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ORIGINAL ARTICLE

Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta-analysis

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Abstract

Background Real-time continuous glucose monitoring (RTCGM) may help in the management of individuals with type 1 diabetes mellitus (T1DM); however, the evidence supporting its use is unclear. The available meta-analyses on this topic use aggregate data which weaken inference.

Objective Individual patient data were obtained from randomized controlled trials (RCTs) to conduct a meta-analysis and synthesize evidence about the effect of RTCGM on glycosylated haemoglobin (HbA1c), hypoglycaemic events and time spent in hypoglycaemia in T1DM.

Methods We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, and Scopus through January 2015. We included RCTs that enrolled individuals with T1DM and compared RTCGM vs control group. A two-step regression model was used to pool individual patient data.

Results We included 11 RCTs at moderate risk of bias. Meta-analysis suggests that the use of RTCGM is associated with a statistically significant but modest reduction in HbA1c (−0·276; 95% confidence interval −0·465 to −0·087). The improvements in HbA1c were primarily seen in individuals over age 15 years. We were unable to identify a statistically significant difference in time spent in hypoglycaemia or the number of hypoglycaemic episodes although these analyses were imprecise and warrant lower confidence. There was no difference between males and females.

Conclusion RTCGM in T1DM is associated with a reduction in HbA1c primarily in individuals over 15 years of age. We were unable to identify a statistically significant difference in the time spent in hypoglycaemia or the incidence of hypoglycaemic episodes.

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Introduction

The global incidence of type 1 diabetes mellitus (T1DM) is increasing among the young.[1–3] Models based on a rising incidence of T1DM have projected that the number of individuals <20 years of age with T1DM may triple by 2050.[4] The long-term clinical benefits of tight glycaemic control in T1DM patients have been demonstrated in several studies.[5] This is achieved using insulin analogues, multiple daily injections (MDI) and insulin pumps. However, tight control is associated with hypoglycaemia, which remains the most feared complication of insulin therapy as it was described in the early 1900s.[6] The prevalence of hypoglycaemia increases with diabetes duration, annually affecting half of patients with TIDM.[7] Therefore, intensive monitoring of blood glucose is as important as the treatment itself.

Novel technologies for monitoring glucose levels that provide patients with vital information are available. Continuous glucose monitoring (CGM) is one of the technologies used to achieve this goal. It provides information from a subcutaneous glucose sensor about interstitial glucose levels. Initial models offered only retrospective accessibility to glucose values. Data could be read only by the physician and provided a summary of glycaemic control in the period prior to the visit. This clinician-orientated approach resulted in glycaemic control improvement in some but not all studies.[8] The newest generation of CGM devices is patient-orientated and offers real-time access to glucose levels. They also provide graphs of glucose trends and alerts to impending hypo- and hyperglycaemia events, thus guiding patients to take further action in real time. Studies assessing these devices have suggested improvements in HbA1c as well as a reduction in time spent in hypoglycaemia or hyperglycaemia.[9–11] This suggested an essential clinical benefit and a potential for more research in the field.

In an effort to further investigate the benefits of real-time continuous glucose monitoring (RTCGM) and to support the development of clinical practice guidelines by the Endocrine Society, we conducted this individual patient data meta-analysis to evaluate the effect of RTCGM on HbA1c, time spent in hypoglycaemia and hypoglycaemic episodes in patients with T1DM. We planned to identify patient characteristics associated with benefit, such as age, sex and other patient characteristics.

Materials and methods

This individual patient data meta-analysis follows a protocol developed by experts from the Endocrine Society and methodologists with experience in evidence synthesis. This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).[12]

Eligibility criteria

We included randomized controlled trials (RCTs) that enrolled patients with TIDM and compared RTCGM to a control group (usually a blinded RTCGM) and reported the outcomes of interest: HbA1c at baseline and follow-up, time spent in hypoglycaemia and number of hypoglycaemic events. Trials that included patients with T2DM or those that did not report the outcome of interest were excluded. We also excluded publications without original data or those with incomplete data (abstracts, clinical reviews and editorials). There were no age restrictions regarding included patients as well as no exclusions based on language or geographic location.

Search strategy

A comprehensive search of several databases was conducted from the inception of each database to January 2015. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus. The search strategy was designed and conducted by an experienced Mayo Clinic librarian with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for randomized controlled trials of T1DM using RTCGM and reported change in HbA1c, episodes (severe, minor, nocturnal) and time spent in hypoglycaemia. The detailed search strategy is included in Table S1.

Study selection and data extraction

Pairs of reviewers independently assessed each abstract for eligibility. Disagreement on abstracts yielded an automatic inclusion. Included trials were retrieved as full texts and screened in duplicate. Disagreements were reconciled by consensus and if not possible by consensus through arbitration by a third reviewer. A list of potential included studies was sent to the Endocrine Society Task Force developing guideline on RTCGM for verification. The corresponding author of each trial was contacted via emails requesting individual patient data. When data were owned by industry, we contacted the sponsoring manufacture company. When emails were not answered, we repeated contact after 2 weeks and attempted to contact other authors of trials. Data from each participant included (when available): demographics (age, sex, ethnicity), HbA1c (baseline, during follow-up, at the end-point), follow-up period, number of events of hypoglycaemia (whether symptomatic or not, value of glucose), time spent in hypoglycaemia, time of the episode of hypoglycaemia (night, day, after exercise/playtime for children), type of device/manufacturer/sensor vs no sensor, BMI, weight, skill level and education provided to patient/parents education, adherence to wearing the device, diabetes duration, insulin delivery system (pump vs MDI).

Assessment of risk of bias

We used the Cochrane risk of bias tool[13] to appraise the methodological limitations of each trial (determined by randomization method, blinding, allocation concealment, loss to follow-up and source of funding).

Statistical analysis

The outcome of interest was HbA1c in both arms at baseline and follow-up, time spent in hypoglycaemia and number of episodes of hypoglycaemia (severe, minor and nocturnal). A two-step regression model was used to estimate the pooled difference in means for HbA1c and time in hypoglycaemia with 95% confidence intervals (CIs). When reported, we pooled the mean number of hypoglycaemic events in each arm, and a 2×2 table was constructed to generate an effect size. We planned a priori subgroup analysis based on age and sex. Sensitivity analyses were performed based on older RTCGM technology, trials with only aggregate data and based on various age cut-offs.

We used the I^2 statistics to measure heterogeneity across the studies. Data were analysed using Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Results

Description of included trials

The initial search resulted in 760 citations, and after abstract screening we identified 134 potentially relevant studies. After full-text screening, we finally included 11 studies (1530 patients) (Fig. 1). Authors of the trials were contacted for data. The data set for 10 trials was successfully retrieved, whereas in one single trial, we did not receive a response from the authors. Therefore, aggregated data reported in the published manuscript of that trial were used.[11] Two trials used older RTCGM technology, which was evaluated in sensitivity analyses that excluded such trials.[10,14] Patient characteristics are summarized in Table 1.

Risk of bias assessment

The overall risk of bias in the included trials was moderate. The reporting of allocation concealment was unclear in the majority of trials. Outcome assessors were not blinded, and the source of funding was industry in most trials. Risk of bias assessment for included studies is described in Table S2.

HbA1c

There was a statistically significant reduction in HbA1C associated with using RTCGM in the overall population (Table 2). The effect was heterogeneous. When analysis was stratified by age (≤12, 13–15, >15), results were statistically significant only in the age groups of >15 years. On the other hand, there was no significant difference in younger patients. Subgroup analysis based on gender failed to demonstrate a statistically significant difference.

Hypoglycaemia

In the overall population and across various age subgroups, there was no statistically significant difference in time spent in hypoglycaemia (<3·3 mmol/l; 60 mg/dl) with the use of RTCGM (Table 3). Similarly, there was no statistically significant difference in terms of the incidence of hypoglycaemic events (<3·9 mmol/l; 70 mg/dl) across age subgroups and in the overall population (Table 4). Subgroup analysis based on gender failed to demonstrate a statistically significant difference.

Sensitivity analyses

Sensitivity analyses were performed to exclude two trials that used older RTCGM technology;[10,14] and the results did not change by such exclusion for any of the three outcomes. Sensitivity analyses using different age cut-offs also showed similar results (Table 5).

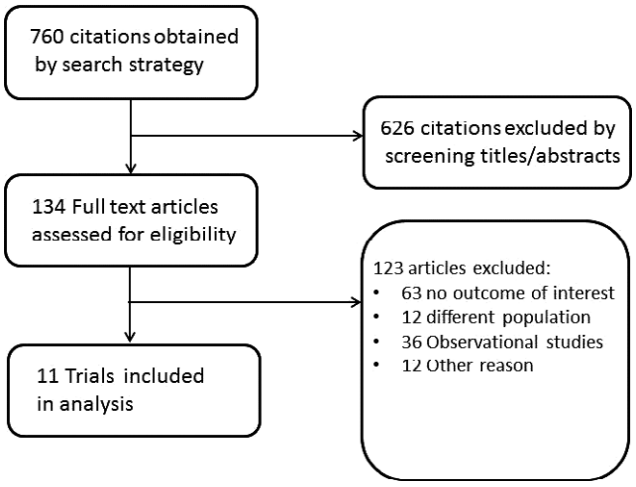

Fig. 1 The process of study selection.

Discussion

Main findings

This individual patient data meta-analysis of randomized trials showed a statistically significant but modest reduction in HbA1c

Table 1. Baseline characteristics for patients included in the trials

	Overall	Blinded RTCGM	Open RTCGM
Adults			
Number of patients	697	315	382
Age (years, mean)	42·4 ± 10·7	43·3 ± 10·9	41·7 ± 10·4
Gender (male)	52%	52·7%	51%
Duration of DM (years, mean)	22·8 ± 11·6	22·7 ± 11·9	22·9 ± 11
Baseline HbA1c (%, mean)	8·2 ±1 ·1	8·3 ± 1	8 ± 1
Baseline BMI (kg/m^2, mean)	25·6 ± 3·9	25·8 ± 4·1	25·5 ± 4
Children/adolescents			
Number of patients	833	386	447
Age (years, mean)	14 ± 4 ·9	13·6 ± 4·9	14·3 ± 5
Gender (male)%	49·5%	50·6%	48·6%
Duration of DM (years, mean)	6·7 ± 4·1	6·7 ± 4·2	6·8 ± 4·2
Baseline HbA1c (%, mean)	8·3 ± 1·3	8·2 ± 1·3	8·3 ± 1·2
Baseline BMI (kg/m^2, mean)	20·6 ±4 ·2	20·3 ± 4·3	2·8 ± 4
Trials with only aggregate data*			
N	62	31	31
Male	18	9	9
Age (years)	23·2 ± 8·4	23·4 ± 8·6	23 ± 8·1
HbA1c (%)	7·4 ± 0·7	7·3 ± 10·6	7·5 ± 0·7
DM duration (years)	10·2 ±7 ·4	11·1 ± 7·6	9·2 ± 7·2

*Only one trial did not provide individual patient data.

Table 2. HbA1c change

	Study	N	HbA1c	95%LL	95%UL	*P*
Overall (adults)†	8	1371	−0·258	−0.464	−0.052	0·014
Overall (with aggregate data)‡	9	1433	−0·276	−0·465	−0·087	0·004
Age ≤12	7	291	−0·047	0·217	0·124	0·592
Age 13–15	7	178	−0·039	−0·320	0·242	0·787
Age >15	7	902	−0·356	0·551	−0·160	<0·001
Male	8	679	−0·264	−0·516	−0·011	0·040
Female*	8	692	−0·215	−0·338	−0·092	0·001
Sensitivity analysis without trials using older technology	6	1070	−0·284	−0·489	−0·078	0·007

**P* value for difference between men and women = 0·73.
†I2 value = 83%.
‡2 value = 82%. This is one-stage model that includes aggregate data from a trial that did not provide individual patient data.

primarily in individuals ages of >15 years. We were unable to identify a statistically significant difference in time spent in hypoglycaemia or the number of hypoglycaemic episodes. There was no difference between males and females. Results were robust and did not change with sensitivity analyses.

Limitations and strengths

The quality of evidence (i.e. certainty in the estimates) derived from this individual patient meta-analysis of randomized trials is moderate for the reduction in HbA1c and low for preventing hypoglycaemia. Limitations of this body of evidence are increased risk for biased estimates and imprecision (i.e. wide confidence intervals that include benefit and harm). Heterogeneity in effect is explained at least partially by age. There are likely other effect modifiers that we could not test (patient education and other demographics and confounder variables). Unfortunately, data were unavailable on several important covariates such as patients' BMI, skill level and education provided to patient, parents' education, adherence to wearing the device, diabetes duration and insulin delivery system (pump vs MDI). Knowing the differential effect in patients with such characteristics would have been very informative to practice and would facilitate patient selection for RTCGM. Another limitation is that most of the studies have evaluated RTCGM use with insulin pumps, while nearly 80% of all individuals with T1D in the US use MDI. There is a need to study the impact of RTCGM in individuals using MDI.[15]

Table 3. Time in Hypoglycaemia <60 (min)

	Study	N	Time (min)	95% LL	95% UL	*P*
Overall	4	706	−8·549	−31·083	13·985	0·457
Age ≤12	3	130	−9·366	19·898	1·167	0·081
Age 13–15	3	109	−13·96528	31·782	3·852	0·124
Age >15	4	467	−8·095	−32·615	16·425	0·518
Female, adults	4	339	−10·893	−50·228	28·443	0·587
Male, adults	4	367	−6·623	−17·886	4·641	0·249

Table 4. Incidence of hypoglycaemic events <70

	Study	N	Mean No. of Events	95% LL	95% UL	*P*
Overall	3	351	0·051	−0·314	0·416	0·785
Age ≤12	2	27	0·392	0·070	0·854	0·097
Age 13–15	2	47	0·536	0·243	1·316	0·177
Age >15	3	277	−0·074	−0·517	0·368	0·742
Female, adults	3	166	0·271	−0·285	0·828	0·339
Male, adults	3	185	−0·139	−0·614	0·336	0·566
Sensitivity analysis without trials that used older technology	2	179	0·010	−0·648	0·667	0·977

The strengths of this systematic review and individual patient meta-analysis of randomized trials are derived from following an a priori established protocol developed by experts from the Endocrine Society, a comprehensive literature search, the application of bias protection measures in study selection, data appraisal and accrual, and the inherent advantages of having individual participant data. In contrast to most published meta-analyses that use aggregated data from published reports, individual data allow stronger inferences. Individual patient data reduce the effect of ecological or aggregation bias and facilitate analysis by standardizing variables across studies.[16]

Comparison with other studies

There were several previous systematic reviews looking at continuous glucose monitoring in T1DM[17–24] that suggested a reduction in HbA1c associated with using this technology. However, all such reviews used aggregate data (i.e. trial-level published effect size). Our meta-analysis is the first to offer individual patient data inferences, therefore yielding more reliable conclusions. Previous reviews predominantly included children with T1DM (all studies, (28) 5/7 studies (29)) and included studies of older generation systems (non-real-time devices). Many trials have been published since that time (15, 18, 19, 21, 22, 23, 24, 26).

Continuous glucose monitoring use in both type 1 and 2 DM patients was evaluated in a systematic review suggesting a significant reduction in mean HbA1c in T1DM adults but the effect on hypoglycaemia was not clear.[25] Another systematic review compared RTCGM to self-blood glucose measurement in T1DM patients with similar insulin regimens and showed a significant reduction in HbA1c in those using RTCGM. An additional finding among those using RTCGM was a lower HbA1c in patients using pumps as compared to those using MDI. The lowering of

Table 5. Sensitivity analysis using different age cut-offs

	Study	N	HbA1c	95%LL	95%UL	*P*
Age < 8	3	72	0·144	−0·225	0·512	0·445
Age 8–14	8	352	−0·080	−0·257	0·097	0·377
Age 15–24	7	336	−0·274	−0·466	−0·082	0·005
Age ≥25	7	611	−0·345	−0·579	−0·112	0·004
			Time in hypoglycaemia (minutes)			
Age <8	No data					
Age 8–14	3	203	−6·150	−15·051	2·752	0·176
Age 15–24	4	200	−10·715	−29·222	7·791	0·256
Age ≥25	4	302	−12·622	−25·847	0·604	0·061
			Mean number of hypoglycaemic events			
Age <8	1	7	−0·083	−0·757	0·590	0·808
Age 8–14	2	67	0·551	−0·012	1·113	0·055
Age 15–24	3	70	−0·098	−0·818	0·622	0·790
Age ≥25	3	207	−0·066	0·605	0·472	0·809

HbA1c was significant with use of RTCGM for over 60–70% of the time.[19] Another systematic review suggested that RTCGM as compared to self-blood glucose measurement or non-real-time continuous glucose monitoring has a beneficial effect on glycaemic control in adults with T1DM, whereas evidence for children and individuals with type 2 DM was not convincing. There was no increase in the incidence of hypoglycaemia in those using RTCGM..[26] More RCTs (11,12,15,17) have been published since these SRs. The current evidence summary updates the evidence base and applies individual patient data analysis.

Clinical implications

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in T1DM.[27] The findings in the intensively teated group also indicated that in those patients that lowered their HbA1C, the rate of hypoglycaemic events increased.[28] However, when interpreting the results of the newer trials, one should consider that the management of diabetes has changed considerably since the DCCT. An example of such changes is the uniform use of insulin analogues.

The findings of this meta-analysis demonstrate that RTCGM use in T1DM has modestly lowered HbA1c without an associated increase in hypoglycaemia. RTCGM use in T1DM patients seems beneficial, although evidence is lacking in children <15 years old. It is plausible that the lack of effect in younger children is due to the fact that the primary goal of monitoring in these patients may have been the avoidance of hypoglycaemia. Qualitative research has demonstrated that mothers of young children with T1DM use the management behaviour of constant vigilance.[29] Mothers have repeatedly voiced that they have tremendous fear of hypoglycaemia and the potential for seizures.[29] In addition, parents of preschool children have high parental stress scores and often have challenges managing children's meals and nutrition;[30] which is another possible explanation for lack of efficacy in younger children.

It has also been shown that in the management of T1DM using insulin pump therapy reduces HbA1c level without an increase in hypoglycaemia, compared with multiple daily insulin injections.[31–33] RTCGM use can further add to the beneficial effect of insulin pump use in T1DM. It can reduce the risk of glycaemic excursions and variability. Increased time spent in the euglycaemic range was noted in studies (12, 14 and 19) of continuous glucose monitoring with the additional benefit of alerting the patient of the trends prior to an adverse event, such as life-threatening hypoglycaemia.

It is difficult to make conclusive statements about hypoglycaemia with RTCGM use. We were unable to identify a statistically significant difference in time spent in hypoglycaemia or the number of hypoglycaemic episodes. If we consider individual trials, HbA1c has been the primary end-point in the trials while hypoglycaemia is often a secondary end-point except in a few trials (19,21,26). With hypoglycaemia being a rare event and a secondary outcome, the lack of the power is not surprising. In addition, hypoglycaemia unaware patients have not been the focus of these trials. Only one study mentioned that hypoglycaemia unaware patients were not excluded (20). Hypoglycaemic exposure has been challenging to quantify in the past due to higher mean absolute relative difference (an accuracy measurement); particularly with older technology.

The beneficial effects of RTCGM use have not only been shown in poorly controlled T1DM (7,11,16,17), but also in individuals who have achieved good control (8,13, 14, 19).

Although studies have reported that patients were satisfied with the technology (15,17), the use of these devices is still challenging in children and adolescents. In one study (15), the use of these devices in children declined over time, with only 41% averaging at least 6 days/week at 26 weeks. Strategies to enhance the usage of such devices should be developed.

The mean age of adults included in this meta-analysis was 42 years. The use and benefits of RTCGM cannot be generalized to older adults with T1DM as minimal data are available in this age group. The use of these devices can be challenging for older individuals, not only from a technological point of view but also due to financial reasons and insurance coverage. Careful selection of patients and adequate support become important in clinical practice.

Additional support, education, office visits, involvement of trained healthcare staff and patient–healthcare provider interactions are required especially at the initiation of a new RTCGM device, particularly in the elderly. At the same time, the concern for cointervention effect of this support can influence the outcomes in the RTCGM trials and act as a confounder. This effect can be minimized by crossover study design (11,12) as such trials did show an improvement in HbA1c as well as time spent in hypoglycaemia in device users.

The longer duration of sensor use has been shown to be associated with the clinical benefits. Greater than 60% sensor utilization was associated with HbA1C reduction in RTCGM users, and the greater the utilization, the more significant the glycaemic improvement (13). In another trial, the patients who were fully protocol-compliant (including sensor wear 70% of the time) showed a significant HbA1C improvement (16). Attempts should be made to identify barriers to the higher utilization of the sensor.

In assessing what may have contributed to the beneficial effects of RTCGM, one RCT (11) showed that there was an increase in number of insulin boluses, increased frequency of using pump features such as temporary basal and manual insulin suspend, raising a question of association of more frequent self-adjustment of insulin therapy by the device users with the beneficial effects on HbA1c and on hypoglycaemia. For RTCGM users, there is additional work involved in changing the tubing, taking care of the tubing, analysing data and integrating it in day-to-day management routine and reacting to the alerts. The balance between benefit and imposing more burden of treatment (additional work)[34] to the patient with the use of RTCGM must be assessed, which underscores the importance of appropriate patient selection and assessing the motivational level of the patients for success with RTCGM.

The lag time between the interstitial fluid glucose measured by RTCGM and plasma glucose continues to be a limitation to the real-time actionable data provided by devices. There have been efforts in the device industry to decrease this lag time. Patients are still recommended to check a finger-stick glucose before intervention. The devices have to be calibrated according to finger-stick glucose for optimal functioning. Ongoing research and improvement in technology will hopefully bring better solutions. Although never formally studied, it seems obvious that adequate patient (or parent) education for using RTCGM, no different than other aspects of type 1 diabetes management, is mandatory. The preferred approaches for providing such education remain unclear at the present time.

Future research

Further research into ways to improve the adherence to the use of these devices is needed. Such research is particularly important in the children and adolescents who show the least adherence. Trials in individuals with T1DM who are older, hospitalized, have hypoglycaemia unawareness or those use MDI are clearly needed. Such trials should designate hypoglycaemia as a primary end-point and classify it as to its severity and whether it requires treatment or assistance from a second person.

Optimal frequency and duration of RTCGM use are unknown. The cost-effectiveness of RTCGM is yet to be determined, and more information can influence the uptake of these devices and coverage by healthcare providers. Data on children <8 years are lacking. Studies assessing the impact of RTCGM on the workload or burden on patients are also important.

Conclusion

In summary, the use of RTCGM for the management of T1DM is associated with a reduction in HbA1c primarily in ages >15 years. We were unable to identify a statistically significant difference in time spent in hypoglycaemia or the number of hypoglycaemic episodes.

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Conflict of interest

Irl B. Hirsch, M.D., Consultant for Roche and Abbott Diabetes Care; Denis Raccah MD, PhD, Member of advisory boards, clinical investigator and speaker during symposia for AstraZeneca, Janssen, Lilly, Novartis, NovoNordisk, Sanofi; Jean-Pierre Riveline MD, PhD, Participated in advisory boards and as a consultant for Abbott Diabetes Care, LifeScan, Sanofi-Aventis, and Eli Lilly and has received honoraria and payment for presentations, travel, and accommodation expenses from Abbott Diabetes Care and Novo Nordisk; Olga Kordonouri, MD, Sanofi (research grants), Lilly (speaker honoraria), Novo Nordisk (advisory board), DreaMed (shareholder). The remaining authors have nothing to disclose.

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