A New Horizon for Glucose Monitoring

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Key Words

Type 1 diabetes · Continuous glucose monitoring · Hypoglycaemia · Children and adolescents

Abstract

Regular self-monitoring of blood glucose is crucial for proper insulin dosing and gives a reliable foundation for reasonable glycaemic control. According to recent data, recommended values for glycated haemoglobin A1c as set by the professional associations remain out of the reach for a large proportion of the paediatric population. In the last decades, the treatment of type 1 diabetes has changed significantly as new devices gain a role in routine clinical care. Real-time glucose levels can be monitored with continuous glucose monitoring (CGM), which provides a broad spectrum of information on glucose trends on a moment-to-moment basis. This information can be useful for patients' decision making and clinicians' understanding of patients' conduct. However, several barriers, including the current price, impede a broader use of CGM in most regions of the world. This review summarizes data from randomized, controlled trials that included a paediatric population, and it provides some evidence-based visions for the possible broader utilization of CGM, also for incorporation into insulin delivery devices that enable a closed-loop insulin delivery.

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Introduction

Vast efforts are invested in the day-to-day management of type 1 diabetes (T1D) with the goal of reaching the target of near-normal glucose values, a recommendation of the Diabetes Control and Complications Trial made more than 20 years ago [1]. According to the Type 1 Diabetes Exchange Registry data, only about 1 out of 4 adult or paediatric patients [2] on average meets the current recommendations for good metabolic control, i.e. glycated haemoglobin A1c (HbA1c) <7.0% (53 mmol/mol) [3] and <7.5% (58 mmol/mol), respectively [4]. Similar outcomes are reported in European studies [5, 6], with [6] or without [7] improvement in metabolic control over time.

In order to delay the onset and slow down the progression of clinically important macro- and microvascular complications [8], insulin delivery has been intensified in an effort to mimic its physiological pattern. Multiple daily injections (MDI) are being supplanted with continuous subcutaneous insulin infusion (CSII) as a treatment of choice [2], with the result being improved metabolic control [2, 9].

Hypoglycaemia remains the most significant adverse effect of insulin treatment, partially due to circadian glycaemic fluctuations, and partially due to the lack of continuous feedback information on glucose levels after

Fig. 1. PRISMA diagram of study selection process. Closed loop = Closed-loop insulin delivery system; QoL = quality of life; Threshold CGM = low-glucose-threshold-triggered suspension of insulin infusion CGM.

meals or during the night, although some follow-up studies report a decreasing incidence [6]. As a result, this represents the most significant barrier to achieving HbA1c target levels [10], in addition to its deleterious effects on the health and well-being of affected patients.

Instant glycaemic control is typically enabled via self-monitoring of blood glucose (SMBG) in an effort to provide patients with reliable guidance for decisions on treatment measures (dietary or insulin) to correct hypo- or hyperglycaemia [4, 11]. However, SMBG pinpoints the blood glucose level at a particular moment in time and thus fails to expose ongoing glycaemic fluctuations. The lack of consistent SMBG monitoring is aggravated by its sheer day-to-day burden, especially in children and adolescents.

Modern real-time continuous glucose monitoring (RT-CGM) provides patients with a series of interstitial glucose measurements at intervals of 1–5 min that can be used for real-time adjustments of the treatment regimen [12]. CGM systems are currently recommended for children and adolescents with T1D if they are able to use CGM devices on a near-daily basis [11–13]. Technological developments in recent years have allowed for an improvement of CGM in terms of accuracy and simplicity of use, and, consequently, more successful implementation. Hence an advantageous mode of treatment can be offered to children and adolescents with T1D, if reimbursement by insurance is available, given its prohibitive cost [14–16].

The reported benefits, efficacy and limitations of CGM use beyond SMBG differ significantly between studies,

depending greatly on the age of patients and the frequency of use [17–25]. The aim of this review is to highlight current data from randomized controlled clinical trials on RT-CGM use in the paediatric population.

Data Source

All articles from 2006 to May 2014 found in MEDLINE containing the words ‘CGM system’, ‘continuous glucose monitoring’, ‘glucose sensor’ or ‘real-time glucose monitoring’ in children and/or adolescents (<18 years) with T1D were screened (fig. 1). To be included in the review, the studies had to be randomised, controlled trials (RCTs) comparing the use of RT-CGM with SMBG in a paediatric T1D population, that reported changes in metabolic control, i.e. HbA1c as outcome measure, the rate of severe hypoglycaemia events or the time spent in a hypoglycaemic state (as defined by the investigators) and the frequency of CGM use as a secondary outcome measure.

RT-CGM and HbA1c

Eleven trials, containing and analysing data on 1,098 children and adolescents with T1D report diverse and varied results (table 1).

The first RCT on the continuous use of CGM by 81 children and adolescents (out of 156 patients) with poorly controlled T1D was reported in 2006 [26]. A significant

Table 1. Overview of RCTs that included a paediatric patient population with regard to the use of RT-CGM

Year	First author [ref.]	Paediatric patients analysed, n	Mean age of paediatric patients, years	Study duration, months	Baseline HbA1c	Type of intervention	Primary end point	Paediatric HbA1c outcome: intervention vs. control
2006	Deiss [26]	81 ^a (156)	14.4 (26.8)	3	9.56%	RT-CGM vs. SMBG	ΔHbA1c	−0.67%, <i>p</i> = 0.0447 (−0.6%, <i>p</i> = 0.003)
2008	JDRF [27]	224 <25 years old (322)	14.9 (23.5)	6	7.84%	RT-CGM vs. SMBG	ΔHbA1c	n.s. (n.r.)
2009	JDRF [29]	62 <25 years old (129)	n.r. (30.6)	6	6.45%	RT-CGM vs. SMBG	time with hypoglycaemia	n.r. (−0.34, <i>p</i> < 0.001)
2009	Raccach [30]	46 (115)	n.r. (28.5)	6	9.20%	RT-CGM vs. SMBG	ΔHbA1c	n.r. (−0.41%, <i>p</i> < 0.004, per protocol)
2009	O'Connell [31]	32 (62)	16.2 (23.2)	3	7.40%	RT-CGM vs. SMBG	Δtime within target glycaemic range	−0.6%, <i>p</i> = 0.025 (−0.43%, <i>p</i> = 0.009)
2010	Bergental [32]	156 (443)	12.2 (32.2)	12	8.3%	SAP vs. MDI-SMBG	ΔHbA1c	−0.5%, <i>p</i> < 0.001 (−0.6%, <i>p</i> < 0.001)
2010	Kordonouri [33]	154 (154)	8.8 (8.8)	12	11.3%	SAP vs. SMBG	ΔHbA1c	n.s.
2011	Battelino [34]	53 (116)	n.r. (25.8)	6	6.9%	RT-CGM vs. SMBG	time with hypoglycaemia	n.r. (−0.27%, <i>p</i> = 0.008)
2012	Battelino [35]	72 (153)	12.0 (28)	6	8.5%	RT-CGM vs. SMBG	ΔHbA1c	−0.46%, <i>p</i> < 0.001 (−0.43%, <i>p</i> < 0.001)
2012	Mauras [36]	146 (146)	7.5 (7.5)	6	7.9%	RT-CGM vs. SMBG	0.5% HbA1c reduction	n.s.
2012	Riveline [37]	24 (178)	n.r. (36.4)	12	9.0%	RT-CGM vs. SMBG	ΔHbA1c	n.r. (−0.48%, <i>p</i> < 0.001)

Figures in parentheses denote the total number of patients in the study population. Δ = Change; JDRF = Juvenile Diabetes Research Foundation; n.r. = not reported; n.s. = not significant.

^a Not specified as full analysis set.

improvement (*p* = 0.003) was achieved in the RT-CGM group when compared to the SMBG group (a decrease in HbA1c of -1.0 ± 1.1 vs. $-0.4 \pm 1.0\%$), and also in the sub-group analysis of the children and adolescents (-0.72 ± 1.13 vs. $-0.05 \pm 0.78\%$, adjusted *p* = 0.0447) [12].

The Juvenile Diabetes Research Foundation Trial [27] included 224 children and adolescents (114 aged 8–14 years and 110 aged 15–24 years) in addition to 98 adults. The difference in HbA1c reached statistical significance only in the adult group (HbA1c -0.53% , 95% CI -0.71 to -0.35 , *p* < 0.001), but not in the paediatric groups. When the RT-CGM in the patients was compared to the controls, the number who attained HbA1c levels <7% was significantly greater in the younger group of children (8–14 years of age; *n* = 15 vs. 7; *p* = 0.02) but not in the other group (14–24 years of age; *n* = 8 vs. 9; *p* = 0.8). Subsequent post hoc analysis of frequent RT-CGM

users (at least 6 days/week on average) demonstrated a significant improvement in HbA1c level compared to those who did not make use of RT-CGM as often (*p* < 0.001 in the group that was 8–14 years old, *p* = 0.002 in the group that was 15–24 years old and *p* = 0.02 in the group that was ≥25 years old) [28].

An RCT on well-controlled T1D patients [29], with 62 children or adolescents among the 129 patients analysed, showed a significant difference between treatment groups that favoured RT-CGM (HbA1c -0.34% , 95% CI -0.49 to -0.20% , *p* < 0.001) at the end of the study, even in the context of more patients maintaining an HbA1c of <7% (59 vs. 38, *p* < 0.001). Results in 3 pre-specified age groups, i.e. 8–14 years, 15–24 years and >25 years) were reported as generally similar to those of the overall analysis.

A comparable conclusion was made in a French RCT [30] with a significant between-group difference (*p* <

0.004) observed among the patients who were fully compliant, i.e. who wore their sensor for >70% of the time according to protocol (a reduction in HbA1c of 0.96 ± 0.93 compared to $0.55 \pm 0.93\%$, $p = 0.004$; the paediatric population was too small to reach significance), but not in the whole intention-to-treat population analysis of 115 patients (46 children), where the difference in favour of the intervention group failed to reach statistical significance [-0.81 ± 1.09 vs. $-0.57 \pm 0.94\%$ (intergroup comparison), $p = 0.087$].

A separate analysis of 32 adolescents out of 62 participants included in an Australian RCT [31] demonstrated a statistically significant between-group difference in HbA1c change that favoured the RT-CGM group over the control group (HbA1c -0.6% , 95% CI -1.1 to -0.1% , $p = 0.025$). The mean end-of-study HbA1c level was 0.43% lower (95% CI 0.19 – 0.75% , $p = 0.009$) in the intervention group than in the control group. Within the intervention group, the HbA1c was 0.51% lower (95% CI -0.98 to -0.04% , $p = 0.04$) in the participants using the sensor $\geq 70\%$ of the time than in those using it $< 70\%$ of the time. Fourteen of 26 participants (56%) in the intervention group had an end-of-study HbA1c level of $\leq 7\%$ compared with 5/29 (17%) in the control group ($p = 0.004$).

A large RCT compared sensor-augmented pump (SAP) therapy with the use of SBGM and MDI [32]. In a group of 156 children and adolescents out of the 443 patients included in the analysis, a between-group difference in HbA1c level at 12 months of -0.5% (95% CI -0.8 to -0.2% , $p < 0.001$) in favour of the SAP group was reported, along with significantly more children and adolescents in the SAP group attaining the age-specific target HbA1c level compared to the MDI group (44 vs. 20%, $p < 0.005$). The change in HbA1c level was also significant in the analysis of the whole population (a between-group difference in HbA1c of -0.6% , 95% CI -0.7 to 0.4% , $p < 0.001$), which favoured RT-CGM.

A paediatric RCT [33] with 154 participants (mean age 8.8 ± 4.4 years) concentrated on T1D at disease onset: children were randomised 9.6 ± 6 days after the first insulin administration by either SAP or CSII for 12 months. Children who used an SAP for at least 3 days per week had a significantly lower HbA1c than those using it less often or not at all ($p = 0.032$) with more than half of these patients achieving an HbA1c level $< 7.0\%$ without any severe hypoglycaemic events. However, there was no statistical overall difference between the 2 groups ($7.4 \pm 1.2\%$ in the SAP group vs. $7.6 \pm 1.4\%$ in the CSII-only group) or in the proportion of patients achieving an HbA1c $< 7\%$ (39.5 vs. 33.8% of the patients, respectively).

An RCT with 116 well-controlled (HbA1c $< 7.5\%$) patients [34], among them 53 adolescents, demonstrated a between-group difference of -0.27 after 6 months (6.69 vs. 6.95%, 95% CI -0.47 to -0.07% , $p = 0.008$ adjusted for baseline HbA1c, centre and age group), favouring the RT-CGM group. For the paediatric population, the HbA1c was reduced by -0.23% (6.92 vs. 7.15%, $p =$ not reported).

In a cross-over RCT [35] with 153 participants, 72 paediatric patients (with a mean age of 12 years) were randomised into a sensor off/on or sensor on/off treatment sequence (each lasting 6 months with a 4-month wash-out gap in between). The mean difference in HbA1c between the 2 paediatric groups was -0.46% (95% CI -0.26 to -0.66% , $p < 0.001$) and -0.43% (95% CI -0.32 to -0.55% , $p < 0.001$) in the whole population. After withdrawal of the sensor (during the 4-month wash-out period) for the on/off treatment sequence, glucose levels went back towards baseline levels. In the paediatric group, mean sensor use was 73% (median 78%) of the required time (with a mean of 74% in the last 4 weeks).

A recent RCT [36] focused on the young end of the paediatric population. One hundred and forty-six children aged 4–9.9 years, with a mean HbA1c level of 7.9%, were randomised to an RT-CGM group or a standard-care group for 26 weeks. The primary outcome of decreasing HbA1c by $\geq 0.5\%$ with no severe hypoglycaemia was reached by 13/69 children (19%) in the RT-CGM group and 19/68 (28%) in the control group ($p = 0.17$), with a mean change in HbA1c of $-0.1 \pm 0.6\%$ in each group ($p = 0.79$). Parental satisfaction with RT-CGM, no change in hypoglycaemia event rates (3 vs. 6 for the RT-CGM and control groups, respectively) and an unexplained low frequency of sensor use (only 41% used the sensor ≥ 6 days/week) were reported. The number of patients with a target HbA1c $< 7\%$ was similar in both groups (i.e. 11 vs. 10).

A French RCT [37] included 178 patients, 8–60 years of age (24 children), with poor blood glucose control (a mean starting HbA1c of 9%), who were randomised into 3 groups (patient-led RT-CGM, physician-led RT-CGM and control MDI or CSII without RT-CGM). No separate analysis for the paediatric patients was provided. After 12 months, the reduction in HbA1c was significantly greater in both the RT-CGM groups combined (-0.48% , 95% CI -0.63 to -0.33% vs. the control group, $p < 0.001$) and separately, i.e. the patient-led RT-CGM group (-0.50% , 95% CI -0.70 to -0.29% , $p = 0.0006$) and the physician-led group (-0.45% , 95% CI -0.66 to -0.24% , $p = 0.0018$) compared to the control group (0.02%, 95%

CI -0.18 to 0.23%). Significantly more patients achieved the HbA1c target of 7.5% in the RT-CGM groups compared to the control group [9.7% for the patient-led group ($p = 0.025$), 14.6% for the physician-led group ($p = 0.026$) and 1.6% for the control group].

RT-CGM and Hypoglycaemia

No increase in the rate of severe hypoglycaemia events was reported between the RT-CGM and SMBG groups in any of the RCTs, regardless of the age of children, even when a significant decrease in HbA1c was achieved. Three trials reported a reduction in the time spent in hypoglycaemic state.

The first trial demonstrated strong statistical evidence of a difference between these treatment groups with regard to the time per day spent in a hypoglycaemic state, favouring the CGM group with a glucose level of ≤ 70 mg/dl (54 vs. 91 min, $p = 0.16/0.04/0.06$ using ranks/truncating outliers/square root transformation), ≤ 60 mg/dl (18 vs. 35 min, $p = 0.05/0.02/0.02$), ≤ 50 mg/dl (4 vs. 8 min, $p = 0.12/0.05/0.04$) or an area under the curve of 70 mg/dl (0.26 vs 0.49, $p = 0.03/0.01/0.008$). There was no difference in the rate of severe hypoglycaemia events (10 vs. 11%).

The second trial [34] demonstrated a significantly shorter time spent with glucose levels <3.5 mmol/l (63 mg/dl) in the RT-CGM group than in the SMBG group (0.48 ± 0.57 vs. 0.97 ± 1.55 h/day, respectively; ratio of means 0.49, 95% CI 0.26 to 0.76, $p = 0.03$). The primary outcome of the time spent with glucose levels <3.5 mmol/l was reduced by 48% (0.34 vs. 0.65 h/day in the controls) and 64% ($p < 0.001$) with 44 of 53 paediatric patients who used RT-CGM for >20 days, analysed in a post hoc per protocol analysis.

The third, cross-over-designed trial [35] comparing SAP-treated patients with and without RT-CGM, demonstrated less time spent with a sensor glucose level <3.9 mmol/l (70 mg/dl) during the RT-CGM on-period compared with the RT-CGM off-period. i.e. 19 vs. 31 min/day ($p < 0.009$).

RT-CGM and Low-Glucose Threshold-Triggered Suspension of Insulin Infusion

RT-CGM integrated into an insulin pump has an additional feature of a low-glucose-threshold-triggered temporary suspension of insulin delivery. Recent studies

show that the use of this feature in an SAP can lead to a significant decrease in the rate of hypoglycaemic events and the time spent in a hypoglycaemic state. An Australian RCT [38] included 65 children divided into 3 age groups [4 in the preschool group (between 4 and 7 years of age), 27 in the pre-pubertal group (between 7 and 12 years of age) and 34 in the pubertal group (between 12 and 18 years of age)] as well as 30 adults (between 18 and 50 years of age). All participants with a hypoglycaemia unawareness score of at least 4, as determined by the modified Clarke questionnaire, were randomised to therapy with either a regular insulin pump or an SAP with low-glucose-threshold suspension of insulin (set at 60 mg/dl or 3.3 mmol/l). The baseline rate of severe and moderate hypoglycaemia was significantly lower for patients in the pump-only group with an incidence rate/100 patient-months of 20.7 (95% CI 13.8–30) compared to 129.6 (95% CI 111.1–150.3) in the suspension-of-insulin group. After 6 months of intervention, the number of severe and moderate hypoglycaemia events decreased from 28 to 16 in the pump-only group and from 175 to 35 in the suspension-of-insulin group. The adjusted incidence rate ratio was 3.6 (95% CI 1.7–7.5, $p < 0.001$) in favour of the suspension-of-insulin group. A sensitivity analysis performed in the same way for patients <12 years of age ($n = 15$ per group) demonstrated an adjusted incidence rate ratio of 5.5 (95% CI 2.0–15.7, $p < 0.001$), also in favour of the suspension-of-insulin group, but the significance was lost when 2 outliers were excluded from the analysis. The time spent with hypoglycaemia of <70 mg/dl (3.9 mmol/l) and <60 mg/dl (3.3 mmol/l) was significantly shorter in the suspension-of-insulin group during the day and at night. The level of HbA1c did not change from that at baseline in either group.

The reduction of nocturnal hypoglycaemia was recently demonstrated in 2 other RCTs that included paediatric participants [39, 40].

RT-CGM and Quality of Life

CGM use is recommended only for children who are capable of using these devices on a near-daily basis, as the extent of positive metabolic effects depends directly on the relative time of CGM use and loses significance if the device is worn infrequently [11–13]. CGM use of at least 6 days per week has proven to be effective in lowering HbA1c level and avoiding biochemical hypoglycaemia [28]. For this reason, it is important that the CGM system

is fully adopted by young people and their parents, in order to promote a more regular and frequent use, as consistent usage is hard to achieve in routine care [41].

However, data on quality of life, treatment satisfaction and fear of hypoglycaemia in the paediatric population are scarce. To evaluate this, participants in the JDRF trial completed a questionnaire using the Continuous Glucose Monitoring Satisfaction Scale, responding to open-ended questions regarding CGM [42]. Frequent users (at least 6 days/week) had higher overall scores, higher benefit scores and lower hassle scores (all $p < 0.001$) compared with infrequent users (i.e. <4 days/week) as well as high overall satisfaction (CGM Satisfaction Scale scores: 3.6–3.8 out of 5.0). The scores and the frequency of use were, however, lowest among the youth. In another large study, 144 paediatric patients, 141 caregivers and 334 adult patients completed the Insulin Delivery System Rating Questionnaire, which was used to assess treatment perception, satisfaction and preference [43]. Increased convenience was associated with improved treatment satisfaction in all user groups including the children.

In an RCT including children of 4–9 years of age [36], 90% of the parents responded that the use of CGM makes adjusting insulin easier, shows patterns in blood glucose not seen before and makes them feel safer, knowing that they will be warned about low blood glucose before it happens. On the CGM Satisfaction Scale at 26 weeks, parents generally reported a high degree of satisfaction with CGM, with an average item score of 3.9 out of 5 and 86% of the scores ≥ 3.5 .

More high-quality studies on quality of life related to the use of RT-CGM in the paediatric population are urgently needed.

Conclusion

T1D requires a life-long enthusiasm for problem-solving, improving metabolic control and sustaining quality of life. Technological advancement can enable patients, their families and care-givers as well as clinicians to make better-informed decisions on how to control blood glucose levels, but only when this is fully adopted in day-to-day care. Current data suggest that the use of CGM in the paediatric population is safe and efficacious, with clinically relevant improvement in markers of metabolic control or possibly C-peptide [44]. Only regular and widespread use of RT-CGM in the paediatric population together with adequate clinical expertise will

provide a realistic assessment of its comprehensive role in paediatric T1D management. Studies identifying factors predictive of adherence to CGM use are warranted because the existing data do not clarify this important issue [28, 31, 36]. Patients, families and care-givers need adequate and continuous training and support from diabetes care teams [45, 46]. The full potential of CGM remains unexploited; its use in closed-loop insulin delivery is under rapid development and several clinical trials have demonstrated this type of delivery to be safe and efficient in shortening the time a patient has hypoglycaemia as well as lowering the rate of hypoglycaemia in children and adults, even at home [47–51]. However, longer-term studies with closed-loop insulin delivery on larger populations are warranted. Finally, further technical developments improving accuracy, reliability and acceptability, particularly for the paediatric age group, are required.

Acknowledgements

The work was supported in part by the Slovenian National Research Agency grants J3-4116 and P3-0343, by a development grant from the EU-Wide Certified Diabetes Educator Course (project No. UK/13/ILP-LdV/TOI-617) and by an ESPE Research Unit Grant for 2013–2014.

Besides the submitted work, T.B. received honoraria for participating on the speaker's bureaux of Eli Lilly, Novo Nordisk, Sanofi, Roche, Dexcom and Medtronic, and consulting fees as a member of the scientific advisory boards of Bayer, Andromeda and Eli Lilly. N.B. received honoraria for participating on the speaker's bureaux of Medtronic and Bayer. Grants to the institution were made by Novo Nordisk, Medtronic, Abbott, Glusense, Dyamid and Sanofi.

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