The Role of Glycaemic Variability in Paediatric Diabetes

Currently, HbA$_{1c}$ remains the gold standard for assessing the risk of late complications in paediatric patients; however, it has obvious limits as it is only a parameter for average glucose levels. There is substantial variability in individual mean glucose concentrations for a given HbA$_{1c}$ level. Evidence is building relating to the importance of glycaemic variability for various outcomes in type 1 diabetes. In patients with type 2 diabetes a significant association was reported between the mean amplitude of glycaemic excursions (MAGE), an established parameter for glycaemic variability, and urinary 8-epimer of prostaglandin F2alpha (8-iso-PGF2$\alpha$), a parameter related to superoxide overproduction and subsequent development of later complications. This suggests that different therapeutic strategies should be evaluated for their potential to minimise glycaemic excursion, as well as their ability to lower HbA$_{1c}$. F2alpha, Therefore, wider use of real-time continuous glucose monitoring (CGM) in clinical practice would provide the required monitoring tool to minimise glycaemic variability. A new measure of glycaemia, derived from the duration of normal, low and high readings, could supplement HbA$_{1c}$ as an integrated measure of control. Furthermore, measurements of MAGE, composite hypoglycaemic score and lability index could provide information about the tendency for a mean blood glucose level to comprise stable or labile data points. For some patients, a decreased amount of glycaemic instability alone, even without any improvement in HbA$_{1c}$, may represent an improved outcome.

Paradigm Shift in Paediatric Diabetes Treatment

There has been a recent paradigm shift in the treatment of paediatric diabetes. Previously, it was thought that the best way to overcome barriers to treating children would be to spare them from an insulin regimen consisting of many daily injections. Consequently, treatment consisted of two daily injections of pre-mixed insulins. This was accompanied by the need to follow a strict diet and daily schedule in order to match the insulin intake. Indeed, some centres are reporting good results with this approach. However, the majority of paediatric diabetologists now believe that the gold standard treatment for children with diabetes is intensified insulin therapy. Intensified insulin therapy aims to mimic as closely as possible the physiological insulin profile of

Recent developments indicate that the efforts of diabetes teams who are implementing approaches focused on age-appropriate education of patients, families and other care-givers in intensified insulin treatment in paediatric diabetes care have been successful. Also, the increased availability of continuous glucose sensors is likely to have a significant impact on paediatric diabetes therapy and education in the future. Families previously relying on self-monitoring blood glucose (SMBG) need to understand the difference between estimating the absolute blood glucose value (point accuracy) and the change in blood glucose (rate accuracy) and how to take into consideration the inherent interstitial time lag. The selection of patients capable and motivated to use continuous sensors accompanied with proper age-appropriate education remain important factors for the long-term success of these technological advances in diabetes therapy as long as closed-loop systems are not available.

Treatment Targets in Paediatric Patients

The Diabetes Control and Complications Trial (DCCT) and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, confirmed that an improvement in long-term glucose control obtained with intensified insulin therapy can also reduce the incidence of complications and delay the progression of existing complications in type 1 diabetes in paediatric patients. Although only a subgroup of adolescents participated in the DCCT longitudinal studies in the paediatric population, such as the Berlin Retinopathy Study, they have revealed comparable results (see Figure 1). Reductions of glycated haemoglobin (HbA$_{1c}$) <9% lead to the most dramatic fall in the rate of retinopathy. Nevertheless, with every drop in HbA$_{1c}$, lower rates of retinopathy are achieved. Adolescents, particularly those with suboptimal control, should understand that a reduction of HbA$_{1c}$, even if it is significantly above the target of 7.5%, is likely to have a major impact on their long-term prognosis when maintained over time. For each individual, the target should be the lowest achievable HbA$_{1c}$ without inducing severe hypoglycaemia. An HbA$_{1c}$ level <7.5% for children of all ages – slightly above the target for adults – has been adopted by many paediatric diabetes centres.
observed in non-diabetic individuals. This kind of regimen is also believed to allow the flexibility required with the lifestyle needs of children with diabetes. To match these challenges, the choice of rapid-, short-, intermediate- and long-acting insulins and insulin analogues (see Figure 2), as well as devices such as insulin pumps and glucose sensors, have led to many recent new developments in the treatment options for children with diabetes.

**Insulin Pump Therapy for Children**

Over the last decade, continuous subcutaneous insulin infusion (CSII) has increased in popularity among paediatric patients with diabetes. Theoretically, CSII offers the most physiological method of insulin delivery due to its ability to more closely simulate the normal pattern of insulin secretion, namely continuous 24-hour adjustable ‘basal’ delivery of insulin superimposed with prandial-related ‘boluses’. In addition, CSII offers more flexibility and more precise insulin delivery than multiple daily injections (MDIs). Although randomised, controlled trials in young children have not yielded the same beneficial effects as the non-randomised paired comparison studies, it is incorrect to conclude that paediatric pump therapy offers no real advantages to MDIs. The results of the large European Pedpump data collection indicate the safety of pumps for all age groups and document the flexibility of CSII, with many children taking seven or more daily prandial or correction boluses. The low rate of hypoglycaemia makes pumps an attractive choice, particularly for pre-school children. Poor motivation and support leading to a low number of boluses or not following the rules for preventing diabetic ketoacidosis (DKA) in CSII may lead to adverse outcomes. This may be a caveat to prescribing CSII, and it highlights the importance of individualising the decision as to the modality of therapy according to developmental stage and tasks.

**Insulin Analogue**

Insulin analogues are safe for use in paediatric patients. As pre-prandial insulin treatment is often problematic in young children with unpredictable and irregular eating habits, the post-prandial injection of rapid-acting insulin analogues offers the ease of adjusting the administration time and dosage according to mealtimes and the size of the meal in injection therapy and CSII. In accordance with the pharmacokinetic results obtained in adults, insulin aspart and insulin glulisine were rapidly absorbed and eliminated in paediatric patients also. Post-prandial administration of insulin aspart was shown to be a safe and effective alternative to pre-prandial administration in a study of 76 children and adolescents, as well as in a trial of pre-school children two to six years of age. Inulin suspensions with protamine (NPH) or zinc have been used for several years for delaying insulin action for basal insulin substitution. In most countries, the two basal analogues – insulin glargine and detemir – have not been formally approved for children below six years of age. However, there are reports of successful use of glargine in children from one to five years of age. Randomised and observational studies with insulin glargine as the basal insulin have also shown reductions in nocturnal hypoglycaemia. In a six-month multicentre trial, 347 children (aged six to 17 years) with type 1 diabetes received comparable doses of insulin detemir or NPH insulin plus pre-meal insulin aspart. At follow-up, mean HbA1c decreased by approximately 0.8% to 8% in both treatment groups, but children in the insulin detemir group had a significant 26% reduction in nocturnal hypoglycaemia compared with NPH insulin. In another cross-over study of 68 adolescents comparing the bedtime injection of semilente zinc–insulin with insulin detemir, both insulins were equally effective in terms of the fasting plasma glucose levels. Despite an average 1.7-fold higher insulin dose to achieve the fasting blood glucose target, the incidence of mild and severe night-time hypoglycaemia was lower with detemir. Compared with NPH, insulin detemir is also associated with less weight gain or weight reduction in paediatric patients and less variability.

**New Approaches in Educational and Psychosocial Concerns**

Ideally, a child with diabetes should have access to a specialised multidisciplinary team of diabetes healthcare professionals, including a paediatric diabetologist, a diabetes nurse educator and a dietician, as well as additional access to a psychologist, social worker and others. In many countries, age-appropriate educational programmes have been developed and evaluated for efficacy. The diabetes healthcare team will require special skills to accommodate patients based on the age of the child, level of comprehension and education of the child and his or her family and be capable of dealing with language and cultural needs that vary demographically. Recently, a mobile diabetes education and care
team was shown to be effective in improving the quality of care in children with type 1 diabetes who have limited access to specialised diabetes care in rural areas. Regardless of the insulin regimen prescribed, frequency of SMBG correlates with improved glucose control and increased treatment adherence. Historically, youths were encouraged towards independence in diabetes care, but recent studies indicate that premature withdrawal of parents from diabetes care is associated with adverse outcomes. Support from school and day care is also important in the management of diabetes in this age group because many children require insulin with lunch or at other times when they are away from home. The social and professional integration of parents – particularly mothers – with younger children at the onset of diabetes needs to be improved through support measures outside the family. In a recent survey of 580 German families, 31% of mothers reduced their working time or stopped working and 33% outside the family. In a recent survey of 580 German families, 31% of mothers reduced their working time or stopped working and 33% of mothers reported handicaps in their professional career development, especially those with a child with age at onset below six years (44%). Negative financial consequences were observed in 44% of the families. Patient and family education and close contact with the diabetes team are associated with reduced hospitalisations and emergency room visits and improvements in glycaemic control, and additional telephone contacts may be beneficial.

Retrospective Glucose Sensors
Education may also be the key to success for CGM. Currently, three subcutaneous enzymatic sensors in four systems are available. They are the Continuous Glucose Monitoring System Gold (CGMS Gold, Medtronic MiniMed, Northridge, California), the Guardian Telemetered Glucose Monitoring System (Medtronic MiniMed), the FreeStyle Navigator Continuous Glucose Monitor (Abbott Laboratories, Alameda, California) and the DexCom STS. They differ in terms of needle length, sensor wear, number of calibrations and time from placement to display. The CGMS has been reported to serve as a tool to reveal daily glucose trends missed by SMBG, to serve as an educational tool to improve metabolic control and to decrease the rate and magnitude of hypoglycaemia in young patients with type 1 diabetes. Age does not appear to be a limiting factor, as these systems can be also applied in the pre-school group. However, a recent meta-analysis of five randomised paediatric studies indicated that the technology that allows a realtime assessment of glycaemia by the patient does not lead to a significant improvement of HbA1c, but only a retrospective analysis by the doctor will suffice. However, others have reported its usefulness in the management of individual patients, particularly adolescents experiencing difficulties with adherence to diabetes management and in detecting unrecognised hypoglycaemia. CGM can also be used to contrast the effectiveness of various therapeutic strategies in research settings. The power of CGM as a research tool was demonstrated in providing proof of the association of fluctuating blood glucose levels and behavioural changes that parents frequently report in their diabetic children.

The Realtime Sensors
In contrast to the physician-based analysis of retrospective data of the Holter-type sensors, the realtime sensors shift the focus to the patient and the family, enabling them to react to subcutaneous glucose readings in a ‘biofeedback’ fashion. In a multicentre study with adult and paediatric participants, the efficacy of realtime CGM using the Guardian® RT system was evaluated in 81 children and adolescents with type 1 diabetes in whom glycaemic control was suboptimal despite intensive insulin therapy. The results of the study demonstrated that realtime CGM using the Guardian RT system improved glycaemic control compared with SMBG, especially in the group continuously using the system. The constant availability of glucose measurements permitted the patients to adjust their own insulin doses, food intake and physical activity and thus improve their glycaemic control. A pilot trial of one month in 10 type 1 diabetic children was reported in which the realtime CGM and the insulin pump were combined into a sensor-augmented pump system. The international, multicentre ONSET Trial will compare the effect of conventional CSII with sensor-augmented pump (SAP) therapy during the first year after onset of diabetes in 160 paediatric patients in a randomised, prospective trial. The ONSET trial will provide evidence for advocating this technology from the onset and thereby learn about diabetes in a feedback fashion. Paediatric experience is also available for the FreeStyle Navigator and the Dexcom STS. Improvements of HbA1c were seen with realtime CGM both in paediatric patients on a pump and those on MDI insulin regimens.

Educat ing Patients About the New Technology
Teaching patients to determine how to utilise all the data provided by CGM remains a challenge. Families previously relying on SMBG need to understand the difference between estimating the absolute blood glucose value (point accuracy) and change in blood glucose (rate accuracy) and how to take into consideration the inherent interstitial time lag. All of the available sensors show a lower point accuracy compared with SMBG. However, a patient able to read trends in CGM will be able to live easily with this limitation when sufficient experience is gained in analysing glucose trends. Practical algorithms need to be developed to calculate the current and future insulin infusion rates. Patient variability in assessing the glycaemic excursion of the meal may also affect the function of such an open-loop system. From the beginning it is critical to understand the reasons for delays between glucose changes and a displayed value. For reasons that are not completely understood, all subcutaneous sensors need a certain time after placement before they give a stable signal. Apparently, the trauma associated with subcutaneous insertion impairs glucose measurement for some time before reaching an equilibrium. Depending on the system, the ‘blind period’ between placement and display of values ranges from two to 10 hours. Even after an initial stable signal is reached, the reaction of the surrounding tissues with the sensor surface continues to lead to changes of the sensor signal over time (‘drift’), and repeated calibration may allow adjustment for drift for a certain period. Patients need to understand that the glucose measurements are in the interstitial fluid, and the lag time between blood and interstitial fluid sampled glucose levels may be in the range of five to 10 minutes. Although accuracy is slightly improved with more calibrations, the timing of the readings appears more important. Modifying the algorithm to attach less importance to daytime calibrations for night-time values and calibrating during times of relative glucose stability may have a greater impact on accuracy.

Selecting the Right Patients for Continuous Glucose Monitoring
In addition to proper education, patient selection may be integral to CGM success, and the key to sensor success is the motivation to continuously use it. Early studies with the Glucowatch have shown more
frequent use over a six-month period among youths whose parents reported higher scores for treatment adherence and diabetes-related quality of life at baseline. The study illustrates the empirical assessment of the psychological context of CGM use. In a recent study of SAP therapy in 40 CSII-experienced adolescents with HbA1c > 7.5%, the improvement of HbA1c was closely related to use of a sensor. Therefore, psychological assessments about adherence to CGM may demonstrate the power of this technology much better than an uncritical application in unselected patients, not all of them using the information continuously. This observation is summed up in the phrase ‘an expensive watch is not going to make you punctual unless you use it’.

Closed Loop

Several approaches are used in the search for an ‘artificial pancreas’, and the time lag remains one of the major obstacles on the road to such a concept. In a research centre setting, a meal detection algorithm studied in 19 one- to six-year-old children detected a meal at a mean time of 30 minutes from the onset of eating, at which time the mean serum glucose was 21 mg/dl above baseline (range 2–36 mg/dl), although more than 90% of meals were detected before the glucose had risen 40 mg/dl from baseline. In combination with the delay of CSII, such a time lag remains a problem for automated insulin dosing in response to meals and ultimately the development of a closed-loop system.

Improved Outcomes Through Target Setting and Physiological Insulin Therapy

At our institution, the change from former years from the conventional twice-daily regimen of a pre-mixed fixed mixture and, latterly, free mixing of soluble and isophane insulin to multiple dose injections and, more recently, insulin pumps has been associated with a continuous improvement of glycaemic control. This improvement also has to be seen in the context of improvements in patient education, self-monitoring and the development of diabetes teams. Nevertheless, the role of age-appropriate education for children and adolescents with diabetes and their families with the principles of flexible, intensive insulin regimens with clear targets from the onset of type 1 diabetes should not be underestimated (see Figure 3). Such improvements with the introduction of multiple injection therapy have not been observed in all centres. It remains to be clarified in individual cases if daily management with four injections is a true intensive insulin management discriminating between the substitution of basal and prandial insulin needs or rather a conventional insulin therapy injecting insulin four times daily. In our experience, the imitation of the physiological ratio between prandial and basal insulin is a pre-requisite for near normoglycaemic metabolic control with MDIs or CSII in children and adolescents. The basal insulin to cover for the hepatic gluconeogenesis should not be more than 30–40% of the total daily insulin, while the prandial insulin need is usually more than 50% of the total dose. Although the remarkable HbA1c differences between centres are still present, in the international multicentre Hvidore collaboration for paediatric diabetes outcome quality studies it was identified that diabetes management concerns such as access to the diabetes team and, particularly, a setting of clear targets played a major role in the outcome.

Conclusions

It is our prediction that in the next five to 10 years real-time CGM will become the standard of care for the treatment of paediatric patients with type 1 diabetes. However, in order to scientifically prove the promise of CGM in children with type 1 diabetes, appropriate randomised prospective studies assessing this new technology in selected patients are needed. Psychological evaluation may be important in identifying patients likely to wear a sensor continuously. If the HbA1c is high at baseline it may be because families are not using the tools correctly, and, possibly, sensor technology may be better for those with only modest HbA1c elevations. All in all, the emerging evidence for glycaemic variability playing a role in such different areas, i.e. behavioural changes of children and the development of vascular complications, underscores that additional end-points regarding HbA1c need to be considered in future outcome studies. It is likely that with a better understanding of the molecular, medical and psychosocial mechanisms involved, the next advances in the treatment of children with all forms of diabetes are imminent. In the meantime, every effort should be made to investigate the long-term benefit of these recent new developments in paediatric diabetes.
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