Original Article

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Systematic Review of the Effectiveness of Continuous Glucose Monitoring (CGM) on Glucose Control in Type 2 Diabetes

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Abstract

Forty-four percent of people with type 2 diabetes have hemoglobin A1C higher than the generally accepted target. The goal of diabetes management is to prevent diabetic complications by an as tight as possible glycemic control without the risk of severe hypoglycemia. Although UK Prospective Diabetes Study (UKPDS) group has reported that intensified diabetes management can improve glycemic control and decreases the risk of long-term microvascular complications in diabetes, high rate of hypoglycemia becomes a risk in intensive diabetic management. The fear of hypoglycemia often leads patients to forget the fatal consequences of long-term complications to avert hypoglycemic events with loss of control and cognitive dysfunction. Self-monitoring of blood glucose (SMBG) is a fundamental part of diabetes management. However, SMBG fails to detect nocturnal hypoglycemia and asymptomatic hypoglycemia. Hence, monitoring blood glucose system on a 'continuous basis' have been developed. This systematic review aims to support evidence regarding the effects of continuous glucose monitoring system (CGMS) on glycemic control in type 2 diabetes by collecting randomized controlled trials from MEDLINE (pubmed), Scopus, CINAHL, Web of Science and The Cochrane Controlled Trials Register and cited literature in retrieved articles. The finding shows that four studies out of five included studies presented the positive results in favor of CGMS group (HbA1c decrease; 0.6-1.16% in experimental group compared with 0.2-0.5% in SMBG group). CGMS may provide benefit over SMBG use in type 2 diabetes.

Keyword: Systematic review, Continuous glucose monitoring (CGM), Type 2 diabetes, T2DM

INTRODUCTION

Diabetes mellitus is a chronic illness that requires continuing medical care and ongoing patient self-management education including the support to prevent or reduce acute and long-term complications[1-4]. People who have diabetes mellitus face daily challenges in managing glycemic levels, as well as avoiding hypoglycemic and hyperglycemic excursions. Both severe hypoglycemia and extreme hyperglycemia have an immediate impact on mental and physical functioning. The maintenance of glycemic control within near-normal limits can avoid such a situation and at the same time, significantly decrease the development of secondary micro- and macrovascular complications. Self monitoring of blood glucose (SMBG), a kind of capillary blood glucose measurement using portable device, has been used to assess blood glucose level[5]. Because of many factors, such as pain and inconvenience, many diabetes feel uncomfortable with frequent finger-sticks for SMBG[6]. In addition, SMBG gives a single instant reading without any information on glucose trends and thus may miss significant

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glucose fluctuations[7]. Moreover, even with frequent blood sampling for spot glucose measurements, some patients do not adequately manage their glycemic levels. Therefore, continuous real-time glucose reading becomes a need for such patients[5]. The continuous glucose monitoring, also called CGM devices display blood glucose concentrations measured in near real-time at the subcutaneous tissue. It is useful to provide greater insight into glucose levels throughout the day, supply trend information to determine benefits of medication changes and may help identify and prevent unwanted periods of hypo- and hyperglycemia[8]. The CGM 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. Since 2001, there have been several studies regarding the effect of CGM systems in diabetes. In type 1 diabetes, several randomized controlled trials (RCTs) showed the benefit of CGM[9-14]. In type 2 diabetes, the clinical benefit of CGM has not yet been answered conclusively. Therefore, the present review was conducted to estimate the benefit of CGM use in T2DM by systematic collection of all available RCTs.

METHODS

Literature Review

A systematic review was conducted to identify the effectiveness of CGM in type 2 diabetic adults in which the use of CGM was compared with usual care (with or without SMBG). These studies were searched through the MEDLINE (pubmed), Scopus, CINAHL, Web of Science and The Cochrane Controlled Trials Register. The bibliographic databases were searched from the inception to January 2013. The following MeSH terms were used; diabetes mellitus and continuous glucose monitoring. This was followed by keyword search using as keywords – CGM, non-insulin dependent diabetes mellitus, NIDDM. Historical search of reference lists of relevant randomized controlled trials, systematic and narrative reviews were also undertaken. Only publications in English were included in this review.

Study Selection

Studies included in this review had to be randomized, controlled trials in which any type of continuous glucose monitoring system was compared with usual care (with or without SMBG). Participants with the age of > 18 years were included. Studies in pregnancy, critically ill patients, post-surgery, post-transplant and ICU patients were excluded. Studies with a follow up of < 8 weeks were also excluded because the red blood cells where the non-enzymatic glycation takes place have an average life span of 120 days and the average half-life of 60 days or 8 weeks.

Outcomes of Interest

The primary outcome was the change in HbA1c level from baseline compared with control group. Secondary outcomes were amount of time spent in hypoglycemia and hyperglycemia.

Data Extraction

The data from individual study were abstracted, The data recorded were the year of publication, country, study design, outcome measures, duration of study, sample size, types of CGM.

Methodology Quality Assessment

The methodological quality of each study was assessed using Maastricht Amsterdam scale[15] which has been developed based on the scale of Jadad *et al*.[16] and the Delphi list[17]. These 12 items evaluated internal validity of the study results. Each item has a rating scale of "yes", "no", or

"unsure". Studies that met at least 6 of 12 quality criteria were of high quality. Those scoring less than six of the criteria were of low quality or having high risk of bias.

RESULTS AND DISCUSSION

Literature Search

The primary search by electronic databases identified 180 citations. After screening the abstracts, 19 trials were found as randomized controlled trials. Among them, five trials met prespecified criteria and were included in the review[18-22]. The result of literature search is shown in Figure 1. Three out of five studies are regarded as high quality papers with score ≥ 6 (Table 1).

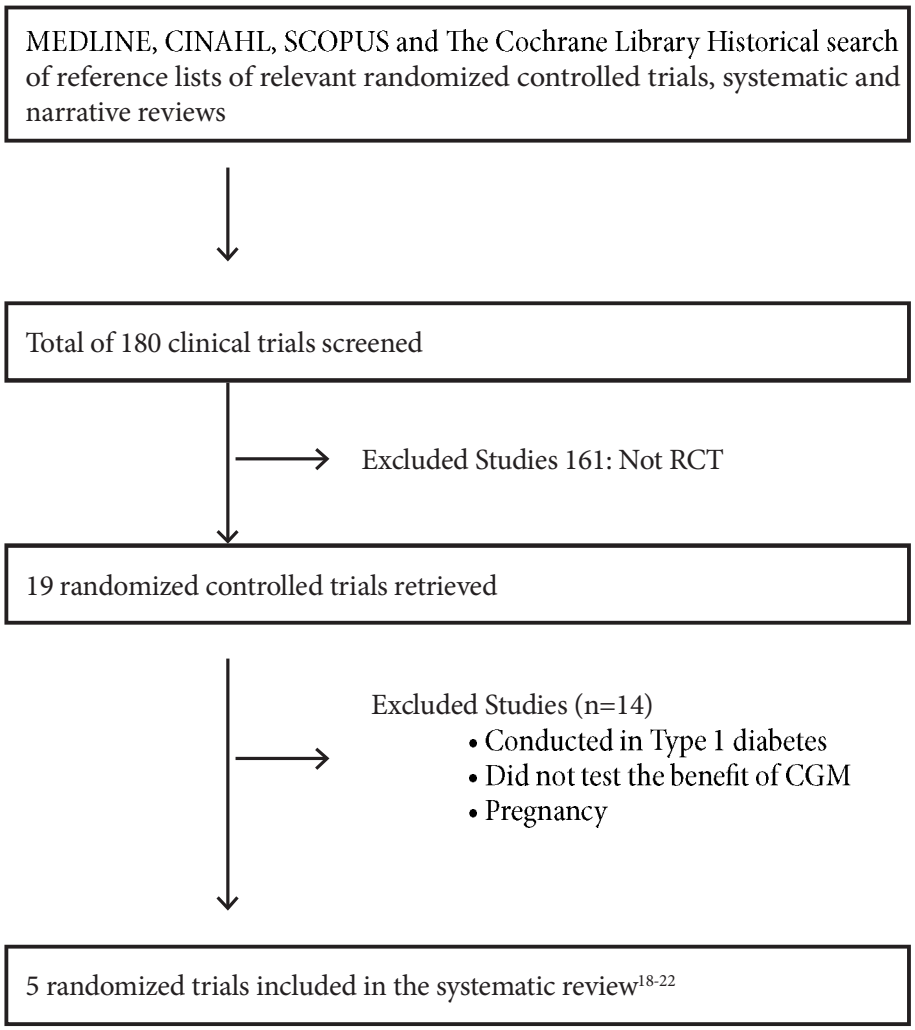

Figure 1. Result of systematic literature search

Table 1. Methodological quality assessment (Maastricht-Amsterdam scale)

	Yoo[22]	Cosson[20]	Ehrhardt[19]	Vigersky[18]	Allen[21]
Randomization adequate	+	+	?	?	+
Treatment allocation concealed	+	?	?	?	+
Patient blinded	-	-	-	-	-
Care provider blinded	-	-	-	-	-
Outcome assessor blinded	-	-	-	-	-
Drop-out rate acceptable	+	?	?	?	+
Intention-to-treat analysis	-	?	+	+	?
Free from selective outcome reporting	+	+	+	+	+
Groups similar at baseline	+	+	+	+	+
Co-intervention avoided or similar	+	+	+	+	+
Compliance acceptable	?	+	?	?	?
Timing of the outcome assessment similar	+	+	+	+	+
Total Score	7	6	5	5	7

+ = Yes, - = No, ? = Unsure

Characteristics of the selected studies

The characteristics of included trials are summarized in Table 2. There was a study which analyzed separately for two follow-up periods and presented the results in two separated papers[18,19]. This study was taken into account as two trials with different follow up results. Among five trials, only one trial was multi-centered study[20]. Three trials were performed in the USA[18,19,21] and the other two were in Korea[22] and France[20]. One study conducted to test the effects of a counseling intervention using continuous glucose monitoring system feedback on physical activity self-efficacy, physical activity levels and physiological variables and HbA1c was a secondary outcome. In this study, CGM group was compared with usual care (not known with SMBG or not)[21]. The remaining studies compared CGM use with SMBG use. The two studies were performed in T2DM patients who were not treated with prandial insulin[18,19] and the other two included participants treated with either anti diabetic agents or insulin injections[20,22]. One studied patients treated with no insulin[21].

Table 2. Characteristics of included studies

Study	Country	Duration	Number of subjects	Intervention	Primary Outcome	Secondary Outcomes
Vigersky *et al.*[18] (2012)	USA	52 weeks	100 I: 50 C:50	RT-CGM (DexCom SEVEN) vs. SMBG	• A1C	• Blood glucose assessed by RT-CGM and SMBG • Weight • Blood pressure • Change in diabetes-related stress
Ehrhardt *et al.*[19] (2011)	USA	3 months	100 I:50 C:50	RT-CGM (DexCom SEVEN) vs. SMBG	• A1C	• Change in mean and distribution of blood glucose • Weight • Blood Pressure • Diabetes – related stress
Cosson *et al.*[20] (2009)	France	3 months	25 I:11 C:14	RT-CGM (The GlucoDay system) vs. SMBG	• A1C	• Compare the 48 h CGM data at baseline with those obtained after 3 months: - Glucose control - Glucose variability - Hypoglycemia
Allen *et al.*[21] (2008)	USA	8 weeks	46 I:21 C:25	RT-CGM vs. SMBG	• Physical activity self efficacy	• Physical activity levels • Blood pressure • Body mass index • A1C

Table 2. Characteristics of included studies

Study	Country	Duration	Number of subjects	Intervention	Primary Outcome	Secondary Outcomes
Yoo *et al.*[22] (2008)	Korea	3 months	57 I: 29 C:28	RT-CGM (Guardian RT) vs. SMBG	• A1C	• Fasting blood glucose • Post prandial 2 h blood glucose • Lipid profiles • Weight • Waist circumference • Body mass index

I= Intervention, C= Control, RT- CGM = Real Time Continuous Glucose Monitoring, RCT= Randomized Controlled Trial

Table 3. Summary of HbA1c between intervention and control groups

Study	Intervention			Control			p-value‡
	n	Baseline (%)	Change (%)	n	Baseline (%)	Change (%)	
Yoo (2008)	29	9.1 ± 1.0	NA	28	8.7 ± 0.7	NA	0.01
Cosson (2009)	11	9.22 ± 0.99	- 0.63± 0.34	14	9.07 ± 0.60	- 0.31 ± 0.29	NA
Ehrhardt (2011)	50	8.4 ± 1.3	- 1.0 ± 1.1	50	8.2 ± 1.1	- 0.5 ± 0.8	0.006
Vigersky (2012)	50	8.4 ± 1.3	- 0.8 ± 1.5	50	8.2 ± 1.1	- 0.2 ± 1.3	<0.0001
Allen (2008)	21	8.9 ± 1.15	- 1.16 ± 1.04	25	8.4 ± 1.06	- 0.32 ± 1.02	<0.05

NA – Not available, ‡ P value for change score between intervention and control groups

Main Outcome

HbA1c

All five studies that showed the effectiveness of CGM in type 2 diabetes gave the significant difference from baseline and four studies reported significant difference in change score between groups[18,19,21,22] (Table 3). The study by Cosson et al. did not analyzed the between group difference. Two studies with different follow up periods revealed significant difference between groups both in short-term and long-term periods[18,19] suggesting the lasting effecting of CGM use beyond the active intervention phase. Vigersky (2012) showed that subjects who wore the sensor for ≥ 48 days had the greatest drop in mean, unadjusted A1C compared with those who wore it for < 48 days (-1.31% vs. - 0.76%)[18].

Secondary Outcomes

In type 2 diabetes, two studies reported the amount of time spent at hypoglycemia and hyperglycemia[20,22]. One study presented no significant result in the outcome of the amount of time spent at hypoglycemia (defined as < 70 mg/dL) and also the amount of time spent at hyperglycemia (defined as > 150 mg/dL)[20]. Another study also showed no significant difference in the amount of time spent at hypoglycemia (defined as < 60 mg/dL), but the amount of time spent at hyperglycemia (defined as > 250 mg/dL) was significantly reduced from 17.8% at baseline to 8.98% (P=0.001) in CGMS group[22].

Table 4. Secondary outcomes

Studies	Experimental	Control	Level of Significance
	Amount of time spent at Hypoglycemia (%)		
Cosson 2006 (<70 mg/dL)	3 ± 4	7 ± 9	NS
Yoo 2008 (< 60 mg/dL)	Mildly increase No reports of clinically symptomatic hypoglycemia	NA	NS
	Amount of time spent at Hyperglycemia (%)		
Cosson 2006 (> 150 mg/dL)	58 ± 27	39 ± 24	NS
Yoo 2008 (> 250 mg/dL)	17.8 % to 8.98 %	NA	NA

NA – Not Available , NS – Not significant

DISCUSSION

Hypoglycemia can cause severe morbidity and sometimes death, usually depending on its severity or duration. In type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) reported 62 severe hypoglycemic episodes per 100 patient-years[23]. However, the true risk may be higher in clinical practice because patients at high

risk for severe hypoglycemia were excluded from the study. In type 2 diabetes, severe hypoglycemia appears to be much less common, but when T2DM patients receive insulin, they may become as susceptible to hypoglycemia as T1DM patients. Using the CGMS in type 2 diabetes achieved the detection of numerous hypoglycemia which cannot be identified by SMBG. That opens the possibility for treatment adjustment and improvement in metabolic control[24]. Continuous glucose monitoring can detect nocturnal hypoglycemia in patients with primary adrenal insufficiency and hence prevent an impaired quality of life and serious adverse effects in these patients[25]. Our review also suggests that the reduction in HbA1c level by CGM use can be accompanied by low risk of hypoglycemia since the amount of time spent at hypoglycemia was reported to be lesser than the control group.

The American Diabetes Association (ADA) recommends SMBG as an essential aspect of diabetes management in insulin-treated patients and a desirable aspect in non-insulin treated patients with diabetes[1]. However, there is controversy over the benefit of SMBG in those patients with T2DM who are not taking insulin. Like SMBG, the role of CGM use in non-insulin treated Type 2 diabetes is not established yet. Using insulin can predispose to high risk of hypoglycemia whereas oral agents particularly metformin, thiazolidinediones, and DPP-4 inhibitors are not prone to result in hypoglycemia. Therefore, the benefit of SMBG and CGM is seemed to provide limited value in non-insulin treated T2DM. In our review, participants from the two studies by Ehrhardt[19] and Vigersky et al.[18] did not use prandial insulin and participants from the study by Allen et al. did not use any type of insulin at all. These three studies reported the significant difference in HbA1c reduction in favor of CGM group. In accordance with the result, CGM use in non-insulin treated T2DM may provide benefit.

There are several CGM devices, which differ in terms of sensor type, mechanism and location, frequency of testing and data presentation (retrospective and real time). In retrospective CGM (r-CGM), patients have to use the device for 48 or 72 consecutive hours and the data will then be downloaded by health care professionals. In real-time CGM (RT-CGM) which is fitted with alarm to warn the users in case of hypoglycemia or hyperglycemia, the device allows the patients to know the glucose data every five minutes and provides day-to-day information on diabetes. In this case, patients are needed to be educated about the disease management, application of the device and interpretation of the glucose data in order to manage themselves by CGMS data. In our systematic review, three studies[18,19,22] used RT-CGM and two studies[20,21] analysed in a retrospective manner. Significant results were seen in all Rt-CGM studies[18,19,22] and one r-CGM study[21]. Since the real-time CGM is a 'patient-centric' technology and comprises the co-operation of patients themselves in the disease management, RT-CGM seems to be more effective than retrospective ones and the positive result of our review seems to be more influenced by Rt-CGM. The types of data presentation in CGM use (real-time or retrospective) are a good point to focus in future studies.

The first randomized controlled trial using a real-time glucose sensor (the Gluco Watch) was conducted by the DirecNet study group[26]. In that study, there was no significant improvement in HbA1c levels in the group using the GlucoWatch compared with the control group. This RT-CGM device (Gluco Watch) is then discontinued for some technical and compliance problems in 2007. However, since then, there have been several studies regarding the effectiveness of RT-CGM, apart from GlucoWatch, in improving HbA1c levels, mainly for type 1 diabetes[27,28,29], although there have been few studies in type 2 diabetes[28,30]. The participants in the three

studies[27,28,29] used the RT-CGM continuously for nearly three months and the average reduction in HbA1c (mean ± SD) was 0.4± 0.05%[28], 0.3%[29], and 1.0±1.1%[27] respectively. In our review, participants from three studies used the RT-CGM intermittently within the intervention period. Subjects from the two papers by Ehrhardt *et al*.[19] and Vigersky *et al*.[18], completed four cycles of 3 weeks (2 weeks of RT-CGM and 1 week off). Patients in the study by Yoo et al.[22] performed monthly RT-CGM (3 days last at a time) for three months. According to our result, intermittent use of RT-CGM can be a novel way to provide benefit in T2DM.

It was already known that in addition to pharmacological intervention, lifestyle intervention also plays a major role in the management of type 2 diabetes. The significant improvement in blood glucose and lipid profile of patients with lifestyle intervention was noted after one year compared with those without this intervention, suggesting the value of lifestyle intervention in T2DM management[4]. Continuous glucose monitoring can provide immediate information to adjust the dosages of medication, and/or to manage the dietary or exercise regimen, which could lead to better lifestyle for diabetes patients. In our review, two studies[20,22] allowed patients to adjust the medication on the basis of the CGM results whereas CGMS or SMBG data were not applied to adjust medication in other three studies[18,19,21]. This finding suggests that the glycemic values from CGM devices allowed the care provider or patient to notice the glycemic effects of meals or exercise and able to manage lifestyle skills that results in better glycemic control for patients with T2DM. Moreover, from the glycemic values displayed by CGM devices, patients can be easily educated about the effects of their medication and lifestyle on diabetes. Therefore, continuous glucose monitoring can enhance the process of pharmacological intervention and non-pharmacological intervention as well.

CONCLUSION

Recent evidence shows that the use of CGM in type 2 diabetic adults may be beneficial over SMBG use. However, in order to support this evidence, quantitative evaluation of the studies like meta-analysis will be needed. The evidence for the effectiveness of CGMS on pregnancy, critically ill patients and infants is still required. Moreover, more randomized controlled trials with better quality are demanded to provide the evidence stronger for the effectiveness of CGM use in diabetes.

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