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ISPAD Clinical Practice Consensus Guidelines 2024: Glycemic Targets

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Short title: Glycemic targets

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Abstract

The ISPAD guidelines represent a rich repository that serves as the only comprehensive set of clinical recommendations for children, adolescents, and young adults living with diabetes worldwide. This chapter builds on the 2022 ISPAD guidelines, and updates recommendations on the glycemic targets for children and adolescents living with diabetes. A new target of HbA1c of ≤6.5% (48mmol/mol) for those who have access to advanced diabetes technologies like continuous glucose monitoring (CGM) and automated insulin delivery (AID). This target should be encouraged for all children and adolescents living with diabetes when safely achievable. In other settings, the HbA1c target is ≤7.0% (53mmol/mol).

Summary of what is New or Different

1. This chapter recommends a target HbA1c of ≤6.5% (48mmol/mol) for those who have access to advanced diabetes technologies like continuous glucose monitoring (CGM) and automated insulin delivery (AID). This target should be encouraged for all children and adolescents living with diabetes when safely achievable. In other settings, the HbA1c target is ≤7.0% (53mmol/mol). The emphasis on the lower HbA1c target is deliberate, based on the growing evidence that achieving HbA1c levels below previous targets can significantly reduce the risk of developing diabetes complications and that when adequate technology and

healthcare professional support are available, these lower glycemic targets can be safely achieved without increasing the risk of hypoglycemia or adding to the care burdens.
2. These glycemic goals may be individualized based on an assessment of the potential challenges for the person with diabetes and their caregivers.
3. The relationship between glycemic targets and rates of excess body weight are discussed.
4. The glycemic target chapter is also more succinct compared to previous iterations. This chapter is meant to provide updated guidance on overall glycaemic management alongside other ISPAD consensus guidelines that provide further context and information, including specific populations (e.g. pre-schooler children, limited care settings), or situations (e.g. exercise).

1. The Purpose of setting Glycemic Targets

Setting glycemic targets for young persons living with diabetes is vital, as optimizing glycemia can greatly minimize both immediate and long-term complications [1-6]. This is especially important for children and adolescents with diabetes, as they face many years of managing the condition and lifetime consequences of dysglycemia [7]. Achieving healthier glycemic outcomes has significant benefits for healthcare systems and economic costs, underscoring the importance of targeting glycemic ranges to avert future complications [8]. Yet, it is also important to recognize the day-to-day challenges glycemic targets can impose on persons living with diabetes, their caregivers, and even their health care team. These targets should be seen as part of a balanced approach to long-term management; at times flexibility will be necessary.

Recent data from diabetes registries show that while a minority of young people are meeting current glycemic targets, median HbA1c levels have gradually decreased over the past decades[9-13]. This progress can be attributed to several factors, including better, consistent communication of glycemic goals by healthcare teams, advancements in treatments like insulin analogs and CGM, a well-trained medical workforce, and the development and implementation of automated insulin delivery systems (AID). Additionally, clinical benchmarking activities that use published glycaemic targets in their reporting, have been shown to be associated with improvement in whole population glycemic metrics[14-17]. However, challenges such as social determinants of health, limited resources for pediatric diabetes care, and restricted access to advanced treatments continue to impede broader achievement of target glycemia and contribute to health inequities [18-20].

For over 20 years, organizations like ISPAD, the American Diabetes Association (ADA), and the National Institute for Health and Care Excellence (NICE) in the UK have established and regularly updated glycemic targets based on evolving evidence. While lower glycemic targets are associated with improved glycemia [21], the path to achieving these targets can be challenging. In 2022, ISPAD set the HbA1c target at 7.0% (53 mmol/mol), with a provision for lower targets where feasible, particularly when there is access to gold standard treatments like AID [22]. Other societies have adopted lower targets. For instance, Sweden [23], and NICE[11] have lowered their targets to 6.5% (48 mmol/mol). Additionally, in 2022 ISPAD communicated that an HbA1c of 6.5% could be safely achieved for pre-school children [24]. The ADA recommends an HbA1c of <6.5% as a reasonable goal if “it can be achieved without significant risk of hypoglycemia, or negatively impacts on well-being or undue burden of care”, but also allows flexibility, stating “individualized goals”. with <7.0% as the “appropriate” target [25].

Healthcare professionals and persons with diabetes have various tools for monitoring glycemia, including self-monitored blood glucose (SMBG) using a glucose meter, CGM and HbA1c. While HbA1c has traditionally been the standard measure, it also has limitations that CGM can address. Despite this, CGM is not yet accessible to all young people, meaning that SMBG and HbA1c measurements remain critical in many settings, including for benchmarking. Combining data from these sources also can offer the most comprehensive view of glycemia, and in turn, the best opportunity to tailor care to both the immediate and long-term needs of everyone.

2. Measures of Glycemia and Targets

For educational purposes, three methods of measuring glycemia and their targets are provided in Figure 1. This has been updated from 2022 to specifically emphasize the lower HbA1c target of 6.5% (48mmol/mol) for those with access to advanced technologies or those who can safely reach that target without additional undue care demands.

a. Glycated Hemoglobin

- ISPAD recommends an HbA1c target of ≤6.5% (48mmol/mol) for those who can safely reach that target with the support of advanced technologies (CGM and AID) and/or where the pursuit of the lower target does not add burden such that quality of life is impacted **[C]**
- ISPAD recommend an HbA1c target of ≤7% (53mmol/mol) in all other scenarios **[A]**

Landmark trials have shown that the relationship between the developments of long-term complications and glycemia is continuous and non-linear [2, 26]. These robust data justify an HbA1c target of ≤7% (53mmol/mol) (Category A evidence). However, evidence for a lower target of ≤6.5% (48mmol/mol) is still emerging as described below (Category C evidence). Overall, further research is needed to evaluate the outcomes of children achieving HbA1c levels of ≤6.5%. This should include more comprehensive studies and detailed mathematical modelling of existing data sets. Such analysis would help quantify the incremental improvements in complication rates and assess any potential increased risks when comparing the HbA1c thresholds of ≤7% (53 mmol/mol) and ≤6.5% (48 mmol/mol). Yet, at this time communicating a single threshold is a pragmatic approach to convey clear messaging that can be implemented in clinical practice. This threshold also facilitates the ability to benchmark outcomes adding to the body of evidence demonstrating safety and validity of lower target setting to improvements in glycemia [14-17]. Goal setting is important to reduce therapeutic inertia, and therefore regular measuring of HbA1c (and other metrics) is an important foundation of clinical care – with an accepted convention of 3 monthly assessment, given that HbA1c reflects ~90 days of glycemia. HCP and care teams should consistently and clearly communicate the importance of glycemic targets to optimize long-term health outcomes for youth with diabetes [21].

Refer to the ISPAD CPCG 2024: Diabetes Technologies: Insulin Delivery [27] for the evidence regarding efficacy and safety of advanced technologies, including cost effectiveness [28, 29].

Current glycemic target recommendations are also based on the following observations:

1. **Diabetic Retinopathy**: Independent risk factors for developing diabetic retinopathy include not only glycaemic management, but also age of onset and duration of diabetes [30, 31], which emphasizes the need to pursue optimal glycemic targets in young people with diabetes from diagnosis. Precursors to retinopathy are now measurable with optical coherence tomography angiography, and microvascular changes are seen in youth with suboptimal glycemic levels[32]. Critically, the lowest rates of diabetic retinopathy at the time of transition to adult services are seen where HbA1c is ≤6.5% (48mmol/mol)[33].
2. **Diabetic Kidney Disease**: Multiple studies confirm that lower HbA1c protect against the development of diabetic kidney disease [1-6]. In contrast to the development of diabetic retinopathy, Swedish registry data did not find a similar clear relationship for the development of increased albuminuria at the 6.5% (48mmo/mol) HbA1c threshold[33]. There is evidence that some individuals from racial groups have a predisposition to developing complications early independently of glycemia and socioeconomic status [34, 35]. Indeed, observations from the general population showed that Native Americans at risk of developing type 2 diabetes and HbA1c in a prediabetes range (5.7 – 6.4% (39-47mmol/mol)) had higher incidence of albuminuria, and retinopathy than children with optimal HA1c levels[36]. However, there is limited evidence supporting reductions in diabetic kidney disease onset and progression at HbA1c levels below 7% in type 1 diabetes.
3. **Diabetic neuropathy**: While systematic reviews confirm the relationship between HbA1c and the development of diabetes neuropathy[36], there is, again, a paucity of data to derive a specific threshold that confers significant additional risk. An HbA1c >7% (53mmol/mol) was associated with a higher risk of developing diabetic neuropathy in adolescents with type 1 diabetes for >5 years, but the risk associated with a lower threshold of 6.5% (48mmol/mol) was not assessed[37]. Further data, or modelling, are needed to confirm the additional benefit of using a target of 6.5% (48mmol/mol) for protecting against the development of diabetic neuropathy and other vascular complications.
4. **Cognition:** Optimal glycemia is associated with improved cognitive function, including memory, learning and attention [13, 38-41]. Yet, in settings where hypoglycemia-protective technologies such as CGM and AID are not available or adopted, there may be unacceptable risks of severe hypoglycemia and associated negative impact on cognitive function. Overall, with respect to cognition, a lower target of 6.5% should be

carefully guided on individual basis, particularly in situations with limited access to glucose monitoring and technologies that suspend insulin when glucose is low or projected to be low.

5. **Burden:** Recognizing and addressing the psychosocial and behavioral needs of youth with diabetes and their families is a key element of their care. The relationship between the demands of care and HbA1c is complex, for example while some reports describe the challenges of diabetes technology, improved quality of life and glycemia have been consistently demonstrated [27]. Burden of care can be considered in the following domains; psychological, behavioural, social, quality of life, and economic. Avoidance of complications with lower HbA1c will lower the health cost of diabetes and can be safely achieved with advanced diabetes technologies, with proven health economic benefits. Adoption of these technologies are associated with potential barriers, which includes perceived and actual workload, physical discomforts, frustrations with technical glitches and alarms, as well as concerns about device size/visibility and stigma [42-44]. Potential benefits of diabetes technologies must also be recognized, with improvements in individual and parental health of life [45], as well as autonomy, greater flexibility in social activities and eating, improved sleep, and higher treatment satisfaction being reported [27].
6. **Body Mass Index (BMI)**: Due to overweight and obesity being established independent risk factors for developing cardiovascular disorders, any relationship between glycaemic targets and BMI is an important consideration. This is especially relevant given that while international registries are demonstrating an overall improvement in HbA1c, there are also increasing prevalence of higher BMI-standard deviation scores (SDS) [46, 47]. Earlier landmark studies have shown increased excess weight gain and obesity with intensive treatment [26]. However, there are apparent external influences on BMI independent of HbA1c, as is apparent with the U-shaped curve with the highest HbA1c observed in groups with unhealthy weight [48]. Some studies have reported inverse associations between HbA1c and BMI-SDS[49-51]. However, other studies have found high BMI-SDS significantly related to higher HbA1c levels [47, 52], or reported children with type 1 diabetes can achieve glycemic targets on intensive insulin therapy without excessive weight gain [53, 54]. Use of advanced technologies such as AID is associated with improved glycemia without change in BMI [55, 56]. The emergence of increased overweight and obesity in the pediatric population living with diabetes underpins the importance of dietetic education, to ensure the benefits of improved glycemia are not offset by increasing BMI. These data highlight the need for additional research and innovative care approaches to address rising rates of overweight and obesity and risk for premature cardiovascular disease in this vulnerable population.

b. **Continuous Glucose Monitoring**

- Children and adolescents with diabetes should strive for the following % times spent in the following glycemic ranges **[B]:**

>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)

These times in range are chosen to align with previously-published recommendations (45)

- It is recognized that time spent in range (TIR) may need to be >80% to achieve an optimal HbA1c target of ≤6.5% (48mmol/mol) **[E]**.
- It is also recognized that an emerging metric requiring additional validation of >50% Tight Time in range (TTIR) (3.9–8 mmol/L or 70–144 mg/dL) may allow for greater sensitivity for assessing changes in mean glucose and glucose variability (CV) [C]
- CGM-derived Glucose Management Index metrics can be considered as a standalone method for evaluating glycemic outcomes **[C].**

Average sensor glucose, due to its strong correlation with HbA1c and its association with the risk of microvascular complications[57] and glycemic variability (which can predict hypoglycemia), is a key metric included of standardized CGM reports, known as ambulatory glucose profiles (AGPs). When available, CGM targets can be considered as an alternative or adjunct to HbA1c targets. As CGM technology is still relatively new, further research linking CGM data to the development of diabetes complications is needed to refine these glycemic targets with greater certainty.

Given the strong correlation between CGM metrics and HbA1c [58], it is reasonable in a clinical setting to use CGM along with the Glucose Management Index metric as a standalone method for setting glycemic targets. This could be especially relevant in situations where CGM data is easier to obtain than an HbA1c (telehealth, limited access to HbA1c measurement).

Time spent in tight glucose range (TITR) (3.9–8 mmol/L or 70–144 mg/dL) has recently been suggested as a new metric to characterize optimal glycemia [59, 60]. ISPAD has previously endorsed TITR as a metric in pre-school schoolers with T1D, especially during the remission period [61]. TITR may be preferable to TIR when targeting lower HbA1cs since it may be more sensitive to glycemic changes at lower average sensor glucose levels and it may also better characterize glucose variability [62].

Generally, TITR targets have been set at 50%; however, to reach the lower HbA1c target of ≤6.5% (48mmol/mol), an even greater TITR of > 55% may be needed [63]. While we await additional, high quality evidence for this metric in youth with diabetes [64], as well as guidance on how best to message and use this metric for clinical care, it is logical that increasing time spent in a tight range may reflect lower glucose variability and reduce the long-term risk of complications. Importantly, when selecting any CGM metric to use in care settings it is essential to adopt an educational framework that places the child and caregiver at its core and is sensitive to holistic health needs that extend beyond glucose levels.

Self-Monitored Blood Glucose

- In the absence of CGM, pre-prandial SMBG targets should be 4.0 – 8.0mmol/L [70 – 144mg/dL], and 4.0 – 10mmol [70-180mg/dL] post-prandial. **[B]**

- In the absence of CGM, SMBG should be undertaken at least 6 times a day in persons with diabetes taking insulin **[B]**

SMBG meter values should be targeted to correspond to an HbA1c ≤7% (≤53mmol/mol), to align with the CGM time in range (TIR) target of >70% between 4 – 10mmol [70-180mg/dL], and the strong correlation of CGM metrics with HbA1c reviewed earlier. For educational purposes 3.9mmol/L (70mg/dL) has been intentionally rounded to 4.0mmol/L, however some centres may use 3.9mmol/L as usual practice. Fasting target ranges glucoses of 4.0 – 8mmol/L [70 – 144mg/dL] are recommended to achieve this HbA1c target. SMBG glucose levels prior to bed of 4.0 – 8mmol [70-144mg/dL] are appropriate, however caregivers may have more confidence with higher levels within the 4.0 - 10mmol/L (70-180mg/dL] range in certain scenarios; for example, if there has been preceding hypoglycemia, exercise, hypoglycemic unawareness.

3. Practical Considerations and Limitations.

Each mode of measuring glycemia comes with its own limitations and practical considerations. HbA1c has long been the accepted benchmark for glycemia. However, it has several limitations such as i) for a given HbA1c, there is a wide range of mean glucose concentration values, and for any given mean glucose value there is a wide range of HbA1c values[65], ii) racial differences[66] and iii) unreliable measurement in certain conditions including anemia, hemoglobinopathies and liver disease [58]. CGM may be impacted by various pharmaceutical agents[67], and can be intermittently inaccurate, however, overall accuracy in modern CGM technology is very high [68-70]. SMBG retains a place in measuring glycemia where this is the only mode available, but maintaining the >6 self-tests per day to guide management has long been recognized as a significant barrier to improving overall glycemia [71]. Overall, the strengths and limitations of each mode of measuring glycemia should be considered and interpreted in accordance to the environment and/or clinical characteristics of the person with diabetes.
In addition, while advanced technologies are enabling people with diabetes and healthcare professionals to aim for near-optimal blood glucose levels, the demands of care and the limitations of current treatment options prevent this being a reality for most young people with diabetes and their caregivers.

4. Conclusion

Future research is needed to evaluate differences in risk of complications and perceived care burdens between the currently proposed HbA1c target of 6.5% (48 mmol/mol) and the former 7.0% (53 mmol/mol) target. The former might be achieved using mathematical modelling to assess the relative risk of diabetes complications based on historical and contemporary data. These data would help inform the benefits of a lower HbA1c weighed against any increased burden of care, and assist an individualised approach to setting glycemic targets.
As we move forward, there is also a need to utilize standardized CGM metrics alongside emerging diagnostic techniques that can predict diabetes complications. This approach will help bridge the gap until long-term registry data can confirm the relationship between CGM metrics and complication development.
Herein, we advocate for a shift in HbA1c targets that aligns with advancements in diabetes technologies and care. This approach is pragmatic to the immediate needs of individuals and their caregivers while embracing anticipatory and preventive care strategies for the long term. To achieve uniform glycemic targets across the ISPAD community, ongoing efforts are needed to address global disparities in access to these technologies

Conflicts of Interest

MdB- Research funding from Novo Novonordisk, Medtronic, Ypsomed, Dexcom, and Insulet. Honoraria, travel expenses or speaking fees from Novo Nordisk, Sanofi, Pfizer, Medtronic, Boerhinger Ingelheim, Ypsomed, Dexcom, and Insulet. Advisory Boards for Tandem and Dexcom, Nascence technology, and Tautoko Biomedical
KD- received honoraria for participation in the speaker's bureau of Abbott, Eli Lilly, Medtronic, NovoNordisk A/S, and Pfizer. Advisory board for Medtronic and Novo Nordisk.

DM- Research support from the NIH, JDRF, NSF, and the Helmsley Charitable Trust and his institution has had research support from Medtronic, Dexcom, Insulet, Bigfoot Biomedical, Tandem, and Roche. Dr Maahs has consulted for Abbott, Aditxt, the Helmsley Charitable Trust, Lifescan, Mannkind, Sanofi, Novo Nordisk, Eli Lilly, Medtronic, Insulet, Dompe, Biospex, Provention Bio, Kriya, Enable Biosciences, and Bayer.
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CS- speaker honoraria from Medtronic and Eli Lilly and advisory boards for Abbott.
LM- Research support from the NIH, JDRF, and the Helmsley Charitable Trust. Her institution has received research support from Dompe, Lilly, Mannkind, Medtronic, Provention Bio, Sanofi, and Zealand. Dr DiMeglio has consulted for Abata, Tandem, Biomea Fusion, and Vertex. She also received payment from Sanofi for a CME talk (content independently developed by her).
JC, MD, YN, LP- No conflicts of interest to declare
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Author Contributions: MB and LD co-directed the guideline development process. MB, JC, MD, KD, DM, LM, FM, YN, LP, CS and LD contributed equally to the content of individual chapters. MB synthesized these contributions to develop the original full draft of the guideline. Subsequently, MB, JC, MD, KD, DM, LM, FM, YN, LP, CS and LD participated in revising both the original manuscript and subsequent versions. LD, as the editor of the guideline, supervised the overall development and revision process.
Methodology: A literature search was conducted to gather updated evidence, using a combination of relevant medical subject headings (MeSH, Emtree) and free text terms specific to each chapter's focus. Studies published from 2021-2022 onward, related to children and young adults, were retrieved from MEDLINE. The Project Officer, in collaboration with chapter leads and co-authors, performed the literature searches. The resulting articles were then uploaded to COVIDENCE for screening and review. Two authors/experts involved in drafting this guideline version, independently screened the articles. Any disagreements were resolved by a third reviewer. Where relevant, further literature was included.
Recommendations were graded as per the ADA evidence grading system for “standards of Medical Care in Diabetes [72]. This hierarchical A-E grading system sets A as having the highest level of evidence, and E having the lowest.
The draft chapter was posted on the ISPAD forum to allow feedback from the greater ISPAD membership. Modifications were made with authorship consensus, with the chapter receiving endorsement from the ISPAD editorial team.
Literature search terms are summarized in Supplementary material.
Abbreviations:
AGP: Ambulatory Glucose Profile
AID: Automated Insulin Delivery
BMI: Body Mass Index
CGM: Continuous Glucose Monitoring
HbA1c: Hemoglobin A1c
ISPAD: International Society for Pediatric and Adolescent Diabetes
SDS: Standard Deviation Score
SMBG: Self-Monitored Blood Glucose
TIR: Time In Range
TITR: time in tight range

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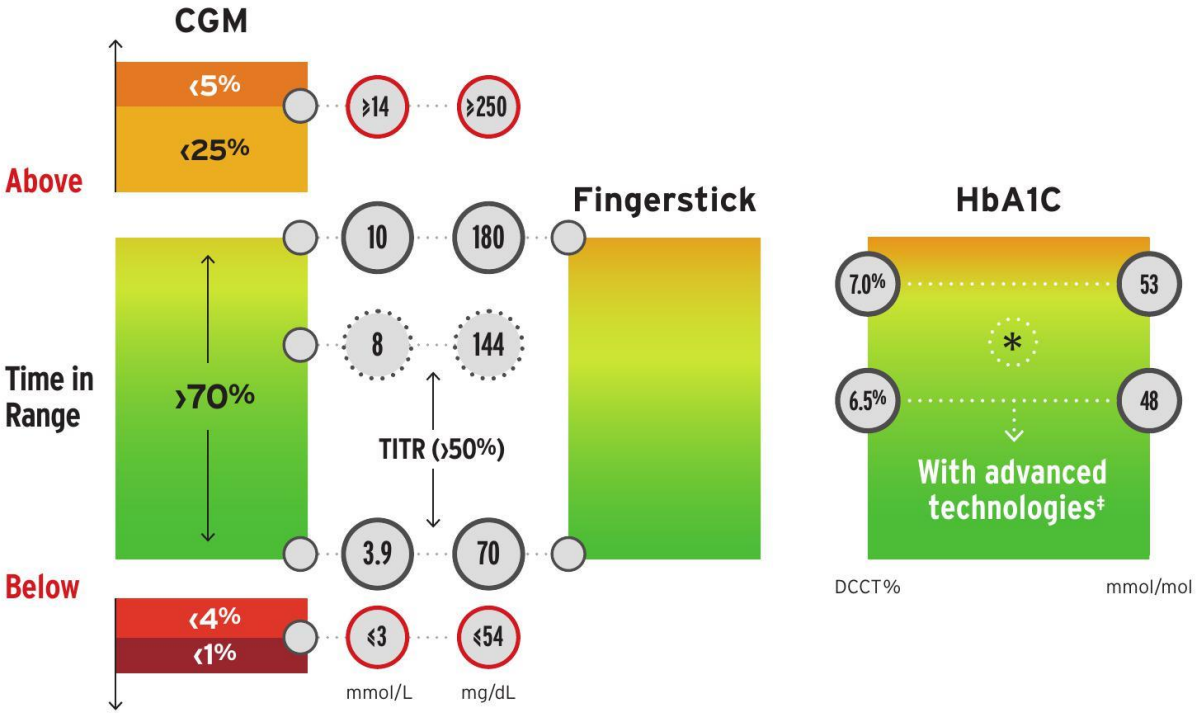
Figure Legends

Figure 1. Summary of Glycemic metrics

* For those who don't have access to advanced technologies or unable to safely attain the lower target.
‡ And/or where the pursuit of the lower target does not add burden such that quality of life is impacted.



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