

Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover, Germany

# Tackling hypoglycemia in children: teams, targets and technology

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Article based on the Somogyi Award Lecture 2020

## Summary

On the occasion of the Somogyi Award lecture this review focusses on the current advances in tackling hypoglycemia in pediatric patients with type 1 diabetes providing evidence for the importance of multidisciplinary teams, ambitious glycemic targets and implementation of diabetes technology. Meal-related intensified insulin replacement with differential substitution of basal- and bolus insulin is the therapy of choice in the care of children and adolescents with type 1 diabetes. The use of insulin pumps and continuous glucose monitoring devices is increasing rapidly, with the type of insulin therapy (insulin pen or pump) depending on the age of the patients and family preference. Education appropriate to the age and current challenges is essential for the children's participation in everyday life as undisturbed as possible. New parameters like time in range and time below range suitable for identifying high glycemic variability as risk factor for severe hypoglycemia complement the HbA<sub>1c</sub> targets and the ambulatory glucose profile (AGP) in a shared decision making on therapeutic adjustments between the diabetes team and people with diabetes. Automated insulin delivery as a hybrid closed loop or dosing advice using artificial intelligence are becoming a clinical reality. However, diabetes education as a team approach, defining clear targets with outcomes evaluated in multinational registries like SWEET remain important for shaping the future of pediatric diabetology.

■ **Key words:** pediatric diabetology, hypoglycemia, type 1 diabetes, automated insulin delivery

## A hypoglykaemia elleni küzdelem gyermekekben: ellátóteamek, célok, eszközök

Összefoglalás: A 2020. évi Somogyi-díj nyertese az 1-es típusú diabetesben szenvedő gyermekek hypoglykaemiás állapotainak megelőzésével kapcsolatos legújabb adatokat ismerteti áttekintő közleményében. Bizonyítékokat szolgáltat a multidiszciplináris teamek, az ambiciózus glikémiás célok és a diabetestechnológia alkalmazásának fontosságára. Az 1-es típusú diabetesben szenvedő gyermekek és fiatalok kezelésének választandó módja az étkezéshez igazodó intenzív inzulinkezelés a különböző bázis- és bólusinzulinokkal. Az inzulinpumpák és a folyamatos glükózmonitorozó eszközök használata folyamatosan nő és az inzulinkezelés módja (pen vagy pumpa) a gyermek életkorától és a család választásától függ. Az edukációnak a gyermek életkorának és a felé irányuló kihívásoknak meg kell felelnie ahhoz, hogy a gyermek zavartalanul részt vehessen a mindennapi életben. Az új paraméterek, mint a „time in range” (a céltartományban eltöltött idő) és a „time below range” (a céltartomány alatt eltöltött idő) a HbA<sub>1c</sub> mellett alkalmasak a súlyos hypoglykaemia rizikófaktóráknak tekintett nagy glikémiás variabilitás felismerésére, valamint az „ambulatory glucose profile” (ambuláns glükózprofil – AGP) lehetővé teszi a diabetológiai team és a diabeteses emberek közös döntéshozatalát a terápiás változtatásokban.

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A hibrid, zárt rendszerű („closed loop”) inzulinpumpákban megvalósuló automatikus inzulinadagolás és a mesterséges intelligencia használata az adagolási tanácsokban napjainkban már klinikai realitássá válik. Ugyanakkor a diabetesesdukáció mint teammegközelítés a világos célok megfogalmazásával és a kimenetel multinacionális regiszterek, mint a Sweet program segítségével történő kiértékelésével fontosak maradnak a gyermekdiabetes jövőjének megtervezésében.

■ **Kulcsszavak:** gyermekdiabetes, hypoglykaemia, 1-es típusú diabetes, automatikus inzulinadagolás

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A wide variation exists in worldwide incidence rates of type 1 diabetes, with the highest occurring in Finland and the lowest in parts of China.<sup>1</sup> Nearly hundred years after the discovery of insulin substitution of this life-saving hormone remains the cornerstone treating type 1 diabetes. A curative therapy of type 1 diabetes is still not in sight.<sup>2</sup> Despite many newly identified risk parameters, the pathogenesis ultimately remains unclear. Nevertheless, the progress in genetic and immunological diagnostics requires the development of population screening before manifestation as a basis for novel therapeutic approaches already today.<sup>3,4</sup> Hope comes from collaborations like the INNODIA Clinical Network which consolidates as a pan-European reference point for conducting studies to prevent or cure T1D. With standardized clinical and bio-research platforms built in INNODIA this allows to conduct multifaceted clinical trials aimed at preventing and curing T1D.<sup>5</sup>

Long-term high glucose has been identified as the culprit for poor long-term outcomes.<sup>6</sup> While the DCCT study provided conclusive evidence for the importance of achieving best possible HbA<sub>1c</sub> levels in adolescents and young adults,<sup>7</sup> the Berlin Retinopathy study established that glycemic control matters also during pediatric care<sup>8,9</sup> and also the time before puberty matters for long-term outcomes.<sup>10</sup> Meanwhile, glycemic variability even with intensified insulin therapy remains a challenge and hypoglycemia is considered as a major obstacle in achieving good glycemic control.<sup>11</sup>

### **The Somogyi phenomenon in pediatrics**

Children and adolescents with type 1 diabetes present a particular challenge to clinicians, owing to physiological and psychological development, their heterogeneous and often unpredictable

lifestyles (diet, exercise, support in management of diabetes and sleeping patterns), frequent intercurrent infections and long periods without adult care (school). This goes along with rapid changes in insulin sensitivity making them prone for high glucose variability. More than half a century ago *Michael Somogyi* observed that “hypoglycemia begets hyperglycemia” potentially leading to overinsuliniation and brittle diabetes.<sup>12</sup> Thus, it does not come as a surprise that the term “Somogyi effect” for a child that awakes with high glucoses and ketonuria in the morning following a nighttime hypoglycemia tempting to increase the insulin dose was coined in a paper describing the difficulties of managing type 1 diabetes in children.<sup>13</sup> In *Michael Somogyi’s* memory, the Hungarian Diabetes Association has established the “Somogyi Award” in 2004 to honor the person who significantly contributed to the better understanding of hypoglycemia and its counter-regulatory mechanisms. On the occasion of the Somogyi Award lecture this review focusses on the current advances in tackling hypoglycemia in pediatric patients with type 1 diabetes providing evidence for the importance of multidisciplinary teams, ambitious glycemic targets and implementation of diabetes technology.

### **Insulin, love and care: the need of a team approach**

Modern insulins have been tested in specific pediatric investigational studies<sup>14,15,16,17,18</sup> and have certainly enriched the options for tailoring of the insulin regimen to the individual child.<sup>19</sup> However, insulin therapy needs to be embedded in a holistic care concept.<sup>20</sup> Multidisciplinary teams, which are now standard for the care of chronically ill children with various diseases, have originally been created for pediatric diabetes care.<sup>21</sup> Children and adolescents

should be educated age-appropriately according to their stage of development as well as the specifics of everyday life relevant to the respective age group.<sup>22</sup> Separate medical and psychological advice has been developed also for parents. Issues like hypoglycemia awareness, prevention and treatment need to be discussed also with occasional caregivers like teachers or physical exercise instructors. In the multimodal training, the family is taught the correct glucose measurement using a measuring device selected according to individual needs in addition to insulin therapy. Extensive knowledge about the composition of food as well as healthy nutrition choices for children and adolescents need to be delivered by the dietitian. Although the diet does not differ from that of those without diabetes the two principles still hold true which were introduced by the founder of German pediatric diabetology *Karl Stolle*: “The treatment of childhood diabetes with free food must always be carried out under the protection of insulin” and “The more frequently insulin is injected, the better the procedure adapts to the physiological conditions.”<sup>23</sup> The aim is to provide an age-appropriate, satisfying, fulfilling and nutrient-covering diet that allows healthy and normal growth (according to percentiles). Sweets are an integral part of the life of adolescents within the scope of “permitted” foods. If the calculation of the carbohydrate content of food is initially based on scales and carbohydrate tables, most families tend to estimate carbohydrates with increasing experience in everyday life.

### ***Education as a basis for self-management***

The diabetes nurse or diabetes educator has a central role within this team. Special situations in everyday life that require increased attention from all those involved are explained. For example, when doing planned sports, an appropriate reduction of the previous amount of insulin should be made in order to avoid hypoglycemia when the body becomes more responsive to insulin. In the sense of a calorie-conscious diet, general additional carbohydrates should be avoided before sport. Behavior in case of high blood sugar levels is an essential training lesson. In addition to recognizing the symptoms of hypoglycemia (self-perception of the

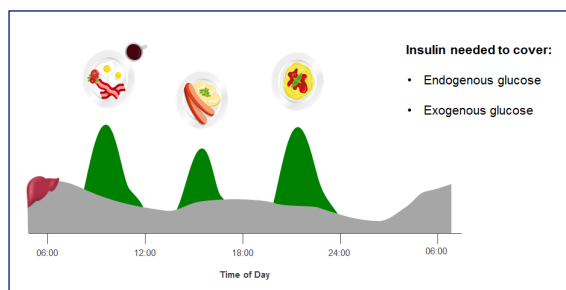
child, external perception by caregivers, etc.), the targeted treatment of hypoglycemia with appropriate amounts of glucose as well as control measurements are part of the hypoglycemia training. Also the use and mode of action of the glucagon emergency treatment with nasal powder, soluble or reconstituted glucagon depending on the local availability should be part of it.

### ***Clinical relevance of hypoglycemia***

However, reassurance is also necessary regarding severe hypoglycemia in young children, as this is not life-threatening and the so-called “dead in bed syndrome” does not occur before puberty. Hypoglycemia acutely elicits a multitude of cardiovascular changes within the body and apparently young children are protected. Studies have shown that not low glucose in the brain but rather QTc prolongation and epinephrine-induced hypokalemia during hypoglycemia, indicating an increased risk of fatal arrhythmias may also be responsible for the syndrome known as “dead in bed”.<sup>24</sup> Repetitive, severe hypoglycemia (in childhood: coma, seizure) does, however, show associations with the development of partial performance disorders or epilepsies,<sup>25</sup> although there are also signs of cerebral damage caused by hyperglycemia.<sup>26</sup> While the results of the DCCT study led clinicians to believe that there is a window of opportunity where risk of hypoglycemia would have to be balanced against achieving good control in terms of HbA<sub>1c</sub> this no longer holds true. Current studies indicate that the risk for hypoglycemia is comparable in different levels of HbA<sub>1c</sub> and is more related to issues of hypoglycemia awareness education and use of diabetes technology.<sup>27</sup>

### ***Finding the right insulin regimen***

While pre-school children are treated with pump therapy from manifestation onwards, intensified insulin therapy with multiple daily injections is the first choice of therapy from school age.<sup>10,28</sup> For insulin therapy in pediatric age, mixed or combination insulins are not used because of the necessary flexibility of therapy adjustment. In addition to human



**Figure 1.** Principle of insulin substitution in children by distinguishing the basal insulin need (for endogenous glucose, approximately 34%) and prandial need (for exogenous glucose, approximately 66%)

and NPH insulins, a variety of long- and short-acting insulin analogues are approved for use here, which can be selected for therapy according to the patient's needs. A growing child needs about 1 IU of insulin/kg body weight/day after the end of remission. Approximately 2/3 of the total amount is administered as meal insulin, 1/3 as basal insulin (Figure 1). Human, short-acting and ultra-rapid analogue insulins are available for insulin administration at meals or for corrections. Although the use of human insulin is often considered old-fashioned due to the necessary injection-eating distance, a very significant advantage in pediatric diabetology of human insulin is the coverage of a main meal and a snack. A primary school child can thus be injected at home for the snack during the long break. Thus, at school only the blood sugar needs to be measured and the snack provided can be eaten (except in the case of extremely high values). In this way an injection at school can be avoided.<sup>29</sup>

### **Why targets matter: explaining center differences**

The Hvidøre Group established a tradition of international benchmarking in pediatric diabetology revealing significant differences.<sup>30</sup> Many studies have tried to explain differences between centers by comparing treatment strategies,<sup>31</sup> but treatment target setting proved the most impactful. In particular, knowledge and agreement of all team members on these targets and delivering this message in

a common language during diabetes care appears to be of paramount importance.<sup>32</sup> The SWEET project (Better Control in Pediatric and Adolescent Diabetes: Working to CrEate CEnters of Reference) was established in 2008 as a three-year EU Public Health Program aiming at harmonizing care of children with T1D through establishing “centers of reference, CoR” in European countries.<sup>33</sup> Even within the European Union the project identified significant heterogeneity in health care delivery<sup>34</sup> and inequalities in reimbursement remain as a major obstacle for the implementation of advanced diabetes therapy for children.<sup>35</sup> From 2011 on, SWEET e.V. is a registered non-profit charity and has developed into a worldwide initiative under the auspices of the International Society for Pediatric and Adolescent Diabetes (ISPAD). The focus has changed from solely establishing and accrediting centers of reference for pediatric and adolescent diabetes to including and collaborating with smaller centers in order to support database development and quality improvement in high-, medium- and low-income countries.<sup>36</sup> Over the past 10 years nearly all of the centers participating in SWEET have been able to increase the proportion of children achieving in-target glycemic control on the background of bi-annual benchmarking, exchange of best practices among centers and increased use of diabetes technology.

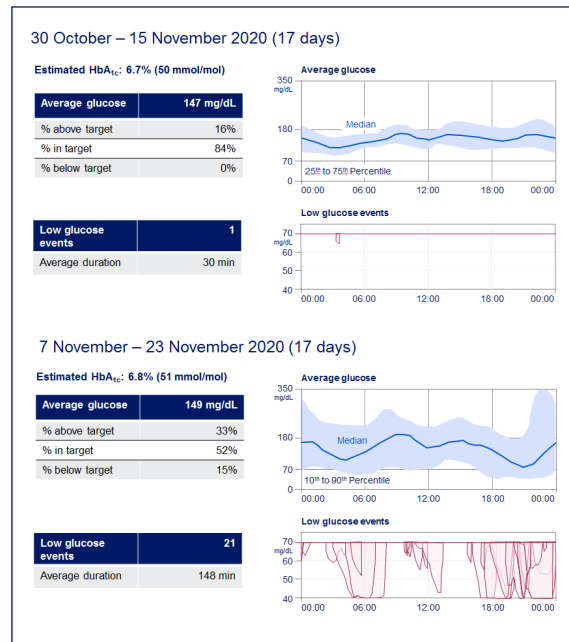
### **Time in the target range as a new parameter of metabolic control**

Currently, the HbA<sub>1c</sub> value is used as a parameter for estimating the success of therapy. According to the latest international guidelines, this value should be <7% (<53 mmol/mol).<sup>29</sup> The HbA<sub>1c</sub> is established as gold standard for estimating the metabolic status and is the only parameter for which a clear association with the long-term outcomes has been established.<sup>7</sup> However, this laboratory value does not allow statements to be made about glycemic fluctuations and is also not suitable as a predictor of severe hypoglycemia, for example.<sup>37</sup> Due to the rapidly increasing use of continuous glucose monitoring (CGM) systems, alternative parameters such as the time-in-range (TIR, time in target range) are gaining in importance as an indicator

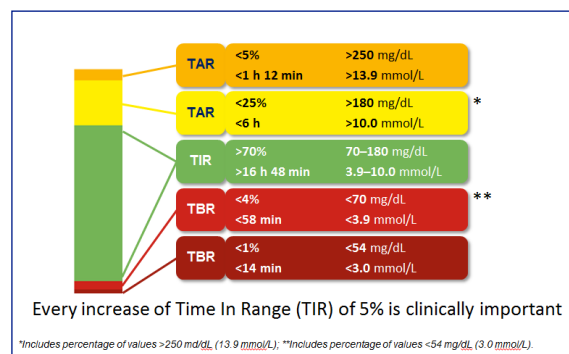
for the duration of the normo-, hypo- and hyperglycemic phases. The Ambulatory Glucose Profile (AGP) calculated by most evaluation software from the continuous measured values is therefore also suitable for therapy adjustment counseling (Figure 2).<sup>38</sup> In analogy to the evaluation of the blood pressure setting, this parameter can be expressed by two values – the percentage time in the target range TIR 70–180 mg/dl (3.9–10.0 mmol/l) in relation to time in the hypoglycemic range TIR <70 mg/dl (<3.9 mmol/l). Recently, within the framework of an expert consensus, target values for the “time in the target range”, i.e. the proportion of the measured sensor values that lies between 70 and 180 mg/dl (3.9 and 10 mmol/l) have been established. The time below 70 mg/dl (3.9 mmol/l) should not exceed 4%, which corresponds to approximately 1 hour per day (Figure 3).<sup>39</sup> The concept of time in range targets is increasingly used also in real-world studies of new therapeutic approaches in diabetes.<sup>40,41,42</sup> During the recent COVID-19 pandemic the need for uploading the data by the family in order to have a meaningful discussion in the virtual diabetes clinic has increased the use of these standards in association with the ambulatory glucose profile allowing a shared-decision-making between the diabetes team and the families without the need for a face-to-face visit.<sup>43</sup>

### Modern therapy through technical support

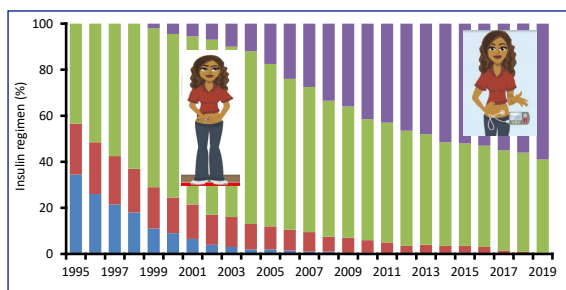
Shortly after the principle of continuous insulin infusion (CSII) was introduced into diabetes therapy, insulin pump regimens were studied also in children<sup>44</sup> allowing intricate programming of basal and prandial insulin.<sup>45</sup> Large pediatric survey of CSII showed that glycemic targets can be frequently achieved, particularly in young children, and the incidence of hypoglycemia was low.<sup>46</sup> It is feasible to start CSII with or without CGM from the onset of the disease leading to a faster recovery of mothers from the initial depression at diagnosis compared to MDI.<sup>47</sup> This finding has contributed to establishing insulin pump therapy as standard method of insulin replacement in childhood and adolescence in Germany with approximately 60% of all pediatric patients using an insulin pump, this number reaching above >95% in preschoolers (Figure



**Figure 2.** Two children with type 1 diabetes with identical HbA<sub>1c</sub> but very different courses in the ambulatory glucose profile. While in the top patient the time in the target range TIR 70–180 mg/dl (3.9–10.0 mmol/l) in relation to the time in the hypoglycemic range TIR <70 mg/dl (<3.9 mmol/l) with 84% / 0% requires no change in therapy, in the lower patient with 52% / 15%, measures to prevent hypoglycemia should be initiated.



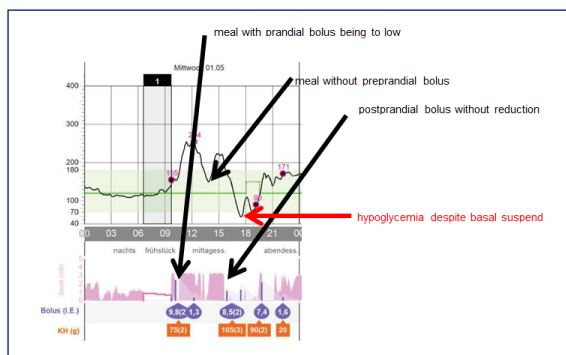
**Figure 3.** Target values for children and adults with type 1 & type 2 diabetes for the time in the target area (exceptions for older people and those with increased risk of hypoglycemia e.g. hypoglycemia perception disorders); modified according to Battelino et al., 2019<sup>39</sup>



**Figure 4.** Paradigm shift in the treatment of type 1 diabetes

Initially, a change from conventional therapy with 2 to 3 daily injections to intensified insulin therapy with 4–6 injections per day. From 2000 onwards, increase in insulin pump therapy, which is now used to treat more than half of all pediatric patients (data of the DPV group, according to Holl et al., 2021<sup>48</sup>).

4).<sup>48</sup> Various stages of automatic insulin regulation are currently under development. In a first step the combination of insulin pump and glucose sensor allowed a prospective interruption of insulin delivery in case of imminent hypoglycemia (PLGM – predictive low glucose management).<sup>49</sup> Patients do not even notice this process if the acoustic alarm function is switched off. Since this form of therapy



**Figure 5.** Diabetes education in hypoglycemia risk reduction is necessary also with hybrid-closed loop insulin delivery

A patients the boluses postprandially without taken into account the corrective increased basal insulin delivery in the meantime is prone to hypoglycemia despite an immediate insulin suspension of the system.<sup>49</sup>

requires trust in the system as well as changing the established habits of “treatment of hypoglycemia”, a detailed structured training of patients and their parents is necessary. In the next step, the first trial of automated insulin delivery including insulin suspension for lows but also correction boluses for highs outside the hospital was performed in the typical pediatric setting of diabetes camp leading to a nearly threefold reduction of hypoglycemic episodes under these challenging conditions.<sup>50</sup> The knowledge of the technical feasibility of the closed-loop as well as the increasing exchange of information via social networks currently leads to an increase in the use of so-called “do-it-yourself” systems (DIY),<sup>51</sup> in which common insulin pumps and sensors are combined with various control algorithms that are freely available on the internet. Ultimately, as health care professionals we have an ethical duty to support people living with diabetes to achieve the best glycemic control they are capable of, whatever the means, if they understand the potential risks of their chosen therapy. Thus, as a diabetes community we need to work together to ensure that life changing closed loop systems can be safely made available to those who wish to use them whether this be a commercial option or DIY. The next commercially available solution are so-called hybrid closed loop insulin pumps, that can dynamically adapt the basal insulin delivery to the glucose values but require manual entry of carbohydrates at mealtime. This results in a significant improvement of time in range especially at night.<sup>52</sup> In a first head-to-head trial of two hybrid-closed loop pumps this system was recently compared with an advanced hybrid closed loop capable of automated correction boluses.<sup>53</sup> Again, this leads to an incremental improvement in achieving glycemic targets. However, despite the increased degree of automation detailed education remains important (Figure 5).<sup>54</sup> For those patients that chose not to wear automated insulin delivery device or where such systems are not affordable, artificial intelligence can be used to calculate pump settings. Indeed, an automated dosing advisor was found to be non-inferior compared to expert diabetologist advice in a multinational multicenter randomized trial.<sup>55</sup> The current challenge for diabetes teams around the world is fighting for affordable diabetes technology and counseling the

individual person with diabetes regarding available systems that matches his or her needs.<sup>56</sup>

### More than insulin: adjunct therapy with SGLT2 inhibitors

Nevertheless achievement of sustained glycemic control remains a challenge for many patients with T1D. Non-insulin-based adjunct treatments offer the potential to complement intensive insulin therapy with MDI or CSII in T1D. Currently SGLT inhibitors represent the most effective compound of the possible class of adjunct agents.<sup>57</sup> The insulin-independent mechanism of action leading to more time in range and less glycemic variability<sup>42</sup> with the option of improving HbA<sub>1c</sub> with no increase or even a decrease in the rate of hypoglycemia.<sup>58</sup> In addition, there is evidence for a possible renal protection and cardiovascular risk reduction if the inherent increased risk for diabetic ketoacidosis with this approach can be managed.<sup>59</sup> Initial evidence of using adjunct therapy in combination with full closed-loop delivery indicate that the 2 to 3 hour per day increase in time in range with SGLT inhibition observed in with MDI and CSII<sup>42</sup> is also observed if this therapy is used in combination with automated insulin delivery.<sup>60</sup>

### Outlook

Building on the research to the better understanding of hypoglycemia and its counter-regulatory mechanisms initiated by *Michael Somogyi* and others these novel therapeutic approaches will hopefully be able to prevent or decrease the risk of hypoglycemia and improve long-term outcomes in people with diabetes.

Children are particularly prone to hypoglycemia and therefore predisposed to the *Somogyi* phenomenon. Pediatric diabetes teams need to implement such strategies in order to prevent hypoglycemia and educate the parents to understand and support their children's treatment and adequate development

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