps and CGM
○ Ability to articulate symptoms of hypoglycemia and hyperglycemia
○ History of severe hypoglycemia/hypoglycemic unawareness
○ History of compliance with therapy
○ Whether child is a high or low glycator
○ Whether child has continued endogenous insulin production (e.g. in the new onset or “honeymoon” period of diabetes)</td></tr>
<tr><td rowspan="4">Glycemic Targets</td><td></td><td>NICE goal A1c ≤48 mmol/mol (≤6.5%) [107]</td><td>ISPAD goal A1c <53 mmol/mol (<7%)</td><td>ADA goal A1c <58 mmol/mol (<7.5%)[121]</td></tr>
<tr><td>Pre-meal</td><td>4.0-7.0 mmol/L (70-126 mg/dl)</td><td>4.0-7.0 mmol/L (70-130 mg/dl)</td><td>5.0-7.2 mmol/l (90-130 mg/dl)</td></tr>
<tr><td>Post-meal</td><td>5.0-9.0 mmol/L (90-162 mg/dl)</td><td>5.0-10.0 mmol/L (90-180 mg/dl)</td><td></td></tr>
<tr><td>Pre-bed</td><td>4.0-7.0 mmol/L (70-126 mg/dl)</td><td>4.4-7.8 mmol/L (80-140 mg/dl)</td><td>5.0-8.3 mmol/L (90-150 mg/dl)</td></tr>
<tr><td>Necessary elements for successful glycemic management</td><td colspan="4">• HbA1c measurements at least quarterly
• Glucose monitoring using CGM or self-monitored BG measurements up to 6-10 times per day
• Regular review of glucose values with therapy adjustments as necessary</td></tr>
</table>

ADA = American Diabetes Association, BG = blood glucose, CGM = Continuous Glucose Monitoring; HbA1c = Hemoglobin A1c; NICE = National Institute for Health and Care Excellence

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