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ARTICLE

Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis

Evelyn Teo[1] · Norasyikin Hassan[2] · Wilson Tam[1] · Serena Koh[1]

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Abstract

Aims/hypothesis The aim of this work was to assess the effectiveness of continuous glucose monitoring (CGM) vs self-monitoring of blood glucose (SMBG) in maintaining glycaemic control among people with type 1 diabetes mellitus.

Methods Cochrane Library, PubMed, Embase, CINAHL, Scopus, trial registries and grey literature were searched from 9 June 2011 until 22 December 2020 for RCTs comparing CGM intervention against SMBG control among the non-pregnant individuals with type 1 diabetes mellitus of all ages and both sexes on multiple daily injections or continuous subcutaneous insulin infusion with HbA_{1c} levels, severe hypoglycaemia and diabetic ketoacidosis (DKA) as outcomes. Studies also included any individual or caregiver-led CGM systems. Studies involving GlucoWatch were excluded. Risk of bias was appraised with Cochrane risk of bias tool. Meta-analysis and meta-regression were performed using Review Manager software and R software, respectively. Heterogeneity was evaluated using χ^2 and I^2 statistics. Overall effects and certainty of evidence were evaluated using Z statistic and GRADE (Grading of Recommendations, Assessment, Development and Evaluation) software.

Results Twenty-two studies, involving 2188 individuals with type 1 diabetes, were identified. Most studies had low risk of bias. Meta-analysis of 21 studies involving 2149 individuals revealed that CGM significantly decreased HbA_{1c} levels compared with SMBG (mean difference −2.46 mmol/mol [−0.23%] [95% CI −3.83, −1.08], $Z = 3.50$, p=0.0005), with larger effects experienced among higher baseline HbA_{1c} >64 mmol/mol (>8%) individuals (mean difference −4.67 mmol/mol [−0.43%] [95% CI −6.04, −3.30], $Z = 6.69$, p<0.00001). However, CGM had no influence on the number of severe hypoglycaemia (p=0.13) and DKA events (p=0.88). Certainty of evidence was moderate.

Conclusions/interpretation CGM is superior to SMBG in improving glycaemic control among individuals with type 1 diabetes in the community, especially in those with uncontrolled glycaemia. Individuals with type 1 diabetes with HbA_{1c} >64 mmol/mol (>8%) are most likely to benefit from CGM. Current findings could not confer a concrete conclusion on the effectiveness of CGM on DKA outcome as DKA incidences were rare. Current evidence is also limited to outpatient settings. Future research should evaluate the accuracy of CGM and the effectiveness of CGM across different age groups and insulin regimens as these remain unclear in this paper.

PROSPERO registration Registration no. CRD42020207042.

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Keywords Continuous glucose monitoring · Glycaemic control · Meta-analysis · Self-monitoring of blood glucose · Systematic review · Type 1 diabetes

✉ Evelyn Teo
e0203427@u.nus.edu

✉ Serena Koh
serena_koh@nus.edu.sg

[1] Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Republic of Singapore

[2] Nursing, Changi General Hospital, Singapore, Republic of Singapore

Abbreviations

CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DKA	Diabetic ketoacidosis
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
isCGM	Intermittent-scanning CGM

Research in context

What is already known about this subject?

- As diabetic complications remain the predominant cause of mortality among individuals with type 1 diabetes mellitus, it is imperative for these individuals to obtain adequate glycaemic control; a key method is through glucose monitoring
- Current reviews regarding the efficiency of continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG) in maintaining glycaemic control revealed methodological limitations

What is the key question?

- How effective is CGM vs SMBG in maintaining glycaemic control among people with type 1 diabetes?

What are the new findings?

- An individual's baseline HbA_{1c} levels significantly affected the effectiveness of CGM: compared with SMBG, individuals with poor glycaemic control (HbA_{1c} >64 mmol/mol [>8%]) using CGM experienced greater HbA_{1c} reduction than those with relatively adequate glycaemic control
- Results from meta-regression indicated that individuals with type 1 diabetes with HbA_{1c} >64 mmol/mol (>8%) would benefit most from CGM usage
- GRADE certainty of evidence was moderate, which further encourages clinicians to recommend CGM instead of SMBG for individuals with type 1 diabetes mellitus, especially those with poor glycaemic control

How might this impact on clinical practice in the foreseeable future?

- This study may offer a step forward in the future of diabetes care, especially among individuals with type 1 diabetes with poor glycaemic control (HbA_{1c} >64 mmol/mol [>8%]) as they are expected to benefit most from CGM

MARD	Mean absolute relative difference
MD	Mean difference
MDI	Multiple daily injections
P-CGM	Professional CGM
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
RevMan	Review Manager
RT-CGM	Real-time CGM
SMBG	Self-monitoring of blood glucose

Introduction

Type 1 diabetes is an emerging global epidemic with a rising incidence rate worldwide [1]. Despite its lower prevalence relative to type 2 diabetes, the annual economic cost of type 1 diabetes to the American healthcare system is significantly higher and costs approximately US$14.4 billion [2]. This economic burden could be attributed to rising insulin costs and costly type 1 diabetes complications [3]. These complications remain the predominant cause of death among the type 1 diabetes population [4]. The landmark DCCT trial reported that intensive insulin therapy delayed the onset of diabetic complications but tripled the risk of severe hypoglycaemia [5]. Since individuals with type 1 diabetes depend on such therapies for survival [6], the recommended goal is to maintain near-normal glucose levels [5]. The key to achieving such a glycaemic target is glucose monitoring [7].

In traditional self-monitoring of blood glucose (SMBG), a glucometer measures blood glucose levels in a capillary blood sample drawn via finger-pricking [8]. SMBG has some disadvantages: (1) it is user-dependent and cannot capture nocturnal and asymptomatic hypoglycaemia; (2) it cannot predict impending hypoglycaemia as the single-instant reading offers no information regarding the direction of changing glucose; and (3) this method is susceptible to user error, such as contaminated fingers [9]. Such limitations can be overcome by using continuous glucose monitoring (CGM) [10]. CGM involves a sensor inserted subcutaneously that automatically measures an individual's interstitial glucose levels around the clock [11]. CGM can predict impending hypoglycaemia and can alert and detect glycaemic fluctuations, based on glucose trends and retrospective and real-time data generated [12]. Three types of CGM systems exist: professional CGM (P-CGM); real-time CGM (RT-CGM); and intermittent-scanning CGM (isCGM). Each system varies slightly in terms of function.

HbA_{1c} remains the gold standard for assessing glycaemic control and is a surrogate marker for long-term diabetic complications risk [13]. However, reviews on the effectiveness of CGM in controlling this variable have revealed research gaps. Methodological limitations were found in ten similar reviews with meta-analysis [14–23] and findings in two were heavily limited by a small sample size [14, 18]. Studies have shown that a small number of included studies in a meta-analysis yields low statistical power which affects overall findings [24]. Moreover, only four of the reviews included a grey literature search [19–21, 23]. This may have contributed to inaccurate effect-size estimates and publication bias that skewed the meta-analysis results [25]. Furthermore, to our knowledge, only one review [20] included the latest CGM technology (i.e. isCGM) in its pooled analysis as it was only introduced in 2017 [26]. However, the search strategy in the review was heavily limited to only two bibliographic databases, thus introducing potential publication bias [27]. Additionally, the effectiveness of isCGM remains unclear in the review as subgroup analysis was not made possible when only one study utilised isCGM. We therefore undertook a systematic review to address the current research gaps. This review provides an update on the latest review by Langendam et al [19], which is the most similar to this review in terms of population, intervention, comparator and outcome. Findings from this review may benefit healthcare practitioners who are interested in diabetes management and current and future research. Currently, CGM research plays an integral part in artificial pancreas development, where a CGM sensor can automatically drive insulin delivery [28]. This paper aims to assess the effectiveness of CGM vs SMBG in maintaining glycaemic control in the type 1 diabetes population.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [29]. The present review was registered on the International prospective register of systematic reviews (PROSPERO registration no. CRD42020207042).

Data sources and searches

A three-step search strategy was employed. In the first step, five bibliographic databases (CINAHL, The Cochrane Library, Embase, PubMed and Scopus) were searched for relevant published journal articles. Relevant subject headings, keywords, and syntax rules were incorporated and truncated according to each database to ensure sensitivity [27]. Search terms used in this study are shown in electronic supplementary material (ESM) Table 1. The second step involved searching for relevant ongoing and unpublished trials in trial registries (CentreWatch, ClinicalTrials.gov, CENTRAL, ISRCTN registry and WHO ICTRP). Grey literature (ProQuest Dissertations and Theses Global) and diabetes-related specialist databases (ADA and International Journal of Diabetes and Clinical Research) were also searched. Last, reference lists of included trials, (systematic) reviews and meta-analyses were searched to obtain more studies. Authors of studies with missing information and inaccessible full text were contacted. Searches were conducted in English from 9 June 2011 onwards since this review is an update of another review [19] where the authors stopped their search on 8 June 2011. Date restriction was placed to prevent duplication of findings [27].

Eligibility criteria and study selection

Studies were included if they met the following criteria: (1) non-pregnant individuals of all ages and both sexes with type 1 diabetes mellitus who were on an intensive insulin therapy regimen (multiple daily injections [MDI] of insulin or continuous subcutaneous insulin infusion [CSII]); (2) any individual/caregiver-led CGM systems; (3) SMBG as control; (4) post-intervention HbA_{1c} level, severe hypoglycaemia event (defined as requiring assistance from another person to administer carbohydrate, glucagon or other resuscitative actions because of altered consciousness) and diabetic ketoacidosis (DKA) events as outcomes; and (5) RCTs. Studies involving GlucoWatch were excluded as this device is no longer available [30]. The full eligibility criteria are found in ESM Table 2. The four-stage PRISMA flow diagram guided the selection process [29]. First, search results from bibliographic databases and additional sources were downloaded into EndNote X9 (version 9.3.3) software and any duplicates were removed [31]. Second, two reviewers (ET and SK) independently screened the abstracts and/or title against eligibility criteria and removed irrelevant articles. Potentially relevant articles were retrieved as full texts. Articles covering the same study were linked. Third, ET and SK independently reviewed the full-text articles against the eligibility criteria and excluded ineligible studies. Last, ET and SK validated the final list of all included studies. A third reviewer (NH) was consulted if disagreements between ET and SK were not resolved through discussion.

Data extraction

Two reviewers (ET and SK) independently extracted relevant data from all included articles using the standardised Cochrane Data Extraction form [32]. Any discrepancies in extracted data were resolved through discussion with NH.

The form was initially piloted on six articles to ensure all necessary information was collected. The data obtained included author's details, study design, setting, age, population, sample size, intervention, control, attrition rate, outcomes (specified above) and intention-to-treat analysis. Diabetes-related specific items, such as CGM systems, SMBG device and baseline HbA_{1c} were extracted.

Risk of bias assessment

Two reviewers (ET and SK) independently assessed the risk of bias using Cochrane Collaboration's risk of bias tool [32]. The tool consists of six domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; and (6) selective reporting. Any disagreements between the two reviewers were resolved through discussion with NH. The κ statistic was measured using GraphPad software [33]. The risk of bias graph and summary were generated by Review Manager (RevMan) software version 5.4 [34].

Data synthesis and analysis

The primary outcome was post-intervention HbA_{1c} level; the secondary outcomes were post-intervention severe hypoglycaemia and DKA events. The primary outcome was expressed as mean difference (MD) with 95% CI. Secondary outcomes were expressed as RR with 95% CI. Results were deemed statistically significant if $p<0.05$ [32]. Results were pooled using DerSimonian and Laird's random-effect model. RevMan software was used to conduct meta-analyses, data transformation and graph generation. Meta-regression was conducted using the 'metafor' package of R and the between-study variation was estimated by the Restrict Maximum Likelihood method [35]. A narrative synthesis was used when the meta-analysis was inappropriate.

Heterogeneity was assessed using χ^2 and I^2 statistics. The statistical significance of the χ^2 test was set at $p<0.10$. I^2 was interpreted as follows: 0–40% (unimportant); 30–60% (moderate heterogeneity); 50–90% (substantial heterogeneity); and 75–100% (considerable heterogeneity) [32]. Publication bias was assessed using funnel plot and Egger's test [36].

Subgroup analysis explored the effectiveness of CGM across study duration, duration of diabetes, CGM systems, participants' initial HbA_{1c} level and insulin regimen. Sensitivity analysis was performed to determine the source of heterogeneity [37]. Certainty of evidence was appraised using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) software [38].

Results

Search results

Two thousand, one hundred and ninety-one studies from five bibliographic databases were downloaded into EndNote for recording and removal of duplicates; this resulted in 1350 records (ESM Fig. 1). Two reviewers (ET and SK) independently screened these records against the eligibility criteria, and excluded 1104 records based on title and 168 records based on abstracts. Full texts of the remaining 78 articles were retrieved and screened against eligibility criteria, and another 56 articles were excluded for reasons outlined in ESM Fig. 1. The resulting 22 articles were included in this review while 21 articles were pooled into meta-analysis.

Study characteristics

The characteristics of the 22 included studies involving 2188 participants are summarised in Table 1. Seven studies were cross-over designs [39–45]. The remaining 15 studies were parallel-group designs. All studies were conducted in an outpatient setting. Sample size varied from 20 [44, 46] to 241 [47] participants. Participants' mean baseline HbA_{1c} was either ≤64 mmol/mol (≤8%) (n = 8) [39, 40, 47, 55–58, 60] or >64 mmol/mol (>8%) (n = 11) [41, 42, 44, 46, 48–53, 59]. Three studies did not report participant's baseline HbA_{1c} [43, 45, 54]. Insulin delivery was via MDI alone (n = 8) [41, 42, 48, 49, 51, 55–57], CSII alone (n = 3) [46, 54, 58] and MDI/CSII (n = 11) [39, 40, 43–45, 47, 50, 52, 53, 59, 60]. The various CGM systems were P-CGM (n = 2) [51, 57], isCGM (n = 2) [47, 50] and RT-CGM (n = 18). Study duration was <8 weeks (n = 3) [40, 51, 57], 14–16 weeks (n = 5) [39, 43, 45, 46, 48] and >24 weeks (n = 13). Duration of diabetes was <10 years (n = 6) [46, 50–52, 56, 57], 10 years to <20 years (n = 4) [39, 40, 48, 59], 20 years to <30 years (n = 5) [41, 47, 49, 55, 58] and ≥30 years (n = 2) [53, 60]. Five studies did not report duration of diabetes [42–45, 54]. The primary outcome (i.e. HbA_{1c} level) was reported in all studies. The secondary outcomes of post-intervention severe hypoglycaemia and DKA events were reported in 13 and 14 studies, respectively.

Quality of included studies

Risk of bias summary and graph are presented in ESM Fig. 2. A κ inter-rater agreement of 0.85 was achieved, demonstrating an almost perfect agreement.

As for random sequence generation, five studies were appraised as unclear risk due to insufficient information [42, 44, 51, 53, 59]. The remaining 17 studies applied adequate randomisation technique. With regards to allocation concealment, five studies were graded unclear risk due to insufficient information [44, 50, 51, 53, 59]. All remaining studies except for

Table 1 Included studies

Study	Intervention							Control							Study design	Study duration	Outcome	ITT
	Glucose monitoring	Insulin regimen	Age, years	Baseline HbA_{1c}, mmol/mol (%)	Duration of diabetes, years	*n*	Attrition rate, %	Glucose monitoring	Insulin regimen	Age, years	Baseline HbA_{1c}, mmol/mol (%)	Duration of diabetes, years	*n*	Attrition rate, %				
Ajjan et al, 2016 [48] UK	RT-CGM (FreeStyle Navigator)	MDI	39±11.5	77.06± 14.21 (9.2±1.3)	15.8± 11.9	29	13.79	SMBG (FreeStyle Freedom Lite)	MDI	43.7± 9.9	74.87± 14.21 (9.0±1.3)	19.6± 12.4	13	23.08	2-arm RCT	100 days	HbA_{1c}	Y
Beck et al, 2017 [49] USA	RT-CGM (Dexcom G4 Platinum CGM system with an enhanced algorithm, software 505)	MDI	46±14	70.5±7.65 (8.6±0.7)	19.0± 14.8	105	2.86	SMBG (Bayer Contour Next USB meter and test strips)	MDI	51±11	70.5±6.56 (8.6±0.6)	21.7± 17.8	53	0	2-arm RCT	24 weeks	HbA_{1c}, SH and DKA	Y
Bolinder et al, 2016 [47] Europe	isCGM (Freestyle Libre)	MDI/CSII	42±13.3	50.71± 5.68 (6.79± 0.52)	20.0± 10.4	120	8.33	SMBG (FreeStyle Lite meter and test strips)	MDI/CSII	45±17.8	50.6±6.7 (6.78±0.64)	21.3± 14.8	121	16.53	2-arm RCT	24 weeks	HbA_{1c}, SH and DKA	N
Bosi et al, 2019 [58] UK	RT-CGM (sensor-augmented pump/Medtronic MiniMed 640G with Smart Guard)	CSII	49.0± 12.2	60.66± 9.84 (7.7±0.9)	28.5± 11.1	76	1.32	SMBG with sensor-augmented insulin pump (Medtronic MiniMed 640G)	CSII	47.4± 12.5	59.67±9.84 (7.6 ± 0.9)	29.7± 13.3	77	6.49	2-arm RCT	24 weeks	HbA_{1c}, SH and DKA	Y
Boucher et al, 2020 [50] New Zealand	isCGM (Freestyle Libre; Abbott Diabetes Care)	MDI/CSII	16.5± 1.9	94.55± 18.58 (10.8±1.7)	7.0±3.5	33	0	SMBG	MDI/CSII	16.7± 2.2	98.92± 17.49 (11.2 ± 1.6)	8.0±4.0	31	0	2-arm RCT	24 weeks	HbA_{1c}, SH and DKA	Y
Bukara-Radujković et al, 2011 [51] Europe	P-CGM (Medtronic MiniMed)	MDI	13.7± 3.3	85.8± 17.49 (10.0±1.6)	6.3±4.0	40	0	SMBG (Accucheck glucometer; Roche)	CSII	11.8± 3.8	87.99± 21.86 (10.2 ± 2.0)	4.4±2.7	40	0	2-arm RCT	72 h	HbA_{1c}	N
Dicembrini et al, 2020 [39] Europe	RT-CGM (Dexcom G5 Mobile system)	CSII	45.7± 8.2	60.66± 4.37 (7.7±0.4)	17.3± 18.5	14	0	SMBG (participants' own glucometer)	MDI	44.7± 8.7	61.75±5.47 (7.8 ± 0.5)	19.0± 19.3	14	0	Crossover trial	16 weeks	HbA_{1c}, SH and DKA	Y
Heinemann et al, 2018 [55] Europe	RT-CGM (Dexcom G5 Mobile system)	MDI	45.8± 12.0	59.57± 10.93 (7.6±1.0)	20.9± 14.0	75	0	SMBG (FreeStyle Lite meter and test strips)	MDI	47.3± 11.7	57.38± 10.93 (7.4 ± 1.0)	21.6± 13.9	74	10.81	2-arm RCT	26 weeks	HbA_{1c}	Y

Table 1 (continued)

Study	Intervention							Control							Study design	Study duration	Outcome	ITT
	Glucose monitoring	Insulin regimen	Age, years	Baseline HbA_{1c}, mmol/mol (%)	Duration of diabetes, years	*n*	Attrition rate, %	Glucose monitoring	Insulin regimen	Age, years	Baseline HbA_{1c}, mmol/mol (%)	Duration of diabetes, years	*n*	Attrition rate, %				
Kordonouri et al, 2012 [54] Europe	RT-CGM (sensor-augmented pump system Paradigm REAL-Time)	CSII	–	–	–	62	18.4	SMBG with MiniMed Paradigm 515/715	CSII	–	–	–	69	11.5	2-arm RCT	96 weeks	HbA_{1c}	N
Laffel et al, 2020 [52] USA	RT-CGM (Dexcom G5 Mobile system)	MDI/CSII	17±3	73.78±10.93 (8.9±1.0)	9.0±5.0	74	4.05	SMBG (Bayer Contour Next USB)	MDI/CSII	18±3	73.78±10.93 (8.9±1.0)	10.0±5.0	79	10.13	2-arm RCT	26 weeks	HbA_{1c}, SH and DKA	N
Langeland et al, 2012 [40] Europe	RT-CGM (Guardian REAL-Time)	MDI/CSII	34±9	60.66±2.19 (7.7±0.2)	18.0±7.0	15	–	SMBG	MDI/CSII	34±9	60.66±2.19 (7.7±0.2)	19.0±9.0	15	–	Crossover trial	4 weeks	HbA_{1c}	N
Lind et al, 2017 [41] Europe	RT-CGM (Dexcom G4 PLATINUM)	MDI	46.7±13	69.3±9.84 (8.49±0.9)	23.4±11.9	82	14.63	SMBG	MDI	42.6±12.2	68.86±9.84 (8.45±0.9)	21.0±11.7	79	7.59	Crossover trial	26 weeks	HbA_{1c}, SH and DKA	N
Little et al, 2014 [53] UK	RT-CGM (Real-time continuous glucose monitor)	MDI/CSII	50.1±12.6	66.13±12.02 (8.2±1.1)	31.0±12.2	48	4.17	SMBG (Bayer Contour Next USB)	MDI/CSII	47.1±11.8	67.22±14.21 (8.3±1.3)	26.7±12.1	48	10.42	2x2 factorial trial	24 weeks	HbA_{1c}, SH and DKA	Y
Mauras et al, 2012 [56] USA	RT-CGM (FreeStyle Navigator)	MDI	7.5±1.8	62.85±8.74 (7.9±0.8)	4.0±1.8	74	6.76	SMBG (FreeStyle Flash blood glucose meter and test strips)	MDI	7.5±1.7	62.85±8.74 (7.9±0.8)	3.5±2.7	72	5.56	2-arm RCT	26 weeks	HbA_{1c}, SH and DKA	Y
Olivier et al, 2014 [46] Canada	RT-CGM (Medtronic Paradigm 522/722 pump)	CSII	12.2±4.4	63.94±9.84 (8.0±0.9)	3.2±3.0	10	20	SMBG	CSII	11.5±3.8	68.31±8.74 (8.4±0.8)	2.1±2.5	10	30	2-arm RCT	16 weeks	HbA_{1c}	Y
Pratley et al, 2020 [60] USA	RT-CGM (Dexcom G5)	MDI/CSII	68.3±5.2	59.57±9.84 (7.6±0.9)	37.3±18.5	103	0.97	SMBG (Bayer Contour Next USB)	MDI/CSII	67.3±5.2	58.48±8.74 (7.5±0.8)	36.0±16.3	100	6	2-arm RCT	24 weeks	HbA_{1c}, SH and DKA	N
Raviteja et al, 2019 [57] North India	P-CGM (IPRO 2 Professional CGM)	MDI	5.8±2.1	64.05±15.96 (8.01±1.46)	1.24±0.97	34	11.76	SMBG (Freestyle Optium glucometer)	MDI	6.3±2.1	62.41±12.9 (7.86±1.18)	1.1±1.5	34	2.94	2-arm RCT	3–5 days	HbA_{1c}	Y
Riveline et al, 2012 [59] Europe	RT-CGM (FreeStyle Navigator)	MDI/CSII	37.5±13.4	74.87±8.74 (9±0.8)	16.4±9.1	62	–	SMBG (home glucose meter)	MDI/CSII	37.8±13.9	72.68±9.84 (8.8±0.9)	18.8±10.6	61	–	2-arm RCT	48 weeks	HbA_{1c}, SH and DKA	N

Table 1 (continued)

Study	Intervention							Control							Study design	Study duration	Outcome	ITT
	Glucose monitoring	Insulin regimen	Age, years	Baseline HbA_{1c}, mmol/mol (%)	Duration of diabetes, years	*n*	Attrition rate, %	Glucose monitoring	Insulin regimen	Age, years	Baseline HbA_{1c}, mmol/mol (%)	Duration of diabetes, years	*n*	Attrition rate, %				
Sequeira et al, 2013 [42] USA	RT-CGM (Dexcom SEVEN plus)	MDI	–	67.22±– (8.3±–)	–	19	21.2	SMBG	MDI	–	67.22±– (8.3±–)	–	20	30	Crossover trial	28 weeks	HbA_{1c}	N
Thabit et al, 2020 [43] UK	RT-CGM (Dexcom G6 system)	MDI/CSII	21±2.28	–	–	16	0	SMBG	MDI/CSII	21.4± 2.57	–	–	15	0	Crossover trial	8 weeks	HbA_{1c}, SH and DKA	Y
Tumminia et al, 2015 [44] Europe	RT-CGM (Guardian real-time)	MDI/CSII	–	69.84± 4.37 (8.54±0.4)	–	10	–	SMBG	MDI/CSII	–	70.06±5.47 (8.56±0.5)	–	10	–	Crossover trial	24 weeks	HbA_{1c}, SH and DKA	N
van Beers et al, 2016 [45] the Nether-lands	RT-CGM (Paradigm Veo system with a MiniLink transmitter)	MDI/CSII	–	–	–	26	11.54	SMBG	MDI/CSII	–	–	–	26	7.69	Crossover trial	16 weeks	HbA_{1c}, SH and DKA	Y

Data are shown as mean ± SD unless stated otherwise

—, information not mentioned in article; N, no; SH, severe hypoglycaemia; Y, yes

one [47] applied adequate allocation concealment. Due to the nature of intervention (e.g. RT-CGM and isCGM), blinding was not feasible. As the lack of blinding was less likely to influence objective outcomes [61], all 22 studies were graded low risk for blinding of participants, personnel and outcome assessment. For incomplete data, one study [46] was rated high risk as ≥20% attrition rate observed in both arms posed a serious threat to the study's validity [62]. The remaining studies were rated low risk for incomplete data. For selective reporting, 18 studies were rated low risk while four studies [39, 40, 44, 51] lacked clarity, hence were rated unclear risk.

Effectiveness of CGM

HbA_{1c} Twenty-one studies that assessed the effect of CGM (intervention) vs SMBG (control) on post-intervention HbA_{1c} levels among 2149 participants were pooled into meta-analysis (Fig. 1). Overall, participants using CGM experienced significantly lower HbA_{1c} level (MD −2.46 mmol/mol [−0.23%] [95% CI −3.83, −1.08]; $Z = 3.50$, p=0.0005) than individuals using SMBG. Substantial heterogeneity was present ($I^2 = 72\%$, p<0.00001). One trial was not pooled into meta-analysis due to missing data [42]; the study reported an overall non-significant HbA_{1c} reduction when comparing CGM with SMBG.

Severe hypoglycaemia Thirteen studies evaluated the effect of CGM vs SMBG on post-intervention severe hypoglycaemia events among 1546 participants (Fig. 2). CGM demonstrated non-significant decrease in severe hypoglycaemia events (RR 0.61 [95% CI 0.33, 1.15]; $Z = 1.53$, p=0.13) when compared with SMBG. Substantial heterogeneity was present ($I^2 = 50\%$, p=0.04).

DKA Fourteen studies evaluated the effect of CGM vs SMBG on post-intervention DKA events among 1644 participants (Fig. 3). CGM intervention demonstrated no significant reduction in DKA events (RR 1.06 [95% CI 0.49, 2.32]; $Z = 0.15$, p=0.88) compared with SMBG. Homogeneity was observed ($I^2 = 0\%$, p=0.59).

Subgroup analyses

Subgroup analyses were performed for the primary outcome (i.e. HbA_{1c} level). Subgroup analyses were stratified according to the following variables: (1) participants' mean baseline HbA_{1c}; (2) insulin regimen; (3) study duration; (4) CGM systems; and (5) duration of diabetes. However, these analyses revealed no significant subgroup difference for study duration (p=0.67) (ESM Fig. 3), CGM systems (p=0.88) (ESM Fig. 4) and duration of diabetes (p=0.90) (ESM Fig. 5).

Subgroup analysis comparing the effectiveness of CGM among participants with mean baseline HbA_{1c} ≤64 mmol/mol (≤8%), HbA_{1c} >64 mmol/mol (>8%) and unreported HbA_{1c} reported significant subgroup difference ($I^2 = 89.7\%$, p<0.0001) (Fig. 4). Among participants with mean baseline HbA_{1c} >64 mmol/mol (>8%), those using CGM encountered significant reduction in HbA_{1c} level (MD −4.67 mmol/mol [−0.43%] [95% CI −6.04, −3.30]; $Z = 6.69$, p<0.00001) compared with participants using SMBG. Conversely, CGM did not significantly decrease HbA_{1c} level in individuals with mean baseline HbA_{1c} ≤64 mmol/mol (≤8%) ($Z = 0.61$,

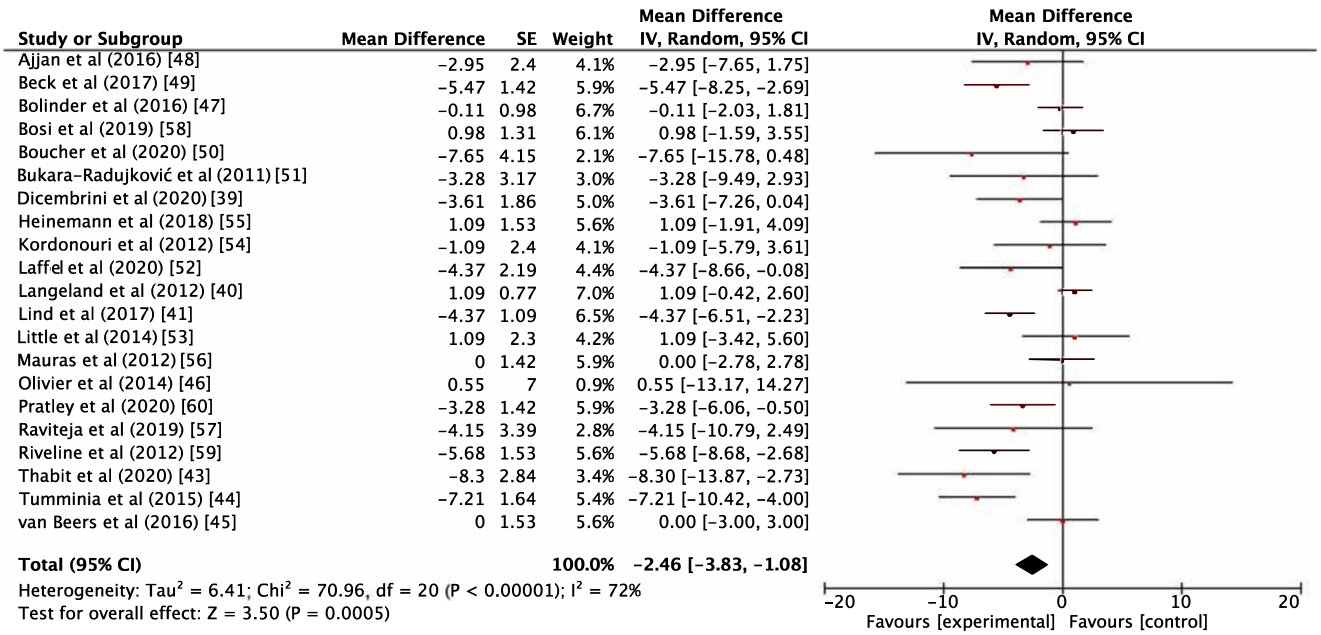

Fig. 1 Forest plot showing the effect of CGM on post-intervention HbA_{1c} (mmol/mol). IV, inverse variance

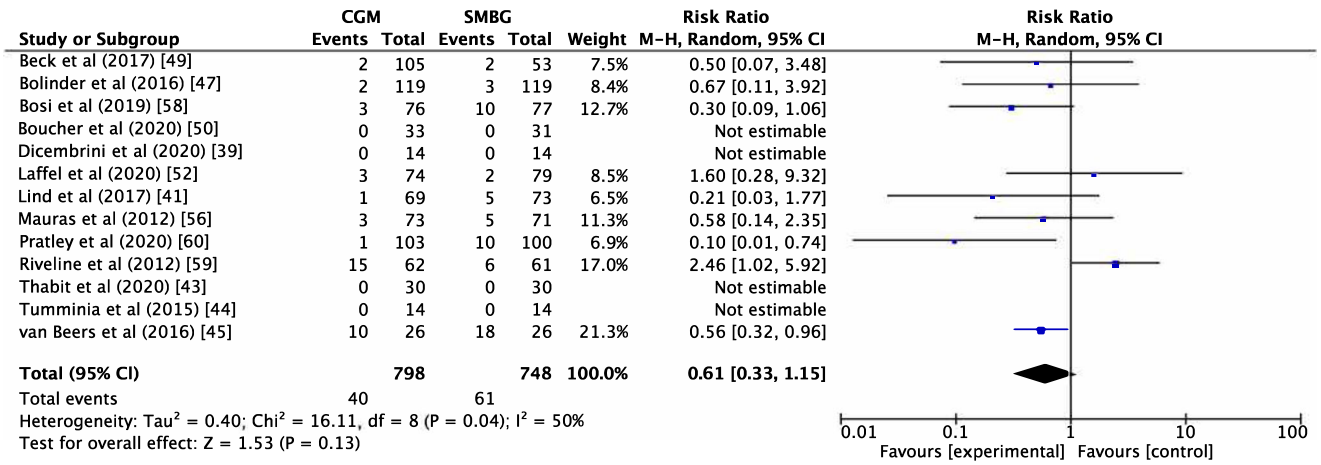

Fig. 2 Forest plot showing the effect of CGM on severe hypoglycaemia events. M-H, Mantel–Haenszel

p=0.54) or unreported HbA_{1c} (Z = 1.15, p=0.25) when compared with SMBG. Additionally, subgroup analysis comparing the effect of CGM among participants who utilised MDI, CSII and MDI/CSII insulin regimens revealed significant subgroup difference (I^2 = 66.4%, p=0.05) (Fig. 5). Compared with SMBG, significant reduction in HbA_{1c} level was experienced by individuals using CGM who were on MDI (MD −2.66 mmol/mol [−0.24%] [95% CI −4.90, −0.42]; Z = 2.33, p=0.02) and MDI/CSII (MD −2.98 mmol/mol [−0.27%] [95% CI −5.03, −0.92]; Z = 2.84, p=0.004). However, individuals on CSII experienced non-significant reduction in HbA_{1c} level (Z = 0.45, p=0.66).

Meta-regression

Meta-regression was conducted with baseline HbA_{1c} as the covariate. The regression coefficient was −2.31 mmol/mol (95% CI −3.76, −0.86, p=0.0017), indicating that baseline HbA_{1c} was significantly associated with the MD.

Sensitivity analysis

Sensitivity analysis was conducted to observe whether removing any single study could reduce heterogeneity. No significant change in results or heterogeneity was observed.

Publication bias

Visual inspection of funnel plot on HbA_{1c} outcome (ESM Fig. 6) appeared to be symmetrical, and a non-significant Egger's test (p=0.212) indicated a lack of publication bias. Visual inspection of funnel plot on secondary outcomes appeared symmetrical, suggesting no publication bias.

GRADE assessment

The GRADE criteria were adhered to [63], and the certainty of evidence for all outcomes was moderate (summarised in ESM

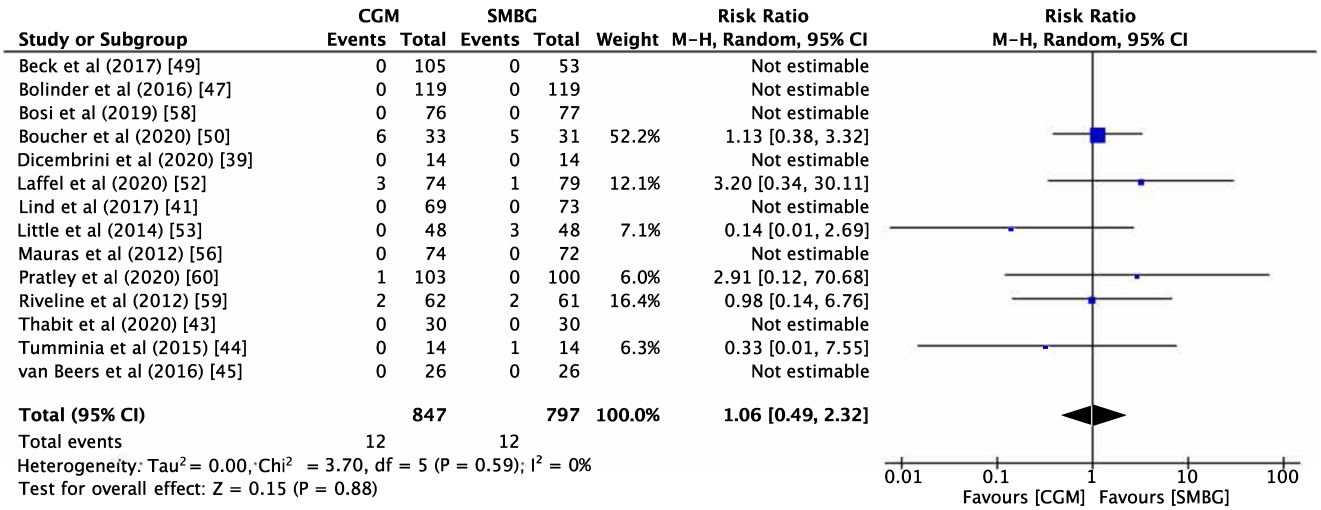

Fig. 3 Forest plot showing the effect of CGM on DKA events. M-H, Mantel–Haenszel

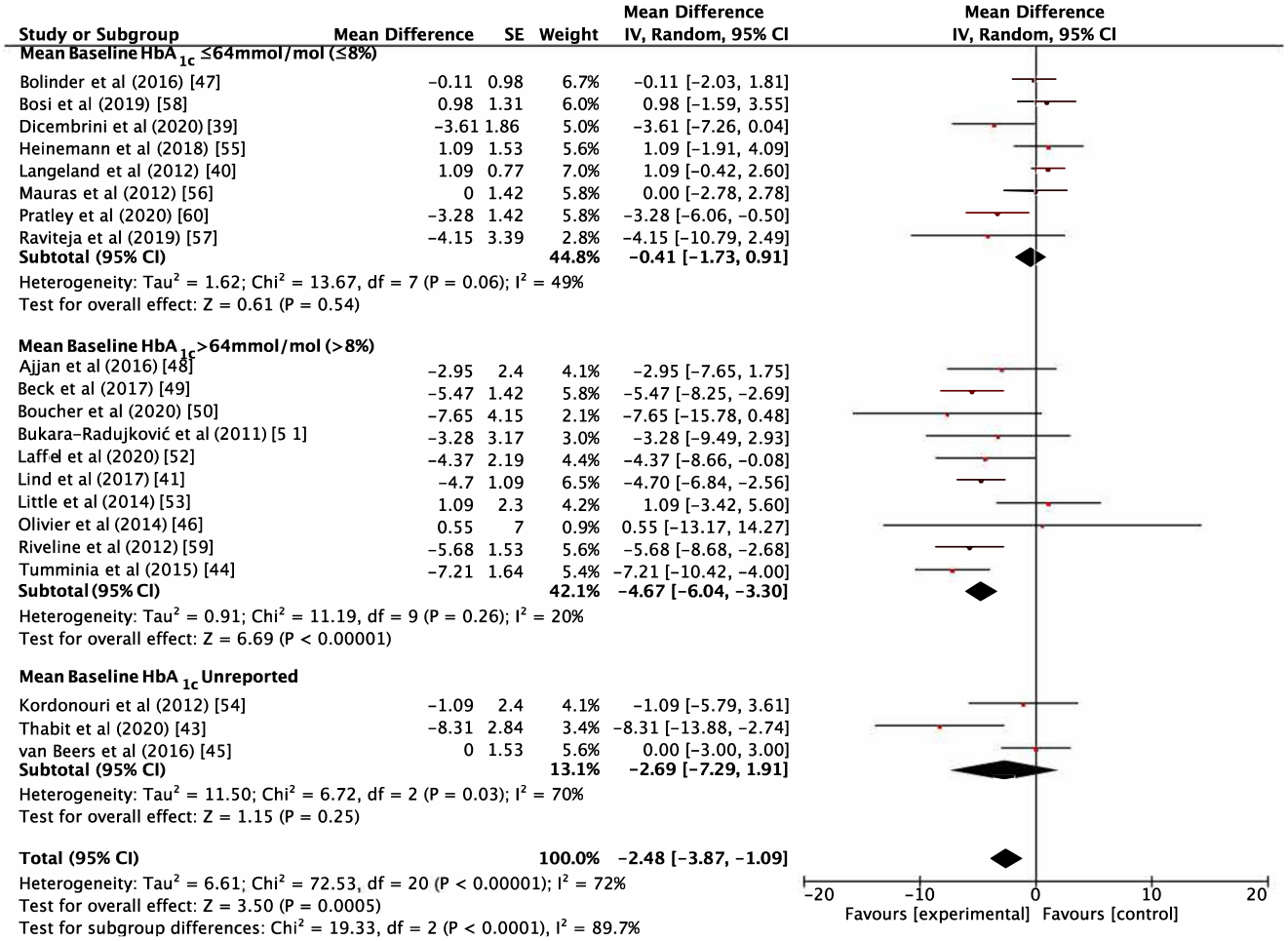

Fig. 4 Forest plot showing subgroup analysis of post-intervention HbA_{1c} (mmol/mol) according to baseline HbA_{1c}. IV, inverse variance

Table 3). All studies were RCTs and were graded 'not serious' for risk of bias as most of them were low risk. Certainty of evidence for HbA_{1c} level was downgraded due to inconsistency as substantial heterogeneity was observed. Certainty of evidence for severe hypoglycaemia was downgraded due to inconsistency as moderate heterogeneity was observed. Lastly, the certainty of evidence for DKA was downgraded due to imprecision as there were few DKA incidents observed.

Discussion

Statement of principal findings

Meta-analysis of 21 studies consisting of 2149 participants with type 1 diabetes mellitus evaluated the effectiveness of CGM compared with SMBG in glycaemic control. Findings revealed that CGM provided a superior benefit over SMBG in reducing HbA_{1c} level, with greater reduction seen in individuals with higher mean baseline HbA_{1c}. CGM had no significant effect on severe hypoglycaemia and DKA events. While the influence of insulin regimens on the effectiveness of CGM remains unclear, the type of CGM system used, study duration and duration of diabetes did not significantly modify the effectiveness of CGM.

Strengths and weaknesses of the study

To our knowledge, this is the first meta-analysis to achieve the following: (1) finding significant benefits of CGM on HbA_{1c} among individuals with poor glycaemic control (HbA_{1c} >64 mmol/mol [>8%]); (2) finding significant association between baseline HbA_{1c} and effect size; and (3) evaluation of the effectiveness of isCGM in individuals with type 1 diabetes. These additional findings provide new evidence to a recent review [20] and an update of a prior review [19]. Furthermore, no publication bias was reported despite applying date restrictions in the search. This enhances the validity of the current findings [64]. Additionally, most of the included studies had similarly high methodological quality ratings,

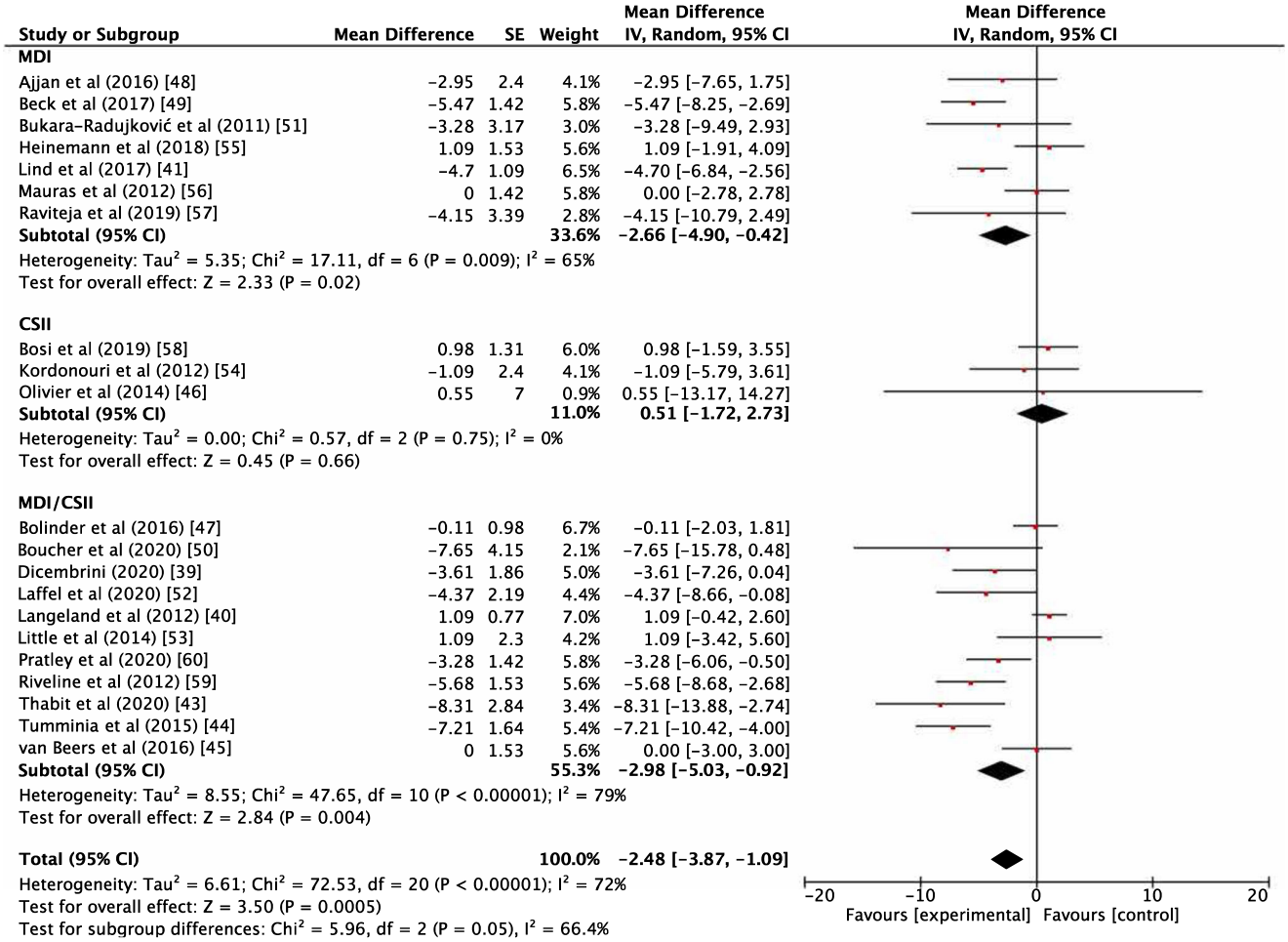

Fig. 5 Forest plot showing subgroup analysis of post-intervention HbA_{1c} (mmol/mol) according to insulin regimen. IV, inverse variance

suggesting low methodological heterogeneity. Thus, it is unlikely that the studies were affected by various biases. Moreover, this paper identified participants' differing baseline HbA_{1c} as the source of substantial heterogeneity. Identification of this factor allows future studies to be designed better to obtain a more accurate CGM effect.

Studies reported that the effectiveness of CGM in controlling HbA_{1c} varies significantly across different age groups [65]. However, the influence of age on the effectiveness of CGM remains unclear in this paper. Subgroup analysis on age (i.e. children, adults, young adults, mixed population) was not possible as some subgroups would be represented in only one study. This prevented any meaningful comparisons from being made [66].

Strengths and weaknesses in relation to other studies

HbA_{1c} level Use of CGM, compared with SMBG, led to an overall significant reduction in HbA_{1c} level, consistent with findings of previous studies wherein CGM resulted in a significant decrease in HbA_{1c} level unlike SMBG [15–17, 19, 21–23]. This finding was expected as CGM can produce abundant data on users' blood glucose levels compared with SMBG. The additional information derived from CGM enables a more granular analysis to guide treatment decisions, which could eventually improve glycaemic control [67]. However, two reviews have previously reported that CGM did not significantly lower HbA_{1c} levels compared with SMBG [14, 18]. The differing findings could be due to the low statistical power yielded by the small sample size in both reviews. Low-powered studies reportedly produced more false-negative results than high-powered studies [24]. Moreover, their findings could be biased as most of the included studies were of low methodological quality [68]. Our review incorporated 17 additional new studies [39–44, 46, 48, 50–54, 56, 57, 59, 60] compared with a prior review [20] which shared five common studies [45, 47, 49, 55, 58] with the current paper. Current findings also revealed a larger effect estimate (i.e. HbA_{1c} decrease) of −2.46 mmol/mol (−0.23%) (95% CI −3.83, −1.08, p=0.0005) as compared with

the prior review which reported a HbA_{1c} decrease of −1.75 mmol/mol (−0.16%) (95% CI −2.79, −0.71, $p<0.001$) [20].

Severe hypoglycaemia and DKA events CGM intervention, relative to SMBG, did not significantly reduce the number of severe hypoglycaemia events. Although these findings concurred with those of three other reviews [19, 21, 22], a recent study reported that CGM significantly lowers the risk of severe hypoglycaemia compared with SMBG [15]. The mixed findings could be attributed to a methodological limitation found in this paper along with the other three reviews [19, 21, 22]. Compared with the aforementioned study [15], the relatively smaller sample arms seen in the four papers on the severe hypoglycaemia outcome yields low statistical power which increases the likelihood of false-negative results [24].

Although CGM reportedly had no significant effect on the number of DKA events, in comparison with SMBG, the current result must be interpreted with caution due to insufficient data. The finding was anticipated to produce the same conclusion as the other previous studies [15, 22, 23]. In all four reviews, including this study, DKA incidents were rare. Meta-analysis of rare events can produce misleading results [37]. Hence, this review could not confer a concrete conclusion on the effectiveness of CGM.

Subgroup analyses

Significant subgroup difference was only observed in the subgroup analyses stratified according to participants' mean baseline HbA_{1c} (≤64 mmol/mol [≤8%], >64 mmol/mol [>8%] and unreported) and insulin regimen (MDI, CSII and MDI/CSII). In participants with mean baseline HbA_{1c} >64 mmol/mol (>8%), those using CGM experienced a significant reduction in HbA_{1c} level relative to those using SMBG, unlike those with mean baseline HbA_{1c} ≤64 mmol/mol (≤8%). Notably, HbA_{1c} >64 mmol/mol (>8%) indicates poor glycaemic control [69]. This phenomenon could be attributed to the tendency of individuals with type 1 diabetes to maintain high glucose levels to avoid hypoglycaemia [70]. This behaviour could be more apparent in individuals with poor glycaemic control since their HbA_{1c} level is higher. As CGM reportedly reduces fear of hypoglycaemia among individuals with type 1 diabetes [71], the need to maintain a high glucose level might be eliminated, especially among individuals with poor glycaemic control. Hence, such individuals may experience greater HbA_{1c} reduction using CGM. Moreover, overall heterogeneity (I^2 = 72%) appears to be caused by clinical heterogeneity. This could be a result of the differing mean baseline HbA_{1c} levels of participants. Differing heterogeneity between subgroups with mean baseline HbA_{1c} ≤64 mmol/mol (≤8%) (I^2 = 49%) and mean baseline HbA_{1c} >64 mmol/mol (>8%) (I^2 = 20%) could be attributed to the difference in behaviour between subgroups. In the subgroup with unreported HbA_{1c} levels, the substantial heterogeneity (I^2 = 70%) observed may be caused by the wide variation in baseline HbA_{1c} in the studies. Results from the meta-regression also indicated that the baseline HbA_{1c} was significantly associated with the effect size. This further suggests that individuals with type 1 diabetes with HbA_{1c} >64 mmol/mol (>8%) are most likely to benefit from CGM.

Although a significant subgroup effect was observed for participants' insulin regimen, the overall evidence on glycaemic control was conflicting. Compared with SMBG users, participants using CGM who were on MDI and MDI/CSII experienced significantly lower HbA_{1c} levels, unlike those on CSII. This analysis is likely to be unreliable for conferring a clear effect of CGM influenced by insulin regimen on HbA_{1c} as a far smaller number of trials and participants was observed in the CSII subgroup (n = 3 studies, 304 participants) than in the MDI (n = 7 trials, 804 participants) and MDI/CSII (n = 11 trials, 1041 participants) subgroups. Due to uneven covariate distribution, the validity of the findings was, therefore, hindered [66].

Implications of findings

Current findings revealed an MD in HbA_{1c} levels of −2.46 mmol/mol (−0.23%) between CGM and SMBG. Although it may appear insubstantial, the DCCT trial found that a decrease in HbA_{1c} level (regardless of magnitude) was always accompanied by a reduction in diabetic complication risk [72]. Furthermore, with the larger MD of −4.67 mmol/mol (−0.43%) observed in individuals with HbA_{1c} >64 mmol/mol (>8%), CGM could substantially lower macrovascular risk among individuals with poor glycaemic control since elevated HbA_{1c} level (>59 mmol/mol [>7.5%]) is correlated with higher cardiovascular disease and mortality risk [73]. This further suggests that CGM is a superior method for monitoring glucose, compared with SMBG, for the type 1 diabetes mellitus population. In all, individuals with type 1 diabetes, especially those with poorly controlled diabetes, are strongly encouraged to use CGM instead of SMBG.

This paper may be relevant to clinicians providing outpatient services. As all studies were conducted in an outpatient setting, the present findings suggest that CGM is effective in managing glycaemic control in the community.

Future research and practice

The effectiveness of CGM systems in the long term and their relationship with diabetes complications requires more comprehensive follow-up studies. Future research could investigate the effectiveness of CGM across different age groups and insulin regimens since not much is known.

Moreover, this review presented limited evidence to support ongoing research (e.g. the use of an artificial pancreas, a combined treatment consisting of CGM, insulin pump and software algorithm that automates glycaemic control). The accuracy of CGM is essential for the safety of the artificial pancreas. It is measured using the mean absolute relative difference (MARD) between CGM glucose value and a reference value (i.e. SMBG) [70]. As none of the included studies reported MARD, future studies could evaluate CGM's accuracy using MARD as an outcome. A recent consensus statement by the Diabetes Technology Society reported that inpatient CGM usage improved overall glycaemic control [74]. As current evidence is limited to the outpatient setting, future studies could be conducted in an inpatient setting.

Current clinical guidelines support the use of CGM in the management of type 1 diabetes [75, 76]. New findings in this paper indicate that individuals with HbA_{1c} >64 mmol/mol (>8%) would benefit most from CGM, coupled with a moderate certainty of evidence. This could further encourage clinicians to recommend CGM as the main monitoring method for the type 1 diabetes population, especially those with poor glycaemic control.

Conclusion

This systematic review and meta-analysis shows that CGM improves glycaemic control (expressed as HbA_{1c} level) in individuals with type 1 diabetes, with the new finding that those with poor glycaemic control (HbA_{1c} >64 mmol/mol [>8%]) especially benefit. However, CGM did not affect severe hypoglycaemia and DKA events. Nonetheless, compelling evidence from this review suggests that individuals with type 1 diabetes with HbA_{1c} >64 mmol/mol (>8%) would benefit most from CGM compared with SMBG. The present findings may serve as a foundation for future studies to evaluate CGM's accuracy, and the influence of user's age and insulin regimen on the effectiveness of CGM.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05648-4.

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Data availability All data generated or analysed during this study are included in this published article (and its supplementary information files). All HbA_{1c} values were converted using the formula on the National Glycohemoglobin Standardization Program website (http://www.ngsp.org/ifcc.asp).

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Contribution statement ET, WT and SK contributed to the study design, main concept, statistical analysis and interpretation of results. ET, NH and SK developed the protocol. ET and SK were responsible for the study selection and data extraction. NH resolved discrepancies between reviewers on text selection and data extraction. ET drafted the paper and NH, WT and SK revised the manuscript for important intellectual content. All authors read and approved the final draft before submission. ET is the guarantor of this work.

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