DOI: 10.1111/j.1464-5491.2010.03177.x

Systematic Review

Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review

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Accepted 18 October 2010

Abstract

Aims This study reviews the effect of real-time continuous glucose monitoring systems in diabetes management.

Methods A systematic search was performed in PubMed/MEDLINE and EMBASE for randomized controlled trials comparing real-time continuous glucose monitoring systems with self-monitoring blood glucose or non-real-time continuous glucose monitoring systems.

Results Nine randomized controlled trials were identified. Two studies used a device which is not on the market any more. In this review we focus on the other seven studies. Performing a meta-analysis was not possible because of extensive clinical heterogeneity. Six of seven studies showed some positive effect of real-time continuous glucose monitoring systems on HbA_{1c} (HbA_{1c} decrease 0.3–0.7% or 3–8 mmol/mol). In some studies, this effect only was shown in subgroups (compliant adult patients). However, the size of effect may be underestimated by better-than-average results in the control group, as self-monitoring blood glucose measurements are carried out more frequently than in usual clinical practice. Despite the goal of lowering HbA_{1c}, no more severe hypoglycaemic episodes were seen, except in one study. In contrast, no positive effect was shown with the real-time continuous glucose monitoring system on hypoglycaemia, but randomized controlled trials were not designed or powered to investigate this issue. Time in different glucose strata was assessed only in some trials: two of them showed a significant but small increase in time in euglycaemia.

Conclusions Current evidence shows that the real-time continuous glucose monitoring system has a beneficial effect on glycaemic control in adult diabetes patients, without an increase in the incidence of hypoglycaemia. Studies in well-selected patient groups (pregnancy, history of severe hypoglycaemias, Type 2 diabetes) are lacking.

Diabet. Med. 28, 386–394 (2011)

Keywords continuous glucose monitoring, continuous glucose monitoring system (CGMS), diabetes, real-time

Introduction

Optimal glycaemic control reduces the risk of chronic organ complications in patients with Type 1 or Type 2 diabetes [1,2]. The Diabetes Control and Complications Trial has shown that achieving good control greatly increases the risk of hypoglycaemia. In practice, hypoglycaemia forms a major limiting factor despite the best efforts of patients and clinicians. In theory, self-monitoring of blood glucose levels coupled with intensive and extensive ongoing education could help to reduce hypoglycaemia. However, the snapshot nature of self-monitoring of blood glucose and the limited number of self-monitorings of blood glucose that are carried out during a day restrict the influence of self-monitoring of blood glucose. The number of self-monitored blood glucose measurements has been shown to correlate with glycaemic control [3]; but with four self-monitoring of blood glucose measurements a day, limited information is available on preprandial, postprandial and overnight values [3]. In addition, the moment of self-monitoring of blood glucose is chosen by the patient and that moment may not always provide the most optimal and useful information.

The continuous glucose monitoring system (CGMS) is a novel technology potentially revolutionizing diabetes treatment by offering a longer-term ongoing display of glucose levels. The first continuous glucose monitoring system offered only 'offline' interpretation of the glucose profiles after disconnecting the sensor and uploading the results. In the past years, 'online' or

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'real-time' continuous glucose monitoring systems have become available, allowing direct feedback of glucose levels and direct intervention. In theory, the real-time continuous glucose monitoring system would provide a good method to improve glycaemic control without the traditional degree of excess hypoglycaemia. The continuous glucose monitoring system essentially comprises a needle (containing a glucose-dependent enzyme generating glucose-dependent electrical currents) which has to be inserted into subcutaneous fat, a transmitter connected to the needle (translating and relaying data by infrared technology) and a separate receiver that displays the glucose profile. Calibrating the continuous glucose monitoring system with a number of self-monitoring of blood glucose measurements is necessary. With real-time continuous glucose monitoring systems, glucose thresholds can be set with an alarm going off with glucose levels outside the target area and thresholds can also be set using rates of change.

The real-time continuous glucose monitoring system generates an avalanche of data, but the question of clinical benefit, indications and clinical requirements for implementation have not yet been answered conclusively. Therefore, we conducted a systematic review of all available randomized controlled trials to estimate the effects of real-time continuous glucose monitoring systems on diabetes management.

Patients and methods

We performed a systematic search for all published randomized controlled clinical trials or meta-analysis/systematic reviews comparing real-time continuous glucose monitoring systems with self-monitoring of blood glucose and/or the offline continuous glucose monitoring system. We searched PubMed/MEDLINE and EMBASE from 1 January 2005 to 1 January 2010. We restricted the search from 2005 onwards as the use of the real-time devices had not relevantly started before this period. A search including the term 'real time' was not comprehensive and important articles were not identified. We therefore extended our search terms. This search strategy for the bibliographic databases combined the following terms (with their synonyms and derivatives) in title/abstract: 'CGMS, monitoring, sensor, continuous, diabetes'* (see Appendix 1). In addition, we limited the review to English-language articles. In this search, two independent reviewers (LBEAH and WLG) screened the articles, using title/abstract or full text if necessary, and reviewed reference lists of included articles.

Inclusion and exclusion criteria

Studies included in this review had to be randomized, parallel-arm, controlled trials in which the real-time continuous glucose monitoring system was compared with self-monitoring of blood glucose (whether or not in combination with the offline continuous glucose monitoring system). Studies included children and adults, as well as Type 1 and Type 2 diabetes and all kind of devices for real-time continuous glucose monitoring (this included devices with current use as well as devices that had already been withdrawn from the market at the time of this review). Withdrawal from the market was not an exclusion criterion in our search, as this could potentially lead to selection bias with exclusion of negative studies as negative studies may be more likely to be associated with these devices.

Reasons for exclusions were studies on post-pancreatic/islet cell transplant patients and studies with settings such as Intensive Care, Cardiac Monitoring Unit, pre- and post-operation and studies with a follow-up of less than 6 weeks, as it takes a minimum of 6 weeks to detect a meaningful change in HbA_{1c}. In the case of a duplicate publication, the publication with the most comprehensive information was used.

Outcomes of interest

The primary outcome was improvement in diabetes control according to an absolute reduction in HbA_{1c} in a head-to-head comparison or a comparison of absolute change from baseline between both groups. The secondary outcomes were: severe hypoglycaemic episodes (as defined by the investigators), time spent in different glucose strata (hypoglycaemic, euglycaemic, hyperglycaemic), local adverse effects, quality of life and compliance.

Data collection

Relevant data were extracted on predesigned forms. These forms included information about author, publication year, country, duration of the trial, number of patients in the study and characteristics of these patients (type of diabetes, age, duration of diabetes, therapy, HbA_{1c} at start of study, frequency of self-monitoring of blood glucose measurements) and information on type of device, type of usage (intermittent/continuous) and duration of usage.

Statistics

We could not perform a meta-analysis because of extensive clinical heterogeneity on many aspects such as design, type of diabetes (mostly Type 1 diabetes, but also Type 2 diabetes, or mixed), age of participants (children, adolescents, adults) therapy (multiple daily injections of insulin or continuous subcutaneous insulin infusion) and glycaemic control.

Quality control

The methodological quality of the studies that met the inclusion criteria was assessed using the components of the study design most closely aligned to internal validity, as proposed by the Dutch Cochrane Centre [4]. These components include: adequate description of randomization, blinding of patients and outcome assessors and adequate description of follow-up and withdrawals. The higher the Cochrane score, the higher the methodological quality of the study. A score ≥ 4 was defined as

of sufficient quality for this review. In case of doubt, consensus was reached in an open discussion with the third author (HWdV).

Results

Literature search and study selection

The search strategy resulted in 1018 articles in PubMed/MEDLINE and 223 in EMBASE. After screening for inclusion and exclusion criteria, 18 articles seemed relevant. Of these remaining 18 articles, nine were excluded after reading the full paper: eight turned out to be non-randomized controlled trial studies and one was of too short a duration (Figure 1). The quality assessment of the remaining nine articles [5–13] showed that all nine articles had a Cochrane score ≥ 4 and were therefore included in this review (see Appendix 2).

Description of studies and patient characteristics

A description of design, characteristics and outcomes of studies included in the systematic review are presented in Tables 1 and 2. Two studies were in fact reports of two separate subpopulations [patients with an HbA_{1c} > 7% (> 53 mmol/mol) and patients with an HbA_{1c} < 7% (< 53 mmol/mol)] from one larger intervention study ([5,12]; Juvenile Diabetes Research Foundation Studies 1 and 2). Study duration ranged from 12 weeks to 18 months. All studies had parallel study design [5–12]; however in one study some variables were only investigated in a single arm constructure [13]. Studies included patients with either Type 1 or Type 2 diabetes or both, different age groups, different insulin treatment regimens and different degrees of glycaemic control as expressed as HbA_{1c} (ranging from poor to excellent). Four of seven studies used self-monitoring of blood glucose and blinded continuous glucose monitoring data as control. Two of seven studies used self-monitoring of blood glucose data as control.

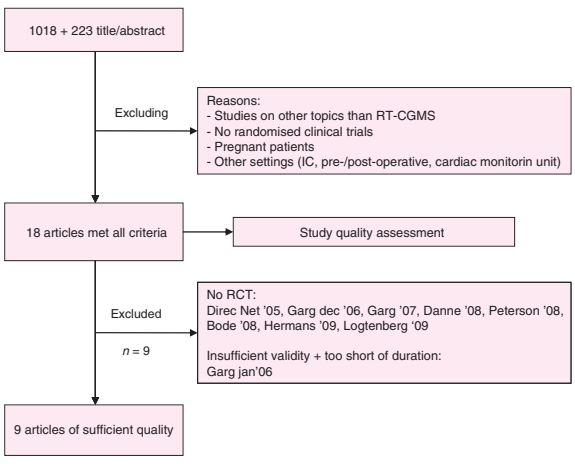

FIGURE 1 Scheme of included and excluded studies. IC, intensive care; RCT, randomized controlled trial; RT-CGM, real-time continuous glucose monitoring.

Studies using a Glucowatch (GW2B) device

Although 'today use' was not a inclusion criterion, we will only describe seven of the studies; the two studies [6,7] that used a real-time continuous glucose monitoring system device (GW2B) that is not on the market anymore have been described separately. This device caused a lot of skin irritations (100% in the DirecNet group [6] and 49% in Cooke *et al.* [7]), which led to very low compliance rates and many users stopped early (27 and 80% of users, respectively). These were both negative studies, but we consider these results not to be representative for the effect of real-time continuous glucose monitoring systems in general because, when using this device, compliance is of great importance. Therefore, in the following section of the Results we will only describe the other seven studies.

Main outcome

HbA_{1c}

HbA_{1c} was reduced to a greater extent in the real-time continuous glucose monitoring system group than in the control group in three studies [8,10,13]. The study by Tamborlane *et al.* also showed a significant difference, but only in the subgroup of patients > 25 years [12]. In another study in very adequately controlled patients (baseline HbA_{1c} 6.5%, 48 mmol/mol), the real-time continuous glucose monitoring system did not show a decrease in HbA_{1c} with that system, but there was an increase in HbA_{1c} in the control group [5]. Raccah *et al.* [11] showed only significant differences in the compliant patient group, but when the complete patient population was analysed only borderline significant results remained. The only study not showing any difference between the real-time continuous glucose monitoring system and the control group was the study by Hirsch *et al.* [9] in poorly controlled patients with continuous subcutaneous insulin infusion. The study of O'Connell *et al.* [10] was the only study with a head-to-head comparison of HbA_{1c} as the primary variable at the end of the intervention showing a statistically significant improvement in HbA_{1c} with the real-time continuous glucose monitoring system. In conclusion, six studies showed some positive effect (0.3–0.7% or 3–8 mmol/mol) of the real-time continuous glucose monitoring system on HbA_{1c} compared with the control.

Secondary outcomes

Symptomatic hypoglycaemia

None of the seven studies demonstrated a positive effect of the real-time continuous glucose monitoring system on the incidence of severe hypoglycaemia. One study [9] actually showed an increase in severe hypoglycaemia. Two studies showed a decrease in HbA_{1c} in the absence of severe or non-severe hypoglycaemia in

Table 1 Characteristics of included trials

	Basics		Inclusion					Methods		
Study	Duration of trial	Sample size (SG/ CG)	Type diabetes	Age inclusion (mean SG vs CG)	Duration diabetes (mean SG vs CG)	Diabetes treatment at baseline (SG vs CG)	Baseline HbA1c inclusion (mean SG vs CG)	Frequency of CGMS use in intervention group (total number)	Methods of control measurements	Type CGMS
Beck *et al.* [5] (JDRF) 2009 United States	6 months	67/62	T1DM	≥8 yr (29 vs 32 yr)	≥1 yr (5–25 vs 4–28 yr)	CSII or MDI (93% vs 79% CSII 7% vs 21% MDI)	≤7.0%, 53 mmol/mol (6.4 vs 6.5%, 46 vs 48 mmol/mol)	Daily; at least 70%	SMBG ≥3x/day Blind CGMS twice	DexCom Seven, (Dexcom) Minimed Paradigm (Medtronic) FreeStyle Navigator (Abbott)
Deis *et al.* [8] 2006 Sweden	3 months	total 156	TIDM	≥8 yr (unknown)	Unknown	CSII or MDI (unknown)	≥8.1%, 65 mmol/mol (unknown)	two intervention groups: SG1. 3 months continue SG2. biweekly 3-days	Unknown	Guardian RT (Medtronic)
Hirsch *et al.* [9] 2008 United States	6 months	66/72	T1DM	12–72 yr (33 vs 33 yr)	> 1 year (21 vs 17 yr)	≥6 months CSII (unknown)	≥ 7.5%, 58 mmol/mol (8.5 vs 8,4%, 69 vs 68 mmol/mol)	daily	SMBG unknown 2x 3 days blind CGMS	Paradigm 722 (Medtronic)
O'Connell *et al.* [10] 2008 Australia	3 months	31/31	T1DM	13–40 yr (23 vs 23 yr)	> 1 year (11 vs 9 yr)	CSII > 3 months (2.4 vs 1.9 yr)	≤ 8.5%, 69 mmol/mol (7.3%, 56 mmol/mol vs 7.5%, 58 mmol/mol)	Continue	SMBG Min 4x/day 2x 6 days blind CGMS at baseline and end	MiniMed Paradigm (Medtronic)
Raccah *et al.* [11] 2009 France	6 months	55/60	T1DM	2–65 yr (28 yr)	≥ 1 year	MDI → CSII during the study	≥ 8.0%, 64 mmol/mol (9.1/9.3%,76–78 mmol/mol)	Min 70%	SMBG Min 3x/day	MiniMed Paradigm (Medtronic)
Tamborlane *et al.* [12] (JDRF) 2008 United States	6 months	165/157 ± 100 per group (group 1: 8–14 yr group 2: 15–24 yr group 3: ≥25 yr)	T1DM	≥ 8 yr (G1:11 yr G2:18 yr G3:42 yr)	> 1 year (G1:6 yr G2: 9 yr G3:22yr)	CSII or MDI (G1: 85%CSII vs 15% MDI G2: 70 vs 30% G3: 85% vs 15%)	7–10%, 53–86 mmol/mol G1: 7.9%,63 mmol/mol G2: 7.9%, 63 mmol/mol G3: 7.3%, 60 mmol/mol)	daily	SMBG Min 4x/day +2x blind CGMS (wk 13 + 26)	DexCom Seven(Dexcom) MiniMed Paradigm (Medtronic) Freestyle Navigator (Abbott)
Yoo *et al.* [13] 2008 Korea	3 months	32/33	T2DM	20–80 yr (55 vs 58)	> 1 year (12 vs 13 yr)	Tablets, insulin, both (45% vs 36% tablets, 14% vs 18% insulin, 38% vs 43% both)	8–10%, 64–86 mmol/mol (9.1%, 76 mmol/mol vs 8.7%, 72 mmol/mol)	1x/month for 3 days	SMBG Min 4x/wk (fasting + postprandial	Guardian RT (Medtronic)
Cooke *et al.* [7] 2009 United Kingdom	18 months	100 RT-SG 102 blind-SG 100 extra care CG 100 standard CG	57%T1DM 41%T2DM	≥ 18 yr (52 yr)	> 6 months (16 yr)	97% MDI 2% CSII	≥ 7.5%, 58 mmol/mol (9.1%, 76 mmol/mol)	0–3 months: > 4x/month and < 4x/week 3–18 months: 'as often as desired'	0–3 months: SMBG daily + blind CGMS 72h at 0,6,12 weeks 3–18 months: SMBG daily + Blind CGMS once a month	GW2B (Cygnus)
DirecNet study group [6] 2005 United States	6 months	99/101	TIDM	7–18 (12.3 vs 12.7 yr)	≥ 1 year (5.3 vs 5.4 yr)	≥ 1 year CSII (46 vs 47%) or MDI (54 vs 53%)	7–11%, 53–97 mmol/mol (8.0%, 64 mmol/mol)	"As much as possible"	Min 4x/day + 2x blind CGMS (begin and at end of study)	GW2B (Cygnus)

*All trials have a randomized, parallel-group design.
GlucoWatch G2 Biographer.
CG, control group; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; JDRF, Juvenile Diabetes Research Foundation; Min., minimum; RT, real-time; SG, sensor group (real-time continuous glucose monitoring system); T1DM, Type 1 diabetes; T2DM, Type 2 diabetes.
DexCom, San Diego,California; Medtronic, Minneapolis; Abbott, North Chicago, Illinois; Cygnus, Michigan area

Table 2 Outcomes of included trials

Study	HbA_{1c}	Severe hypoglycaemia	Time in hypoglycemia	Time in range	Time in hyperglycaemia	Adverse effects	Compliance/miscellaneous
Beck *et al.* [5] (JDRF) 2009	SG: 6.4 → 6.4% (46 → 46 mmol/mol) CG: 6.5 → 6.8% (48 → 51 mmol/mol) ($P < 0.001$)	NS	SG: 91 → 45 min CG: 96 → 91 min (borderline sign)	SG: 1063 → 1063 min CG: 972 → 949 min ($P = 0.003$)	NS	NS	Compliance was very good Decrease in HbA_{1c} without increase in hypoglycaemia was higher in the SG ($P < 0.001$)
Deiss *et al.* [8] 2006	SG1: 9.5 → 8.5% (80 → 69 mmol/mol) SG2: 9.6 → 8.9% (81 → 74 mmol/mol) CG: 9.7 → 9.3% (83 → 78 mmol/mol) ($P = 0.003$ for continuous use (SG1) NS for biweekly use (SG2)	NS	Not measured	Not measured	Not measured	Unknown	Compliance unknown
Hirsch *et al.* [9] 2008	NS	SG: 11 events CG: 4 events ($P = 0.04$)	SG: stable CG: increase ($P = 0.0002$)	Not measured	NS	1 × skin abscess	Compliance very good Compliance was related to reduction in HbA_{1c}
O'Connell *et al.* [10] 2008	SG: 7.3 → 7.1% (56 → 54 mmol/mol) CG: 7.5 → 7.8% (58 → 62 mmol/mol) ($P = 0.009$)	None	NS	NS	NS	Only mechanical problems	Overall compliance unknown Lower HbA_{1c} in patients with > 70% compliance Effect on variability NS
Raccah *et al.* [11] 2009	NS full analysis set ($P = 0.087$) In per-protocol set: SG: 9.2 → 8.2% (77 → 66 mmol/mol) CG: 9.3 → 8.8% (78 → 73 mmol/mol) ($P = 0.004$)	NS	NS	Not measured	SG: Δ = −3.5 (h/day) CG: Δ = −0.7 (h/day) ($P < 0.005$)	NS	Compliance: 75% in adults, 68% in children, 52% in adolescents Variability decreased in the sensor group
Tamborlane *et al.* [12] (JDRF) 2008	In adults: SG: 7.6 → 7.1% (60 → 54 mmol/mol) CG: 7.6 → 7.6% (60 → 60 mmol/mol) ($P < 0.001$) Children and adolescents NS	NS	NS	SG: 854 → 986 min CG:811 → 840 (min/day) ($P < 0.001$) Children and adolescents NS	SG: 497 → 394 CG: 549 → 519 (min/day) ($P = 0.002$) Children and adolescents NS	Very infrequent	Compliance (> 6 days/week): 83% in adults, 50% in children, 30% in adolescents $HbA_{1c} < 7.0\%$ without severe hypoglycaemia was higher in the SG in adults and children

Table 2 (*Continued*)

Study	HbA_{1c}	Severe hypoglycaemia	Time in hypoglycemia	Time in range	Time in hyperglycaemia	Adverse effects	Compliance/miscellaneous
Yoo *et al.* [13] 2008	SG: 9.1 → 8.0% (76 → 64 mmol/mol) CG: 8.7 → 8.3% (72 → 67 mmol/mol) ($P < 0.001$)	NS	Not measured between groups NS within the SG	Not measured between groups NS within the SG	Not measured between groups Significant reduction within the SG	0% skin reactions	Compliance unknown Better exercise time + calorie intake, MAGE, BMI + weight in SG compared with baseline (not compared with CG)
Cooke *et al.* [7] 2009	Less HbA_{1c} improvement in the SG vs. CG Actual data not given ($P = 0.02$)	Not measured	Risk reduction for clinical hypoglycaemia of RR 0.83 (0.67–0.98) for standard control vs. SG	Not measured	Not measured	Skin reactions 49%, difficulties in usage (10%)	Compliance was bad (80% stopped wearing the device) Cost analysis not significant
DirecNet Study Group [6] 2005	NS	NS	Not measured	Not measured	Not measured	100% skin irritation	Compliance was bad (27% stopped, none used the sensor > 3 times a week)

→, baseline to end of study.
The outcomes shown in dark green favour RT-CGMS and the outcomes shown in dark brown favour not RT-CGMS.
CG, control group; CGMS, continuous glucose monitoring system; JDRF, Juvenile Diabetes Research Foundation; MAGE, mean amplitude of glycaemic excursions; NS, not significant; RR, relative risk; RT, real-time; SG, sensor group (RT-CGMS).

the real-time continuous glucose monitoring system group [5,12]. This combined endpoint is of clinical interest as the lowering of HbA_{1c} without an increase in hypoglycaemia is an ultimate goal in diabetic management.

In general, no decrease, but also no increase in hypoglycaemia, was observed.

Time in predefined glucose strata

One study uses 'time-in-target-glycaemia' as the primary endpoint [10]. During the study, no change in the intervention or control group and no difference between the groups was observed. Tamborlane *et al.* showed a decreased time in hyperglycaemia and increased time in target in adults compared with the control group. Another study showed a decrease in euglycaemia in the control group, but not in the real-time continuous glucose monitoring system group [5]. The study of Raccah *et al.* [11] only showed a decrease in time in hyperglycaemia, without any effect on time in euglycaemia. Considering time in hypoglycaemia, two studies showed some improvement. One study only showed an increase in the control group without a change in the sensor group [9], the other showed a borderline significant decrease in time spent in hypoglycaemia in the real-time continuous glucose monitoring system group [5]. The study by Yoo *et al.* [13] showed that, within the real-time continuous glucose monitoring system group, time in hyperglycaemia was decreased as compared with baseline, but data of the control group are lacking.

So, some evidence exists that the distribution of glucose values over the various strata can be improved using the real-time continuous glucose monitoring system, although the minority of this analysis was statistically significant.

Adverse events

The device was well tolerated in all seven studies. Adverse events were infrequent and not significantly different from the control group. Adverse events consisted mainly of skin irritation.

Compliance

Compliance with sensor use was relatively good in all seven studies using different devices, but fell over time. Three trials showed increased HbA_{1c} improvement in patients with better compliance [9–11]; one study showed that, adjusted for baseline values, HbA_{1c} was 0.51% lower in participants who wore the sensor ≥ 70% of the total study period (98%CI 0.04–0.98%, $P = 0.04$) [10]. Another study showed that each 10% increase of time the sensor was used was associated with a 41% increase in the probability of a 0.5% reduction in HbA_{1c} [9]. The last study only showed a significant difference in HbA_{1c} in fully compliant patients, whereas in the whole group significance was only borderline [11]. Compliance was dependent on age group: it was

highest in adults, lower in children and the lowest in adolescents [11,12].

In all, compliance was reasonable and an important factor for the effect of the real-time devices.

Other considerations

Costs were only analysed in one study; Cooke *et al.* [7] showed costs did not differ significantly between treatment and control group.

Quality of life was not assessed in any of the studies.

Three studies investigated effects of real-time continuous glucose monitoring systems on glycaemic variability [10,11,13]. Two of them showed a significant reduction of variability in patients using the device [11,13]. Although, in the study of Yoo *et al.* [13], this was a within-group effect and a head-to-head comparison between the sensor group and the control group was lacking. The other studies did not investigate this endpoint.

Discussion

This systematic review of nine randomized controlled trials, in which we focus on the seven trials about currently available devices, published in the last 5 years indicates that the real-time continuous glucose monitoring system has considerable potential to be an effective tool for improving glycaemic control in adults with Type 1 diabetes. Less convincing evidence is available for children and Type 2 diabetes.

The diversity of study design and populations, the lack of studies in subjects with specific clinical demands such as recurrent severe hypoglycaemia or pregnancy, as well as the complex nature of the intervention itself, preclude simple translation to clinical practice. A number of specific issues have to be addressed before more widespread implementation can be wholeheartedly supported.

Firstly, the choice of the optimal or most relevant variable of glycaemic control to assess the effect of intervention with the real-time continuous glucose monitoring system is a major issue. In most studies, HbA_{1c} was taken as the principal variable of glycaemic control and the primary endpoint. In only one study, a head-to-head comparison at the end of the study was performed; in all other studies, the change in HbA_{1c} between the start and the end of study was compared between intervention and control groups. In general, HbA_{1c} decreased irrespective of the baseline HbA_{1c}, indicating that there is no reason to exclude patients on the basis of baseline HbA_{1c}, except those with a very high HbA_{1c} in whom other issues regarding treatment and self-management require attending to first.

However, HbA_{1c} does not reflect the complexities of glycaemic control and patients can display wildly and widely swinging glucose levels (high glucose variability), or severe hypoglycaemic and hyperglycaemic episodes, with nevertheless a reasonable HbA_{1c} value. The question then is how to attain improvement of glycaemic control in such patients. Glucose variability, for example, by the simple calculation of the standard deviation, could serve as the endpoint in subjects with a wide range of glucose values [14]. Glucose variability was shown to decrease in two of the three studies that used this as an endpoint [11,13].

As an alternative approach, one could use the variable of 'time spent in preset glucose ranges'. Improvement is than defined as decreased time spent in hyperglycaemia or time spent in hypoglycaemia and/or increased time spent in euglycaemia. Comparing the four studies employing this variable, however, shows that there is no consensus on the definition of euglycaemia, hypoglycaemia and hyperglycaemia. Lower limits of euglycaemia ranged from 2.8–4.4 mmol/l and upper limits from 10.0–13.9 mmol/l.

In summary, the best variable to assess glycaemic control and the complexities of control remains a major unsolved issue in the assessment of the true value of the real-time continuous glucose monitoring system.

Secondly, apart from a general effect on glycaemic control, some subjects will present with a specific clinical condition, most notably recurrent severe hypoglycaemia and hypoglycaemia unawareness.

The reviewed studies could not give a clear-cut answer to the question of whether the real-time continuous glucose monitoring system could be helpful in these patients. In some studies, patients with a history of severe hypoglycaemia were specifically excluded [10] and in other studies episodes of severe hypoglycaemia were not endpoints and were not reported [7]. In the Juvenile Diabetes Research Foundation studies [5,12], no difference in the incidence of severe hypoglycaemia was found, but the percentage of patients with severe hypoglycaemia at baseline was not mentioned. The same was true for the study of Raccah *et al.* [11] and the much smaller studies by Deiss *et al.* [8], Yoo *et al.* [13] and Hirsch *et al.* [9]. In summary, no effect of the real-time continuous glucose monitoring system seems apparent on the incidence of severe hypoglycaemia in patients not specifically selected for that problem. This does not at all exclude a beneficial effect on patients with frequent severe hypoglycaemia. Although common clinical sense may suggest trying the real-time continuous glucose monitoring system in patients so afflicted, the evidence of a solid randomized trial to support this line of action is lacking.

Thirdly, compliance is a major issue and some studies clearly reported a positive association between the degree of compliance and the effect on the primary endpoint [9–11]. Compliance decreased during the course of the trial, which could be linked to sensor-related skin problems, waning of the initial enthusiasm for the active intervention, or to the burden of the intervention itself (the constant feedback of data and/or the frequent alarms, especially during the night). As said before, compliance with the Glucowatch was especially poor as almost all patients suffered form severe skin reactions induced by the sensor. We described the studies using this device separately because, even if the sensor itself had been excellent, this device would have been unsuitable for normal practice. Apart from this specific device, no major

adverse events were reported; safety is thus not an issue in these devices.

Fourthly, the trial design and the comparator groups deserve attention. The nature of the intervention precludes blinding of the subjects and the study personnel during the trial. Endpoints related to sensor data (like time spent in hyperglycaemia) can be analysed blindly offline, but "conclusions about clinical events (severe hypoglycemia)" has to be adjudicated by an independent committee "to prevent bias". In randomized controlled trials, it could be that the control subjects perform better than they normally would because they participate in a trial. The frequency of self-measurement of glucose levels required in the studies is higher than in normal daily life and the study control group may therefore not be a realistic reflection of the average diabetes patient. Thus, the effect of the real-time continuous glucose monitoring system might be underestimated.

Not only is the frequency of self-measurement of blood glucose levels important, but also the general counselling and support of the patient must be comparable in both the intervention and the control group and be clearly stated in the description of the study.

Finally, the real-time continuous glucose monitoring system requires an extensive and detailed care and counselling support structure and adequate training of the healthcare professionals. Some studies [9–11] only provided patients with the device without proper training, sometimes because the researchers themselves did not have enough experience, as they admitted in their conclusion [9]. But in assessing the effect on HbA_{1c} with such a new and precise device, a more proactive approach is needed to inform the user how to react on static and dynamic alerts. Without such a collaborative effort, the effect of the real-time continuous glucose monitoring system may be underestimated. This means that the real-time continuous glucose monitoring system requires a substantial professional investment and a major contribution from the patient. These factors may be seen as prerequisite for the implementation of this novel and expensive technique and may limit the number of centres offering the real-time continuous glucose monitoring system.

In conclusion, current evidence shows that the real-time continuous glucose monitoring system has a general beneficial effect on glycaemic control, but that information on specific clinical indications such as recurrent severe hypoglycaemia, Type 2 diabetes or pregnancy is lacking. The technique requires a long-term commitment of the healthcare professionals and the patient to translate the potential effect into common practice. Also, more information is needed on longer-term outcomes, including compliance and quality of life.

Competing interests

Nothing to declare.

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Appendix I

Search:

Pubmed

CGM[Title/Abstract] OR CGMS[Title/Abstract] OR "continuous glucose monitoring"[Title/Abstract] OR "continuous glucose"[Title/Abstract] OR "glucose monitoring"[Title/Abstract])
OR observing[Title/Abstract] OR observed[Title/Abstract] OR observing[Title/Abstract] OR monitoring[Title/Abstract] OR monitored[Title/Abstract] OR monitors [Title/Abstract])

AND (continuous[Title/Abstract] OR continuing[Title/Abstract] OR persisting[Title/Abstract] OR continue [Title/Abstract])
OR Sensor[Title/Abstract] OR glucose sensor[Title/Abstract] OR sensing[Title/Abstract] OR sensoring [Title/Abstract]) AND continuous[Title/Abstract] OR continuing[Title/Abstract] OR persisting[Title/Abstract] OR continue[Title/Abstract])
AND
(diabetes[Title/Abstract] OR diabetes mellitus[Title/Abstract])
AND
"2005/01/01"[EDAT] : "2009/08/01"[EDAT]
AND
English[lang]

B. Embase
"Continuous glucose monitoring system"
2005–2010

Appendix II

Study	Randomised	Blind randomised	Blind analysis	Comparable groups	Loss to follow up	Intention to treat	Equal therapy	Results correctly shown	Score
Beck [5]	yes	?	no	yes	2/129	yes	yes	yes	6
Cooke [7]	yes	yes	no	yes	74/404	no	yes	yes	5
Deiss [8]	yes	?	?	?	5/162	yes	yes	?	≥4
DirecNet [6]	yes	no	yes	yes	1/200	yes	yes	yes	6
Hirsch [9]	yes	?	no	yes	8/176	no	yes	yes	5
O'Connell [10]	yes	yes	no	yes	7/62	no	yes	yes	6
Raccah [11]	yes	?	yes	yes	13/128	yes	yes	yes	7
Tamborlane [12]	yes	?	no	yes	5/322	yes	yes	yes	6
Yoo [13]	yes	yes	?	yes	8/65	?	yes	yes	6