ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES 2022:
Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes

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1. WHAT IS NEW OR DIFFERENT

- Inclusion of continuous glucose monitoring (CGM) targets for children, adolescents, and young adults <25 years
- Emphasis on individualized care plans that make use of effective educational strategies to achieve glucose targets that are person-centered, and designed to empower young people and caregivers. These plans should incorporate cognitive behavioral techniques that encompass:
  - problem solving
  - goal setting
  - communication skills
  - motivational interviewing
  - family conflict resolution
  - coping skills, and stress management
- Adoption of a unified fingerstick capillary glucose (SMBG) target of between 4 – 10mmol/L [70-180mg/dL], which aligns with the target CGM time in range, while emphasizing a tighter fasting target range of 4 – 8mmol/L [70 – 144mg/dL].
- Recognition that disparities in the social determinants of health (SDOH) and inequitable access to modern diabetes therapies represent significant barriers to achieving glucose targets and optimizing clinical outcomes. Health stakeholders are responsible for addressing this disparity.
2. **EXECUTIVE SUMMARY AND RECOMMENDATIONS**

- Achieving glucose levels in target assessed through CGM, HbA1c, and/or SMBG:
  
  Reduces risks of acute and chronic disease complications A

  Minimizes the detrimental effects of hypoglycemia and hyperglycemia on brain development, cognitive function, mood and quality of life B

- Target HbA1c for young people with diabetes should be <53mmol/mol (<7.0%) A and measured every 3 months E

- CGM metrics, recorded over a 14-day period, should have time spent as follows: B
  
  o  >70% between 3.9 – 10mmol/L (70 – 180mg/dL)
  
  o  <4% : <3.9mmol/L (70mg/dL)
  
  o  <1% : <3.0mmol/L (54mg/dL)
  
  o  <25%: >10mmol/L (180mg/dL)
  
  o  <5%: >13.9mmol/L (250mg/dL)

- SMBG should be assessed at least 6 times a day for a person with diabetes taking insulin B, and target between 4-10mmol (70-180mg/dL), but with a narrower fasting target range of 4-8mmol/L (70-144mg/dL). E

- Less stringent HbA1c, CGM, or SMBG targets are only advisable when achieving the standard target is assessed as being detrimental to the overall wellbeing of the person with diabetes or their caregivers. Factors to consider when setting a less stringent target include (but are not limited to):
access to insulin analogs, advanced insulin delivery technology (for example automated insulin delivery), supplies needed to regularly check capillary glucose, or CGM needed to achieve targets safely

Underlying significant psychosocial health concerns exacerbated by efforts to achieving glucose levels in target

- A multidisciplinary education team should clearly and collectively communicate recommended glycemic targets, sharing the same philosophy and goals, and speaking with “one voice” has beneficial effects on glycemic and psychosocial outcomes.

- Individualized care plans are recommended to help a person with diabetes achieve glycemic targets.

- Data collection and between-centre benchmarking can improve the proportion of people with diabetes reaching glycemic targets.

- Addressing social determinants of health, and improving access to the healthcare team, insulin, and technologies improves the proportion of people reaching glycemic targets.

3. The importance of setting glycemic targets

Glycemic targets for young people with diabetes are needed as optimising glycemic control reduces short and long-term complications. In addition to the benefit of protecting against micro- and macrovascular complications, of particular importance in pediatrics is the negative association of hypoglycemia and hyperglycemia on cognition and brain structure, especially in individuals with early onset diabetes. Further, the wider impact of diabetes on healthcare
systems and health economics is an important driver to target better glycemic outcomes to prevent future complications.\textsuperscript{5,6}

Diabetes registries have shown steady improvement in median HbA1c in recent decades yet only a minority of young people attain current glycemic targets.\textsuperscript{7} The improvements that have been demonstrated can be attributed to multiple factors, including how healthcare teams set and communicate glycemic targets, improved therapeutics (insulin analogs, CGM), highly skilled and knowledgeable workforce, and recently, the use of automated insulin delivery systems. Nevertheless, social determinants of health, pediatric diabetes workforce constraints and access to improved therapeutics remains a significant barrier against more young people reaching target glycemia, and further, drives health inequity.\textsuperscript{8,9}

Setting glycemic targets has been standard practice for the diabetes organizations including ISPAD, the American Diabetes Association (ADA), and the National Institute of Clinical Excellence (NICE) in the United Kingdom for 20 years, and are regularly updated when evidence has supported change.\textsuperscript{10} For example, when different stakeholders published divergent HbA1c targets, and lower HbA1c targets were shown not to increase the rates of severe hypoglycemia,\textsuperscript{11} progressively lower targets were adopted. It is important to recognize that setting targets contributes to improving glycemia as shown by the observation that a combination of setting a lower target HbA1c and consistency between members of teams within centres is associated with lower centre HbA1c.\textsuperscript{11,12} It is essential that target setting is a collaborative discussion with the person with diabetes (including caregivers) and health care professionals. Furthermore, prospective audit activity, involvement in data registries and clinical benchmarking including quality improvement implementation is also associated with overall improvements in glycemic outcomes.\textsuperscript{13,14}
Health care professionals and people with diabetes now have a wide array of tools to assess glycemia, including capillary glucose values, HbA1c, and CGM. While traditionally HbA1c has been the gold standard, there are limitations to this measurement as discussed later. Correspondingly, with rapidly increasing adoption of CGM, which arguably avoids these limitations, CGM metric reporting has been standardized and CGM metrics are included in this chapter. The recent COVID-19 global pandemic, and increased opportunities for the use of video or phone appointments between a person with diabetes and/or their carer and the health care professional, has highlighted the utility of CGM metrics to assess glycemic control when laboratory testing of HbA1c is not available. While disparities also exist for accessing telemedicine including implicit bias, well developed workplans can expand the population who can benefit from this health delivery method. Nevertheless, not all young people can access CGM, and are reliant on capillary glucose testing and/or HbA1c measurement. Using all available forms of glycemic data, in combination if available, will give the most accurate account of glycemic control to help guide therapy.

Individualized glycemic target setting above the stated HbA1c target has been emphasized in recent consensus statements. This was included to address concerns that for some young people with diabetes and caregivers particularly in limited resource settings, stringent HbA1c targets may increase the risk of severe hypoglycemia, or cause psychological distress through treatment burden that outweighs the long-term benefit of a lower HbA1c. Although historically lower HbA1c was considered a risk factor for severe hypoglycemia, this association is no longer observed with contemporary intensive management. For example, data registries have demonstrated that the overall incidence of severe hypoglycemia is reducing at the same time as improved overall HbA1c.
Access to diabetes technology including CGM with or without automation of insulin delivery can further reduce this risk while achieving target glycemic control (see ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring, and Chapter 17 Diabetes Technologies: Insulin Delivery). Therefore, outside of limited resource settings, risk of severe hypoglycemia can no longer be justified as a reason for a higher HbA1c target in the majority of cases. However, if setting stringent glycemic targets is considered to have an overall negative impact on psychological wellness (either for the person with diabetes and/or their caregivers), which may include severe anxiety that outweighs the long-term benefit of optimising glucose values, a higher glycemic target may be appropriate in combination with efforts to address the barriers to tighter control. Other exceptions occur in rare situations, for example in a person with diabetes and a limited lifespan or neonatal diabetes, where targeting in-target glycemia will add management burden over any improvement on short or long-term morbidity and mortality.

In ISPAD 2022 Consensus Guidelines Chapter 6 on Diabetes Education in Children and Adolescents, we highlight the importance of the multidisciplinary education team sharing the same philosophy and goals and speaking with “one voice”, with beneficial effects on metabolic and psychosocial outcome. Education should be person-centered, with personalized diabetes educational approach being an integral part of the psychosocial support for young people with diabetes and their families. (See ISPAD 2022 Consensus Guideline Chapter 15 on Psychological Care of children and adolescents with type 1 diabetes).

Therefore, for the majority of young people with diabetes, the priority of the multidisciplinary team is to develop (in consultation with the person with diabetes and their caregivers) an individualised care plan to achieve the ISPAD recommended targets, rather than individualising the glycemic target itself.
4. Measures of glycemia and targets

4.1 Glycated Haemoglobin

4.1.1 Target:

A target of <53mmol/mol (<7.0%) is recommended for all young people with diabetes (Figure 1). Individualised care plans should be a collaboration between the young people with diabetes, their caregivers, and the multidisciplinary team. Where barriers exist to achieving this target (for example access to insulin analogs, advanced technologies like CGM and automated insulin delivery, psychological distress), individualised targets may be selected.

The target of <53mmol/mol (<7.0%) is chosen with the aim of avoiding long term microvascular and macrovascular complications. The curvilinear relationship of HbA1c and the development of microvascular and macrovascular complications indicates that HbA1c values that approach 42mmol/mol (6%) may continue to yield risk reduction, but that the relative gains are less as compared with reducing HbA1cs to the upper limit of the target [53mmol/mol (7%)]. This validates maintaining HbA1c in the 42 – 53mmol/mol zone (6 – 7%) and achieving the lower end of this range during the remission phase or early stage 3 diabetes “honeymoon” or when using contemporary treatment such as automated insulin delivery is appropriate, if it can be achieved without hypoglycemia or significant treatment burden. This would apply to most young people with diabetes who are not living in a limited resource settings. Comparatively, the 2020 NICE guideline sets an HbA1c target of 48mmol/mol (6.5%), (available at www.nice.org.uk/guidance/NG18). The ISPAD target has retained a goal of <7% due to a paucity of evidence that an HbA1c of <6.5% equates to
significant additional benefit to the development of microvascular complications over the 6.5 – 7.0% range.  

4.1.2 Laboratory and practical considerations

Glycated hemoglobin, usually assessed as HbA1c, continues to have the central role in setting glycemic targets, by virtue of several factors; i) Definitive evidence of the association between HbA1c and the development of diabetes complications, ii) A standardised reference method and procedure set by the IFCC and endorsed by all the major stakeholders, iii) Availability of point of care measurement in clinic and in outreach or remote settings, and iv) Barriers to universal access to CGM (and associated glycemic metrics). Every young person with diabetes should have a minimum of four HbA1c measurements per year (at approximately 3-month intervals). It is recommended that centres regularly audit HbA1c levels, benchmark against consensus statements and as possible, contribute data to registries and quality improvement initiatives.

The maximum lifespan of erythrocytes is approximately 100-120 days with an average age at any given time ranging from 40-60 days, and as such, HbA1c reflects average blood glucose concentration in the preceding 8-12 weeks. More recent plasma glucose concentrations contribute proportionately more to the HbA1c concentration – estimated to be 50% contribution from the previous 30 days, with 40% and 10% contributions from the previous 31-90 days and 91-120 days, respectively.

4.1.3 Limitations of HbA1c

Clinical states associated with altered Hb turnover or erythrocyte survival will affect HbA1c measurement and therefore clinical utility (Table 1). As HbA1c is a direct reflection of average glucose levels, highly variable glucose levels with fluctuating hypo- and hyperglycemia can
result in the same HbA1c measurement as an individual with stable glucose levels. This is important as glycemic variability predicts severe hypoglycemia, and there is a growing body of evidence that glycemic variability is an independent risk factor for short and long term complications.\textsuperscript{28,29} Arguably, CGM, by virtue of providing metrics for both average glucose, glucose out of target and glycemic variability, as well as having a very high correlation with HbA1c, provides a better reflection of glycemia. CGM offers an alternative proxy for HbA1c [Glucose Management Index (GMI)],\textsuperscript{30} however, there is some discordance between GMI and laboratory HbA1c, and hence, the term “estimated” HbA1c should be avoided.\textsuperscript{31} Evidence supports the association of diabetes complications and CGM derived measures, particularly time in range.\textsuperscript{32} However as widespread CGM uptake has been a more recent phenomenon, it will take time for large registry data to definitively connect CGM metrics with the development of micro- and macrovascular complications. However, where CGM data are not available, evaluation of fructosamine and/or 1,5—anhydroglucitol (1,5-AG) may be the only alternative.

Fructosamine is the generic term for plasma protein ketoamines or 1-amino-1-deoxy-D-fructose,\textsuperscript{33} and more specifically is the measurement of the total stable irreversible serum glycated proteins at any given time. The half-life of serum proteins is significantly shorter than that of erythrocytes, and the degree of glycation is therefore more reflective of shorter-term alterations in plasma glucose concentrations that is estimated to be 2-3 weeks which is consistent with the half-life of albumin (20 days) which comprises 80% of total serum proteins.\textsuperscript{34,35} 1,5-AG has been proposed in the assessment of glycemic variability.\textsuperscript{36} Low 1,5-AG values are indicative of both high circulating plasma glucose concentration, as well as fluctuations in plasma glucose concentrations (hyperglycemic excursions). 1.5-AG concentration reflects plasma glucose concentrations over the preceding 2-14 days.
4.2 Continuous glucose monitoring

4.2.1 CGM targets

ISPAD endorses previously published standards for time spent in each glycemic band\textsuperscript{37} (figure 1). These are time spent:

- >70% between 3.9 – 10mmol/L (70 – 180mg/dL),
- <4% <3.9mmol/L (70mg/dL),
- <1% <3.0mmol/L (54mg/dL),
- <25% >10mmol/L (180mg/dL),
- <5% >13.9mmol/L (250mg/dL)

Average sensor glucose by virtue of a strong correlation between mean sensor glucose and HbA1c, and association with the risk of microvascular complications,\textsuperscript{38} and measures of glycemic variability (as a predictor of hypoglycemia), are included. These metrics are all reported as part of standardized CGM reports, termed the ambulatory glucose profile (AGP). When available, CGM targets should be used in conjunction with HbA1c targets (Figure 1). In rare occasions, as discussed above, less stringent time in range may be applied where efforts to reach the target may be detrimental to overall wellbeing.

4.2.2 Practical considerations for continuous glucose monitoring

The evidence and best practice for the use of CGM in improving glycemia and psychosocial burden is reviewed in ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring. This includes appropriate expectation setting and education. Early adoption of CGM from diagnosis is associated with long term benefits to HbA1c.\textsuperscript{39,40} Unfortunately, access to CGM is not universal, and can depend on geographic location, local
health care funding policy, and socio-economic status (including insurance). Further, there is racial-ethnic and insurance-mediated bias in recommending CGM by health care providers.\textsuperscript{41}

Skin irritation is a significant negative aspect of CGM,\textsuperscript{42} and is the commonest reason for discontinuation.\textsuperscript{43} Various strategies have been developed to address this issue\textsuperscript{44} and are discussed further in ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring and Chapter 19 Other complications and associated conditions in children and adolescents with type 1 diabetes. Alarm fatigue can also contribute to CGM discontinuation, and as such, a person centred approach should be used when introducing CGM alarms.\textsuperscript{45}

CGM accuracy is an important consideration, especially in the hypoglycemic range. According to the consensus statement, the maximal allowable time spent <3.9mmol/L (70mg/dL) is 4%, however people without diabetes may spend 3.2% of their time in this zone, but rarely <3.0mmol/L [54 mg/dL], depending on the accuracy of the sensor used.\textsuperscript{46} Therefore, reducing time spent in the very low < 3.0mmol/L [54 mg/dL] is most important. Fortunately, each subsequent generation of CGM has improved accuracy to the point that several CGM and intermittently scanned CGM (isCGM) systems are approved to be used non-adjunctively. Confirmation of hypoglycemia using a SMBG is recommended. SMBG confirmation should also occur when there is a discrepancy between symptoms of hyperglycemia or hypoglycemia and an apparently normal sensor glucose value,

4.3 Capillary glucose measurements (SMBG)

4.3.1 SMBG targets:
SMBG targets should be 4 – 10mmol [70-180mg/dL]. SMBG levels should be targeted to correspond to an HbA1c <53mmol/mol (7%). This aligns with the CGM time in range target of >70% between 3.9 – 10mmol [70-180mg/dL], and the strong correlation of CGM metrics with HbA1c reviewed earlier. Tighter fasting target range of 4 – 8mmol/L [70 – 144mg/dL] are recommended in order to achieve the above stated HbA1c target. Previous ISPAD guidelines\textsuperscript{16} and current ADA and NICE guidelines have recommended a variety of glucose value ranges depending on time of day and relationship to meals.\textsuperscript{16} Without empiric evidence that such specific targeting reduces hyperglycemia or hypoglycemia, combined with the potential for healthcare professionals to send mixed messages and overly detailed education, the newly defined SMBG targets offer a pragmatic solution. SMBG glucose level target prior to bed above 3.9mmol/L [70mg/dL] are appropriate, however caregivers may have more confidence with higher levels within the 4 - 10mmol/L [70-180mg/dL] range in certain scenarios; for example, if there has been preceding hypoglycemia, exercise, hypoglycemic unawareness, or no access to CGM with hypoglycemia threshold alarms. Ideal glucose levels prior to and during exercise are dependent on many factors including type and duration of exercise, insulin regimen, and CGM use, and is detailed in ISPAD 2022 Consensus Guidelines Chapter 14 for Exercise in Children and Adolescents with Diabetes. With respect to young people with type 2 diabetes, the evidence that SMBG has an impact on glycemic control in individuals with T2D is limited. The potential benefit vs. cost of continuous glucose monitoring in this population also remains unclear.

5 **A developmental perspective for glycemic target setting**

While glucose targets outlined above can be applied for all young people with diabetes, a challenging time for the individual and their caregivers can occur as the honeymoon period
wanes due to diminishing residual endogenous insulin secretion. Beyond the honeymoon there may be a requirement for more intensive management and associated burden to maintain glycemic targets. Long term HbA1c trajectory is strongly predicted early after diagnosis, which highlights the importance of attaining target glucose levels early in the life-course.\textsuperscript{47-49} As outlined in ISPAD 2022 Clinical Practice Guidelines Chapter 6 on Diabetes Education in Children and Adolescents, it is important that glucose targets be addressed and reinforced during post honeymoon phase where HbA1c increases, and TIR reduces.

The developmental age of the person with diabetes is associated with unique challenges to achieving the aforementioned glucose targets. For example, management in pre-school children can be particularly difficult due to unpredictable eating and activity levels and associated higher glycemic variability.\textsuperscript{50} See ISPAD 2022 Consensus Guidelines Chapter 23 on Managing Diabetes In Preschoolers. At school age, young people are beginning independent care. There is some evidence that focused age-appropriate educational interventions are effective in children and families (See ISPAD 2022 Clinical Practice Guidelines Chapter 6 on Diabetes Education in Children and Adolescents). Further, adolescence is a critical period of independence and physiologic changes associated with increasing insulin resistance, with an increase in HbA1c seen in multiple international registries.\textsuperscript{51} Adolescent and culturally appropriate education tools are needed to reinforce individualised care plans that aim to meet glycemic targets while balancing lifestyle and psychological factors (See ISPAD 2022 Consensus Guidelines Chapter 21 Diabetes in Adolescence).

\section*{6 Health care priorities and future directions}
The social determinants of health, encompassing “the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life (WHO)”, strongly predict the likelihood of an individual to achieve recommended or optimal glycemic targets. ISPAD recognizes that these disparities represent significant barriers to optimal care, and collective efforts are needed to understand and address systemic inequities including medical racism and societal policies that entrench generational poverty. As such, there is a responsibility for health care professionals to advocate on behalf of young people with diabetes who have limited access to healthcare, including technology. Indeed, health providers are known to have implicit bias with respect to offering diabetes technology, which drives inequity. Specifically, healthcare reimbursement policies and wider government policy that drives socioeconomic disparities is essential to improve health equity. For the person with diabetes this should translate to equity in accessing an appropriately resourced multi-disciplinary care team (including dietetic, nursing, psychology, social work, and medical expertise), access to technologies such as CGM and automated insulin delivery, and modern insulin analogs.

References


45. Miller E, Midyett LK. Just because you can, doesn’t mean you should... now. A practical approach to counseling persons with diabetes on use of optional CGM alarms. *Diabetes Technology & Therapeutics*. 2021;23(S3):S-66-S-71.


Caption: Glycemic targets are dependent on the measures available; finger stick capillary glucose (SMBG) levels, HbA1c, and CGM values. The term “finger stick” glucose is used instead of SMBG in the figure as the figure is designed to be easily interpreted by people with diabetes. The different modes of measuring glycemia are closely related, but are no equivalent, and the image is intended as an educational aid. SMBG targets align with the CGM optimal range, however fasting SMBG levels are recommended to fall between 4 – 8mmol/L [70 – 144mg/dL].
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