Hot Topic

Lowering targets for hemoglobin A1c in children with type 1 diabetes: raising the bar

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Prior to June 2014, the American Diabetes Association (ADA) hemoglobin A1c (HbA1c) goals for children and youth with type 1 diabetes (T1D) were age-specific: <8.5% (69 mmol/mol) for children under 6 yr, <8% (64 mmol/mol) for those 6–12 yr old, and <7.5% (58 mmol/mol) for those 13–19 yr old (1, 2). These contrasted with the International Society for Pediatric and Adolescent Diabetes (ISPAD) HbA1c target of <7.5% (58 mmol/mol) in all children <18 yr (3, 4). In adults, the goals are lower, with the ADA targeting an HbA1c < 7% (53 mmol/mol) (or lower if it can be safely achieved). In those with a longer duration of disease, presence of comorbidities (especially heart disease), and hypoglycemia unawareness, higher HbA1c targets are accepted. The lower targets for adults were primarily based on data from the landmark Diabetes Control and Complications Trial (DCCT) (5) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) studies (6).

The DCCT demonstrated that early and intensive insulin therapy with a goal of near normal glycemic control (<6.05%/43 mmol/mol) significantly reduced both the development and progression of retinopathy, neuropathy, and nephropathy (5, 7). The same cohort was then followed up in the observational EDIC study where all the subjects were on intensive therapy and managed by their providers in a non-research setting (6). After a follow-up period of 5 yr, there was no difference in the median HbA1c between the former intensive group and the conventional group (7.9%/63 mmol/mol vs. 8.2%/66 mmol/mol). There was also no difference in the HbA1c between the former adolescents and adults. However, a further widening in the incidence of microvascular complications between the conventional and intensive groups was observed 4 yr into the study (6, 8). This showed that the beneficial effects of earlier intensive insulin therapy persisted even after the differences in glycemic control disappeared. This phenomenon has been referred to as 'metabolic memory'. Almost 12 yr after the EDIC study, it was also demonstrated that intensive insulin therapy has long-term beneficial effects on markers of atherosclerosis (9, 10) as well as reduction of clinical cardiovascular events (11). However, in contrast to adults, the protective effect on the microvasculature may be lost after 10 yr in adolescents (12). It has been postulated that the higher HbA1c of the adolescents throughout the DCCT study, even in the intensively treated group, led to a shortened metabolic memory.

Initial ADA HbA1c targets in children <13 yr, were based mostly on expert opinion. In the DCCT, an increased frequency of hypoglycemic episodes (nearly threefold) was associated with intensive insulin therapy. Among the adolescent cohort, the incidence of hypoglycemia requiring treatment assistance was 86 of 100 patient-years in intensive group and 28 of 100 patient-years in the conventionally treated group. The incidence of coma or hypoglycemic seizure in this cohort was 27 of 100 patient-years (intensive group) and 10 of 100 patient-years (conventional group) (7). Higher HbA1c goals for younger children were set primarily due to concerns of the adverse effects of hypoglycemia on the developing brain. However, there are conflicting data of the effect of both hypoglycemia and hyperglycemia on neurocognitive functioning in young children (13–21). Earlier studies reported neurocognitive dysfunction including decreased long-term spatial memory, and decreased verbal abilities in children with frequent and severe hypoglycemia, especially in children <5 yr old (13–15). Asvold et al. also reported a decrease in problem solving, verbal, and psychomotor abilities in adults exposed to severe hypoglycemia at a young age (16). A study by Strudwick et al. found no association of hypoglycemic seizures with cognitive dysfunction (17). In contrast, more recent studies have reported an association of poorer cognitive functioning with chronic hyperglycemia (18–21). It has also been demonstrated that chronic hyperglycemia can lead to structural abnormalities in the brain (21–24).

Even with the established fact that the pathogenesis of T1D and dysglycemia start well before overt manifestation, there is debate as to when 'the clock' for the development of microvascular complications begins. Danne et al. (25) earlier reported a high incidence of transient microalbuminuria in prepubertal children with diabetes. However, those children with persistent microalbuminuria had poorer glycemic control, higher blood pressure, longer diabetes duration, and frequent background retinopathy. Donaghue et al. also reported that there was a longer latent period before the development of retinopathy and microalbuminuria (2–4 yr longer) in children diagnosed before 5 yr compared with older children (26). A similar observation was reported by Salardi et al. who indicated that longer duration of prepubertal diabetes (diagnosis before 3 yr) was protective against retinopathy but that this protective effect disappears with poor metabolic control (27). These observations led to the concept that the prepubertal period of the disease may have less impact on the development of microvascular complications. In contrast, other studies have shown that the duration of the prepubertal phase does indeed contribute, albeit moderately, to the development of complications (28, 29). Puberty as an independent accelerator of the chronic complications of T1D has also been reported (27, 30, 31). Notwithstanding these conflicting reports, a younger age of diagnosis equates to longer disease duration and thus, a potentially higher risk of future microvascular and macrovascular complications. This association between a longer disease duration and microalbuminuria has also been recently demonstrated in the T1D Exchange study, but with microalbuminuria being infrequent when average HbA1c was <7.5% (<58 mmol/mol), regardless of age and disease duration (32). Furthermore, in our experience, if higher HbA1c targets are accepted by the patient and the family initially, it is often difficult to change perceptions as the child grows older.

Data from the Type 1 Diabetes Exchange (T1D Exchange) have revealed that even with the previously higher ADA targets, many children are not meeting HbA1c goals. Only 64, 43, and 21% of participants <6, 6–13, and 13–20 yr, respectively, achieved ADA HbA1c targets (33). HbA1c (mean ± SD) was 8.2 ± 1.1% (66 ± 12 mmol/mol) in children <6 yr, 8.3 ± 1.2% (67 ± 12 mmol/mol) in the 6–13 yr age group, and 8.8 ± 1.7% (73 ± 19 mmol/mol) in 13 to <20 yr age group. Using the ISPAD target of <7.5% (58 mmol/mol), the figures were even more dismal with only 25% of the entire cohort achieving

goal HbA1c (33). Less than 10% of all children and adolescents were able to meet all set target blood pressure, body mass index and LDL-C (low density lipoprotein cholesterol) goals. Although one may question whether HbA1c targets are too stringent and beyond reach, it is clear that more attention needs to be focused on the achievement not only of glycemic control, but also of blood pressure, BMI and lipid targets if complications are to be further decreased.

The Hvidoere Childhood Diabetes Study Group Centre Differences Study demonstrated that setting lower HbA1c goals is strongly associated with better HbA1c outcomes (34). A similar trend was observed in a recent study by Clements et al. (35). A lower HbA1c target of 7.5% (58 mmol/mol), might have been expected to be associated with more frequent and severe hypoglycemic events, but this was not the case. Maahs et al. compared the occurrence of hypoglycemic events between the Prospective Diabetes Follow-up Registry [Diabetes Patienten Verlaufsdokumenation (DPV)] study and the T1D Exchange study in children <6 yr, using the ISPAD and ADA HbA1c goals, respectively (36). Children in the T1D Exchange had a mean HbA1c of 8.2 ± 1.0 (66 ± 11 mmol/mol) compared with 7.4 ± 0.9 (57 ± 10 mmol/mol) in the DPV cohort; 56% of children in the DPV study cohort had an HbA1c of <7.5% (58 mmol/mol), whereas only 22% from the T1D Exchange achieved this goal. As this difference is particularly striking, if one looks at the proportions achieving the age-independent pediatric A1c goal of <7.5% (58 mmol/mol) proposed by ISPAD, the authors speculated that target-setting may have contributed to the observed discrepancy (Fig. 1). Of course, variations in the health care systems, socioeconomic differences in the two cohorts, or other unmeasured factors could also have contributed to those differences. The DPV had more children on an insulin pump as compared with the T1D Exchange cohort (74 vs. 50%). However, even after adjusting for insulin pump use, the HbA1c in the DPV cohort was 0.7% (7.7 mmol/mol, $p < 0.001$) lower compared with the T1D Exchange cohort. Children on insulin pumps in the T1D Exchange had a better HbA1c compared with those using injections, but no such differences were observed in the DPV cohort. Moreover, there were no differences in the frequency of severe hypoglycemic events between the two cohorts (2.9% for T1D Exchange vs. 1.9% for the DPV cohort). In addition, there were more occurrences of ketoacidosis in the T1D exchange cohort as compared with the DPV study cohort. Further, T1D Exchange data reveal that although severe hypoglycemic events were more common in children <6 yr, after adjusting for age, severe hypoglycemic events were just as high, if not higher, in patients with higher HbA1c levels as compared to those with lower HbA1c levels (37).
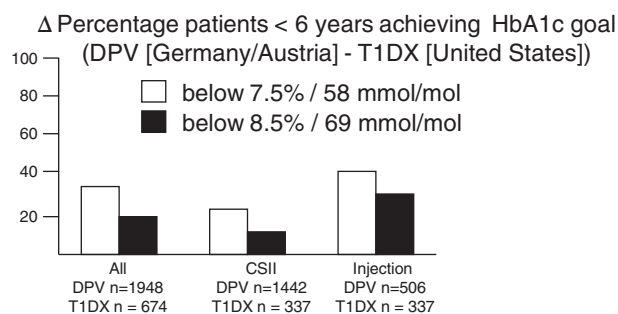

Fig. 1. Percentage difference in the two preschool cohorts of the German–Austrian Diabetes Patienten Verlaufsdokumenation (DPV)-Registry and the American Type 1 Diabetes Exchange in achieving the respective hemoglobin A1c (HbA1c) goals that were proposed in Europe (<7.5%) and the USA (<8.5%). The odds for achieving either target were greater in the DPV but the difference was much more pronounced for the lower goal, without any difference in the hypoglycemia rates (35).

Updated data from the Hvidoere study in young children have also shown that a HbA1c of <7.5% (58 mmol/mol) can be achieved in young children without increasing the risk of hypoglycemia (38). In light of the above evidence, the ADA harmonized its glycemic goals with those of ISPAD (as well as the Pediatric Endocrine Society and the International Diabetes Federation) by using a single HbA1c goal of <7.5% across all pediatric age groups, although many unresolved questions remain (Table 1). With the more widespread use of newer insulin analogs and technological advances, including the use of insulin pumps, continuous glucose monitoring devices, and sensor augmented insulin pump therapy, decreased hypoglycemic events and lower targets can safely be achieved in individual patients. Also, there are new data that the incidence of hypoglycemia has been declining (39–40). Fear of hypoglycemia in both providers and parents of young children has limited the pursuit of more aggressive targets until now. With the lessons learned from the DCCT and EDIC study, we cannot afford to continue accepting the formerly recommended higher HbA1c goals.

The global incidence of type 1 diabetes mellitus (T1DM) is increasing by 2–5% per year (41–43) and expected to double by the year 2020 (44). The annual health care cost of T1D is approximately 14.9 billion dollars (45). Whereas some cost can be attributed to advances in modalities of diabetes management (insulin analogs, insulin pumps, and home blood glucose monitoring including continuous glucose monitoring systems), the major cost (both direct and indirect) lies in the prevention as well as management of microvascular (renal failure, proliferative retinopathy, and blindness), neuropathic (lower extremity amputation) and macrovascular complications (heart disease, stroke, and amputation). Herman and Eastman analyzed the cost-effectiveness

Table 1. Summary of recent findings leading to changing the A1c targets and challenges for future research in this area

What we know now	What we do not know
• Studies assessing neurocognitive function have failed to identify adverse effects of a past history of hypoglycemia in the young child • The years prior to puberty impact the future risk of complications • Hyperglycemia and glycemic variability are associated with changes in the central nervous system white matter, as observed in MRI scans • Lower HbA1c targets are associated with better average benchmarking results without increasing the rates of severe hypoglycemia	• Which patient subgroups are at risk for severe adverse effects of hypoglycemia such as 'dead in bed' • If the years prior and past puberty, impact equally for the future risk of complications • If glycemic variability contributes independently of hyperglycemia to adverse outcomes of diabetes • If lower HbA1c targets (even lower than those proposed today) are associated with better outcomes in the long run (metabolic memory)

HbA1c: hemoglobin A1c; MRI: magnetic resonance imaging.

of intensive therapy in the DCCT (46). Although, intensive insulin therapy was two to three times costlier than conventional therapy, intensive therapy could reduce blindness by 41%, end-stage renal disease by 71%, and lower-extremity amputations by 43%, as compared with conventional therapy. Despite the higher direct and 'up-front' cost of intensive therapy, when the overall 'downstream' cost allocation of complications were incorporated, intensive therapy was more cost-effective for treatment of T1D.

Still, important questions remain unanswered. For example, is the observed reduction in complications related to better glycemic control or might there be other contributory factors? In studies spanning almost two decades from 1990 to 2009, Downie et al. reported a significant decline in retinopathy and microalbuminuria in subjects aged 12–20 yr (47). This decrease correlated with greater frequency of insulin injections (three or more) and increased use of insulin pumps. Median HbA1c decreased from 9.1% (76 mmol/mol) to 8.5% (69 mmol/mol), which was still significantly above the ADA and ISPAD targets. A subanalysis in the same study also showed a reduced risk of retinopathy in those using insulin pumps as compared with those using multiple daily injections, with no difference in HbA1c between the two groups. Rather than thus attributing the decreased complication rate solely to improved HbA1c, it is possible that other factors, such as mealtime insulin use, the use of insulin analogs, and/or less glucose variability may be involved.

It remains to be determined whether even lower HbA1c targets, i.e., <7% (53 mmol/mol), should be sought and safely achieved in older children (13–18 yr), and what the effects would be on reduction of further complications. It is also unclear for a specific population with a given socioeconomic status, what intensity of workforce would be needed to improve the

HbA1c to any target level – the required number of physicians, diabetes educators, behavioral scientists, etc. In fact, there are no studies we are aware of that compare 'intensity of medical care' (which would include the personnel listed above) and HbA1c outcomes. As economic accountability will continue to be an important piece of our pediatric diabetes algorithm, studies assessing these needs would be welcomed.

Finally the effect of repeated benchmarking, multi-center collaborative quality control circles, and longitudinal follow-up of data should not be underestimated. In the German pediatric DPV-registry, longitudinal follow-up from 1995 to 2012, was associated with a decline of average HbA1c by 0.04% per year, with the rates of severe hypoglycemia decreasing as well (48). Similar observations have been reported recently for the Swedish registry (49) and in international registries such as SWEET (50), although the targets have remained unchanged since the first ISPAD guidelines were published in 1995.

For now, the alignment of the ADA and ISPAD HbA1c goal of <7.5% (58 mmol/mol) for all children and youth below 18 yr is timely and welcomed. This population deserves to benefit from what we have learned over the past 30 yr; hopefully more specific targets and strategies to achieve them will become clearer in the near future.

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