

Comparative Analysis of the Efficacy of Continuous Glucose Monitoring and Self-Monitoring of Blood Glucose in Type 1 Diabetes Mellitus

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Abstract

Background:

Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) have been proven effective in improving hemoglobin A1c (HbA1c) and in reducing hypoglycemia in patients with type 1 diabetes mellitus (T1DM). It is not clear, however, if CGM provides further efficacy and safety benefits beyond SMBG in the management of T1DM.

Methods:

MEDLINE (1966–November 2009), COCHRANE REGISTRY (all years), and EMBASE (1980–November 2009), and article bibliographies were searched for randomized controlled trials (RCTs) investigating the use of CGM in patients with T1DM, with clinical outcomes, including HbA1c and hypoglycemia and/or hyperglycemia.

Results:

Fourteen RCTs met eligibility criteria [$n = 1188$ patients, 97.4% with T1DM, age 29.0 ± 14.3 years, diabetes duration 11.7 ± 7.0 years, and baseline HbA1c $8.3 \pm 0.8\%$ (mean \pm standard deviation)]. Compared with SMBG, the use of CGM was associated with a greater reduction in HbA1c [-0.3% (confidence interval: 0.4, -0.2), $p < .0001$]. The number of hypoglycemic events was not significantly different between the CGM and SMBG groups (0.52 ± 0.52 versus 0.52 ± 0.63 events/day, $p = .5$), but duration of hypoglycemia was shorter for the CGM group (75 ± 39 versus 89 ± 19 min/day), with an incremental reduction of hypoglycemia duration of -15.2 min/day, $p < .0001$. Continuous glucose monitoring also resulted in a shorter duration of hyperglycemia than SMBG (172 ± 125 versus 217 ± 152 min/day, $p = .04$).

Conclusions:

The use of CGM is associated with improvement in metabolic control in T1DM, with significant short- and long-term reductions in HbA1c and reduction in the duration of periods of hypoglycemia and hyperglycemia versus SMBG.

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (CI) confidence interval, (HbA1c) hemoglobin A1c, (RCT) randomized controlled trial, (SMBG) self-monitoring of blood glucose, (T1DM) type 1 diabetes mellitus

Keywords: glucose monitoring, meta-analysis, monitoring device, type 1 diabetes

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Introduction

Diabetes is the most important chronic metabolic illness, accounting for the majority of blindness, kidney failure, and nontraumatic amputations of the lower extremities.¹⁻³ It is well established that improved glycemic control can prevent and reduce the progression of microvascular^{1,2} and macrovascular⁴ complications. Self-monitoring of blood glucose (SMBG) is the most important tool in implementing tight glucose control in diabetes patients. Despite frequent blood glucose (BG) measurements throughout the day, SMBG is associated with gaps in glycemic control and the inability to follow glycemic trends to prevent hypoglycemia.^{5,6} To overcome this limitation, continuous glucose monitoring (CGM) has been introduced and provides more detailed information on glycemic control than SMBG.⁷

Two types of CGM devices are commercially available—retrospective and real-time. Retrospective CGM is a Holter-type device that measures interstitial glucose levels and stores the information during a period of 48 to 72 h to facilitate insulin adjustment, recognition of daily BG swings, and prevention of hypoglycemia.⁸ Its retrospective nature, however, represents a significant limitation with patients unable to react to BG changes before they reach abnormal ranges.^{7,9-13} In contrast, real-time CGM technology provides current BG estimates and direction and magnitude of glucose trends, allowing patients to take action that might reduce glycemic excursions outside a target range.⁸ Real-time CGM technology has been shown to facilitate glycemic control and reduce hypoglycemia in insulin-treated patients.^{5,6,8,14}

Comparison studies on the efficacy and clinical benefits of CGM devices and SMBG have produced mixed results, in part, due to small sample size and variability across studies, including differences in age of subjects, type of CGM utilized (retrospective versus real time), and duration of follow-up. Two previous meta-analyses reported no significant difference in improving glycemic control between CGM and SMBG,^{15,16} with one focused solely on T1DM¹⁶ while the other was limited to retrospective data because it was performed prior real-time CGM availability.¹⁵ Accordingly, this meta-analysis aims to determine (1) overall efficacy and safety of retrospective and real-time CGM and SMBG and (2) differences in glycemic control between real-time and retrospective CGM patients with type 1 diabetes mellitus (T1DM) across the age continuum.

Material and Methods

Data Sources and Searches

This systematic review and meta-analysis was conducted in accordance with the QUOROM (Quality of Reporting of Meta-Analyses) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements.^{17,18} We searched electronic databases for relevant articles: MEDLINE (1966–November 2009), EMBASE (1980–November 2009), and the Cochrane Registry (all years). We used a combination of medical subject headings and text terms that included “diabetes mellitus,” “continuous glucose monitoring,” and/or “continuous glucose monitoring system,” with the following limits activated: “humans,” “randomized controlled trials,” and “English language.”

Study Selection

Selection criteria included English language randomized controlled trials (RCTs), subjects with T1DM, use of subcutaneous CGM in outpatient setting, and reporting changes in hemoglobin A1c (HbA1c) and/or hyperglycemia and hypoglycemia. Randomized controlled trials focusing on medication or psychological effects, evaluating nutritional or exercise-related interventions, and including pregnant patients, oral antidiabetic agents, or inpatient settings were excluded. Abstracts were reviewed independently by two authors (Baraka Floyd and Stephanie Hall) based on the inclusion and exclusion criteria without the use of masking.¹⁹

Data Extraction and Quality Assessment

Authors rated studies for quality using the Jadad score²⁰ and extracted study characteristics, subjects' clinical demographics, and outcome measures using a standardized data abstraction instrument. The primary outcome measure was the absolute HbA1c change from baseline to study end. Secondary outcome measures included HbA1c change during intervention, hypoglycemia frequency (BG <70 mg/dl), durations of hypoglycemia (min/day), profound hypoglycemia (min/day BG ≤55 mg/dl), normoglycemia (min/day BG 71–180 mg/dl), and hyperglycemia (min/day BG ≥250 mg/dl).

Data Synthesis and Analysis

For each study, we calculated weighted mean difference for primary and secondary outcome measures with a 95% confidence interval (CI). We pooled individual study

results using both fixed and random effects models, the latter incorporating inverse variance according to methods developed by DerSimonian and Laird.²¹ We used standard approaches to sensitivity analysis in subgroups defined by duration of follow-up, age group, use of real-time or retrospective CGM devices, and use of an intermittent CGM scheme (72 h increments with varying rest periods) or continuous monitoring scheme (24 h/day ≥ 6 days/week) to assess for potential confounding. We explored qualitative and quantitative heterogeneity using Chi-square tests, with a significance value of $p < .05$.

We also assessed publication bias using Begg's funnel plot method.^{22,23} Final results are reported using random effects meta-analysis unless no quantitative heterogeneity was present.

Results

A total of 96 studies were identified electronically; of them, 25 studies were potentially eligible and retrieved for review. Sixteen studies met eligibility criteria and were included in the meta-analysis (Figure 1). Overall quality

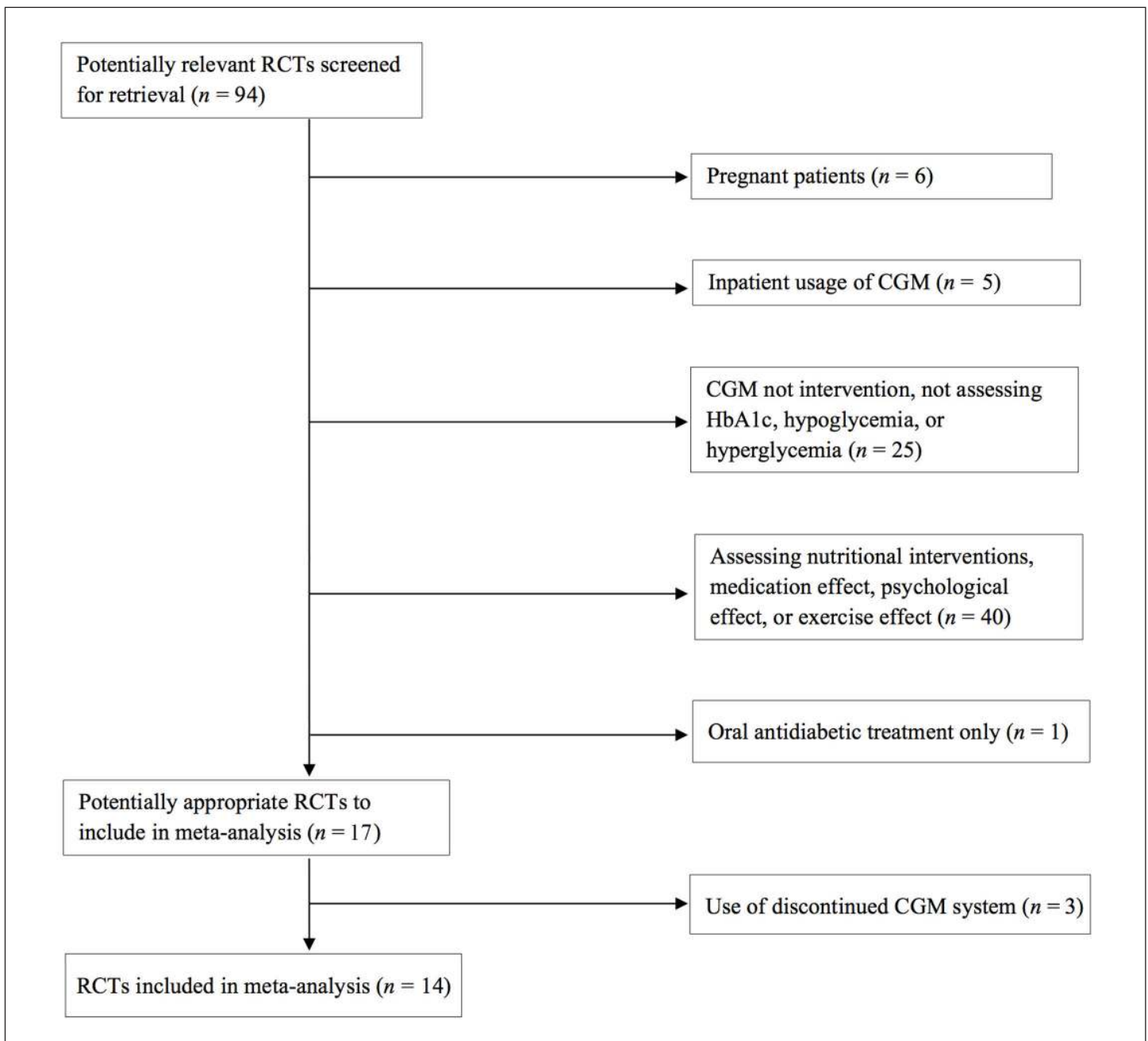


Figure 1. Study selection process.

of selected studies was good, with a median Jadad score of 3 (range 1 to 3). We found no significant evidence of quantitative heterogeneity (Figure 2) or publication bias via the Begg's funnel plot.

The pooled population comprised 1188 participants, 97.4% with T1DM, mean age of 29.0 ± 14.3 years, diabetes duration of 11.7 ± 7.0 years, and baseline HbA1c of $8.3\% \pm 0.8\%$ (mean \pm standard deviation). Eight studies utilized real-time CGM, and eight used retrospective CGM (Table 1). Compared with SMBG, CGM was associated with a significant HbA1c reduction [Δ HbA1c $-0.5\% \pm 0.5\%$ ($p = .002$) versus $-0.2\% \pm 0.3\%$ ($p = .006$); $p = .006$ between groups] and an incremental HbA1c reduction of 0.3% ($-0.3, -0.2$), $p < .0001$ (Table 2, Figure 2).

The hypoglycemia frequency was not significantly different between the CGM and SMBG groups; however, the

duration of hypoglycemia was shorter for the CGM group, with CGM producing an incremental reduction of hypoglycemia duration of -15.2 min/day, $p < .0001$. In addition, the duration of profound hypoglycemia and hyperglycemia were significantly shorter in the CGM group compared with the SMBG group (Table 2).

Duration of Glucose Monitoring and Glycemic Control

Improvements in HbA1c after 4–8 weeks of intervention were greater with CGM (Δ HbA1c $-0.5\% \pm 0.2\%$, $p = .03$) than SMBG (Δ HbA1c $-0.3\% \pm 0.2\%$, $p = .04$). Changes in HbA1c from baseline between CGM and SMBG were not significantly different ($p = .1$). Continuous glucose monitoring was associated with an incremental reduction of HbA1c compared with SMBG. After 12 to 16 weeks of follow-up, CGM was associated with a significant reduction in HbA1c from baseline of $-0.6\% \pm 0.5\%$, $p = .01$,

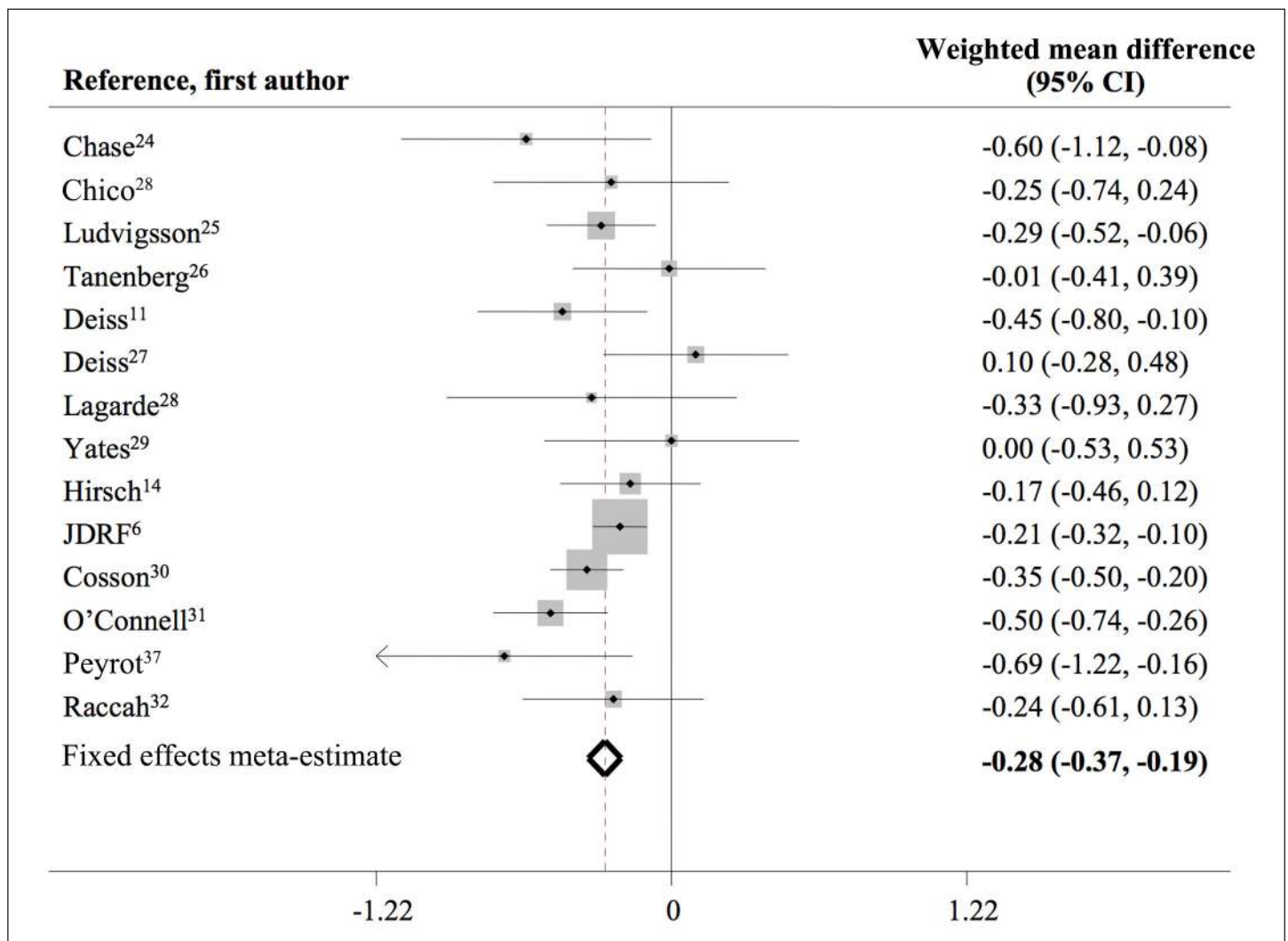


Figure 2. Forrest plot for changes in HbA1c (%) from baseline to end of study among different studies

greater than the use of SMBG, which resulted in ΔHbA1c from baseline of $-0.3\% \pm 0.4\%$, $p = .02$, with a statistically significant difference between groups [-0.3% ($-0.3, -0.2$), $p < .0001$]. Long-term studies of 24–26 weeks reported ΔHbA1c from baseline of $-0.4\% \pm 0.3\%$ ($p = .05$) with CGM and $-0.2\% \pm 0.2\%$ ($p = .04$) with SMBG but were not statistically different ($p = .1$). In long-term studies, the incremental HbA1c reduction estimated by WMD between groups was -0.2% ($-0.3, -0.1$), $p < .0001$ (Table 2).

Monitoring Scheme, Type of Continuous Glucose Monitoring, and Glycemic Control

Continuous use of CGM was associated with significant improvement in glycemic control versus SMBG [ΔHbA1c $-0.6\% \pm 0.5\%$ ($p = .02$) versus $-0.2\% \pm 0.4\%$ ($p = .06$); $p = .03$ between groups], with an incremental HbA1c reduction between CGM and SMBG of -0.4% ($-0.5, -0.2$), $p < .0001$. Compared with SMBG, intermittent use of CGM also resulted in significantly better glycemic control [ΔHbA1c $-0.6\% \pm 0.4\%$ ($p = .03$) versus $-0.3\% \pm 0.2\%$

($p = .02$); $p = .004$ between groups], producing an incremental HbA1c reduction over SMBG of -0.3% ($-0.4, -0.2$), $p < .0001$. The use of retrospective CGM was also associated with a greater reduction in HbA1c levels than SMBG [ΔHbA1c $-0.5\% \pm 0.4\%$ ($p = .04$) versus $-0.3\% \pm 0.3\%$ ($p = .03$)], with no significant difference between groups ($p = .06$). However, the incremental reduction in HbA1c over time between retrospective CGM and SMBG was significant at -0.3% ($-0.4, -0.2$), $p < .0001$. For real-time CGM, differences in HbA1c levels from baseline were significantly greater than SMBG [ΔHbA1c $-0.4\% \pm 0.5\%$ ($p = .02$) versus $-0.2\% \pm 0.4\%$ ($p = .06$); $p = .03$ between groups], with an incremental HbA1c reduction with real-time CGM when compared with SMBG of -0.3% ($-0.5, -0.2$), $p < .0001$ (Table 2).

Age and Continuous Glucose Monitoring

We performed subgroup analyses to determine the impact of age of study patients on glycemic control. Studies were divided into two groups, mean age under

Reference, first author	Number of patients	Age, years	Diabetes duration, years	% CSII	Baseline HbA1c	CGM frequency	SMBG frequency
Chase ^{24b}	11	13.4 ± 13.6	6.2 ± 9.9	54.6%	9.5 ± 0.95	72 h/5 days	Not reported
Chico ^{33b}	75	38.7 ± 11	19 ± 11	0%	8.2 ± 1.5	72 h/3 months	Not reported
Ludvigsson ^{25b}	32	12.5 ± 3.3	7.0 ± 3.9	51.9%	7.7 ± 0.95	72 h/2 weeks	≥2x/day + 7-point SMBG/week
Tanenbergs ^{26b}	109	44.3 ± 11.4	19.9 ± 9.9	45.8%	9.1 ± 1.1	72 h/3 months	≥4x/day
Deiss ^{11c}	162	26.8 ± 13.6	Not reported	48.1%	9.6 ± 1.1	Continuous or 72 h/2 weeks	Not reported
Deiss ^{27b}	30	11.4 ± 13.6	2.2 ± 9.9	Not reported	8.1 ± 1.1	72 h/3 months	Not reported
Lagarde ^{28b}	27	11.4 ± 13.6	4.4 ± 9.9	70.4%	7.85 ± 1.3	72 h/2 months	≥4x/day + 2 AM/week
Yates ^{29b}	36	14.4 ± 13.6	Not reported	47%	7.9 ± 0.85	Eight 72 h periods	4–6x/day
Hirsch ^{14c}	138	33.1 ± 15.5	18.7 ± 11.6	100%	8.45 ± 0.7	Continuous	Not reported
JDRF ^{6c}	322	24.4 ± 5.5	12.5 ± 6	79.7%	7.85 ± 0.6	Continuous	≥4x/day
Cosson ^{30b}	41	53.8 ± 13.6	15.9 ± 9.9	11.1%	9.05 ± 1.05	Two 48 h periods	Not reported
O’Connell ^{31c}	62	23.2 ± 8.4	10.2 ± 7.4	100%	8.4 ± 1.65	Continuous	≥4x/day
Peyrot ^{36c}	28	47.2 ± 13.2	25 ± 12.6	100%	8.6 ± 1.0	Continuous	Not reported
Raccan ^{32c}	115	28.5 ± 15.9	11.8 ± 8.9	100%	9.2 ± 1.24	Continuous	≥3x/day

^a Continuous, wearing the device ≥6 days/week or 70% of the time; % CSII, percentage of patients using continuous subcutaneous insulin infusion.
^b Retrospective CGM.
^c Real-time CGM.

Table 2. Hemoglobin A1c Outcomes and Number and Duration of Hypoglycemic, Hyperglycemic, and Normoglycemic Events^a

Outcome	SMBG				CGM				P value CGM versus SMBG	Meta-estimate	
	HbA1c baseline	HbA1c study end	Δ HbA1c from baseline	P value Δ HbA1c from baseline	HbA1c baseline	HbA1c study end	Δ HbA1c from baseline	P value Δ HbA1c from baseline		Δ HbA1c from baseline (%) [95% CI] ^b	P value absolute Δ HbA1c from baseline
All studies, <i>n</i> = 14	8.3 ± 0.7	8.0 ± 0.6	-0.2 ± 0.3	0.006	8.3 ± 0.8	7.8 ± 0.6	-0.5 ± 0.5	0.002	0.006	-0.3 [-0.3, -0.2]	<0.0001
Duration of intervention											
4–8 weeks ^c	8.9 ± 0.7	8.6 ± 0.8	-0.3 ± 0.2	0.04	9.0 ± 0.8	8.6 ± 0.7	-0.5 ± 0.2	0.03	0.1	-0.2 [-0.3, 0.01]	0.06
12–16 weeks ^c	8.2 ± 0.7	7.9 ± 0.6	-0.3 ± 0.4	0.02	8.3 ± 0.8	7.7 ± 0.6	-0.6 ± 0.5	0.01	0.01	-0.3 [-0.3, -0.2]	<0.0001
24–26 weeks ^c	8.0 ± 0.6	7.8 ± 0.5	-0.2 ± 0.2	0.04	8.1 ± 0.5	7.7 ± 0.4	-0.4 ± 0.3	0.05	0.1	-0.2 [-0.3, -0.1]	<0.0001
Age group (years)											
<25 ^c	7.8 ± 0.6	7.8 ± 0.4	-0.1 ± 0.2	0.003	7.8 ± 0.9	7.5 ± 0.6	-0.3 ± 0.4	0.05	0.04	-0.2 [-0.3, -0.2]	<0.0001
≥25 ^c	8.9 ± 0.6	8.5 ± 0.8	-0.4 ± 0.2	0.2	9.0 ± 0.4	8.3 ± 0.6	-0.7 ± 0.4	0.02	0.01	-0.3 [-0.4, -0.2]	<0.0001
Monitoring scheme											
Intermittent ^c	8.7 ± 0.6	8.4 ± 0.6	-0.3 ± 0.2	0.02	8.7 ± 0.8	8.2 ± 0.6	-0.6 ± 0.4	0.03	0.04	-0.3 [-0.4, -0.2]	<0.0001
Continuous ^c	8.0 ± 0.8	7.8 ± 0.4	-0.2 ± 0.4	0.06	8.0 ± 0.8	7.6 ± 0.6	-0.6 ± 0.5	0.02	0.03	-0.4 [-0.5, -0.2]	<0.0001
Type of CGM											
Retrospective CGM ^c	8.6 ± 0.5	8.3 ± 0.5	-0.3 ± 0.3	0.03	8.7 ± 0.8	8.1 ± 0.5	-0.5 ± 0.4	0.04	0.06	-0.3 [-0.4, -0.2]	<0.0001
Real-time CGM ^c	8.0 ± 0.8	7.9 ± 0.7	-0.2 ± 0.4	0.06	8.0 ± 0.8	7.6 ± 0.7	-0.4 ± 0.5	0.02	0.03	-0.3 [-0.5, -0.2]	<0.0001
Outcome	Mean SMBG value				Mean CGM value				P value CGM versus SMBG	P value weighted mean difference [95% CI] ^d	P value weighted mean difference
Hypoglycemic events (episodes/day BG ≤ 70 mg/dl) ^c	0.52 ± 0.63				0.52 ± 0.52				0.5	0.01 [-0.21, 0.23]	0.1
Duration of hypoglycemia (min/day BG ≤ 80 mg/dl) ^c	89.53 ± 19.22				75.34 ± 39.21				0.1	-15.2 [-20.3, -10.1]	<0.0001
Duration of profound hypoglycemia (min/day BG ≤ 55 mg/dl) ^c	30.63 ± 14.09				27.65 ± 31.10				0.2	-8.8 [-11.8, -5.7]	<0.0001
Duration of normoglycemia (min/day BG = 71–180 mg/dl) ^e	751.44 ± 263.67				810.06 ± 286.40				0.05	67.17 [24.06, 107.49]	<0.0001
Duration of hyperglycemia (min/day BG ≥ 240 mg/dl) ^e	217.53 ± 152.94				172.26 ± 125.90				0.04	-45.3 [-65.5, -25.0]	<0.0001

^a Data are weighted mean ± standard error of the mean.

^b Meta-estimate is the absolute Δ HbA1c generated from the difference between end of study HbA1c and baseline HbA1c for CGM and SMBG groups where the value for each study is weighted by the inverse variance.

^c Based on random effects meta-analysis.

^d Weighted mean difference is generated from the difference between the CGM and SMBG groups weighted by inverse variance.

^e Based on fixed effects meta-analysis.

25 years and over 25 years. In patients <25 years, CGM resulted in a significantly greater HbA1c reduction than SMBG [$-0.3\% \pm 0.4\%$ ($p = .05$) versus $-0.1\% \pm 0.2\%$ ($p = .003$); $p = .04$ between groups], with an incremental HbA1c reduction of -0.2% ($-0.3, -0.2$), $p < .0001$. Similarly, in patients ≥ 25 years of age, CGM resulted in greater improvement in glycemic control than SMBG [$\Delta\text{HbA1c } -0.7\% \pm 0.4\%$ ($p = .02$) versus $-0.4\% \pm 0.2\%$ ($p = .2$); $p = .01$ between groups], producing an incremental HbA1c reduction over SMBG of -0.3% ($-0.4, -0.2$), $p < .0001$ (Table 2).

Discussion

The results of this meta-analysis indicate that the use of CGM and SMBG are associated with improved glycemic control, as evidenced by HbA1c reduction from baseline and that both retrospective and real-time CGM are associated with significant incremental benefit in HbA1c reduction over SMBG. The use of real-time CGM technology³⁷ results in slightly greater reductions in HbA1c levels than retrospective CGM. Greater benefits of CGM over SMBG were observed in studies of more than 12 weeks of intervention and in subjects >25 years old, with the incremental benefit of CGM in patients <25 years old just below the level of clinical significance (0.3%). While continuous use of CGM was associated with the greatest incremental benefit, intermittent CGM use also produced a clinically significant HbA1c reduction. In addition, CGM resulted in less time spent in hypoglycemic ranges than SMBG, but there was no difference in the hypoglycemia frequency. Continuous glucose monitoring was also associated with a reduction in time spent in hyperglycemic ranges and in greater time spent within normoglycemia, suggesting that more detailed information provided by CGM on glucose trends attenuates glycemic derangements and glucose swings.

The duration of CGM monitoring is an important factor in improving glycemic control. Studies using CGM for less than 8 weeks resulted in no significant improvement in HbA1c from baseline compared with SMBG. The incremental benefit in HbA1c reduction with CGM use was observed in most of the studies of 12–16 and 24–26 weeks' duration. Real-time CGM provided a benefit over retrospective technology; however, the use of retrospective CGM was also associated with improved HbA1c from baseline over SMBG. In addition, we observed benefits with intermittent as well as continuous CGM use, indicating that even a small increase in the amount of information about glycemic changes is helpful. The mechanism for improved glycemic control with CGM

likely results from facilitating better planning of daily and supplemental insulin doses, ability of patients using CGM to take preemptive action for rising and falling BG levels, and avoidance of factors negatively affecting glycemic derangements over long-term periods.

Age of study population is an important factor in determining the efficacy of CGM. In patients younger than 25 years, CGM produces a small and nonsignificant incremental benefit in HbA1c reduction compared with SMBG,⁶ likely because of less compliance with using the device. Two studies have shown that the greatest benefit is in patients 25 years and over who are more likely to wear the device with increased frequency than the younger age group.^{6,35}

A key limitation of this meta-analysis is that only study-level data were available for analysis, requiring grouping by mean values of the entire study population, for which the values of individual patients may have been higher or lower than the study mean. We attempted to capture this information by reporting the CI for the meta-estimates. We found no significant quantitative heterogeneity in the evaluation of the primary outcome, but the meta-analyses for hypoglycemia frequency and hypoglycemia and profound hypoglycemia durations did show significant statistical heterogeneity. Heterogeneity for hypoglycemia frequency was explained by the type of CGM, while heterogeneity for hypoglycemia and profound hypoglycemia durations was explained by age. Finally, adherence, a known factor affecting treatment successes and failures in diabetes management,³⁵ could not be evaluated, as only two of the included studies provided a measure of adherence.

The Endocrine Society Clinical Practice Guideline Committee on the use of CGM has recommended against the use of this technology in the intensive care unit or operating room settings.³⁸ This recommendation was based on the limited available data related to accuracy and the concerns regarding potential danger in their use in guiding insulin administration in an acute-care setting. Several studies have reported on the accuracy of CGM in critically ill patients.^{39–41} Most of these studies included a small number of patients and limited their analysis to retrospective comparisons of a reference point-of-care value with CGM data.³⁸ The use of CGM may have an advantage over bedside point-of-care testing in that it has the potential to reduce the possibility of unknown hypoglycemic events that may occur between point-of-care measurements; however, some studies have raised concern on the accuracy of CGM at low BG levels

and limited correlation between CGM and both capillary and arterial samples when the BG is less than 81 mg/dl.⁴² Thus this technology must undergo larger and rigorous testing before it can be recommended for use in the hospital setting.

In summary, the results of this meta-analysis suggest that CGM is a useful clinical tool that is associated with clinically significant HbA1c reductions without an increase in hypoglycemic events. In addition, CGM provides information regarding the direction, magnitude, duration, frequency, and causes of BG excursions and helps identify periods of hypoglycemia and hyperglycemia. Evidence indicates that highly motivated and compliant patients are the best candidates for successful CGM implementation, with optimal results yielded if the sensor is worn at least 6 days per week.³⁵ The benefits of CGM in clinical practice are welcome, but long-term prospective RCTs are needed to evaluate the impact of CGM on the prevention of acute and chronic complications of diabetes.

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