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Efficacy of intermittently scanned continuous glucose monitoring in patients with types 1 or 2 diabetes receiving insulin therapy: a systematic review and meta-analysis

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Abstract

Background Monitoring glucose levels is crucial for managing glycemic control. Methods include self-monitored blood glucose (SMBG), continuous glucose monitoring (CGM), and intermittently scanned continuous glucose monitoring (isCGM).

Objective To assess the efficacy of isCGM versus SMBG in individuals with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) on insulin therapy.

Methods We conducted a systematic review including randomized controlled trials involving patients over 4 years old with T1DM or T2DM on multiple daily insulin regimens, comparing isCGM to SMBG. The outcomes analyzed were HbA1c (%), time below the target glucose range (TBR), patient satisfaction (DTSQ), device-related adverse events, time in range (TIR), and hypoglycemic events. Searches were performed in MEDLINE, EMBASE, and CENTRAL. Two independent reviewers screened studies, assessed the risk of bias, and extracted data. The meta-analyses employed a random-effects model, and the certainty of evidence was evaluated via the GRADE system.

Results Seventeen studies with 1,860 participants were included. The isCGM demonstrated a moderate certainty of evidence for reducing HbA1c (Mean difference [MD]: -0.25%, 95% confidence interval [95% CI]: -0.39– -0.10%; I^2: 82.6% 13 studies; 1,482 patients) and enhancing patient satisfaction (MD: 4.5, 95% CI: 2.18– 6.82; I^2: 92.9%; 10 studies; 1,150 patients). Meta-regression revealed that intervention duration was a significant moderator of HbA1c reduction. isCGM also favored a reduction in TBR, with an MD of -0.15% (95% CI: -0.23– -0.07%; I^2: 96.7% 8 studies; 1,094 patients; low certainty). Mild device-related adverse events were more common in the isCGM group (Relative risk: 2.69, 95% CI: 1.5– 4.81; I^2: 0%; 7 studies; 991 participants; moderate certainty). The overall frequency of participants who discontinued isCGM due to cutaneous adverse events was 1% (95% CI: 0–6%; 7 studies; 533 participants). No clear effects were observed for TIR (MD: 0.02%, 95% CI: -0.05– 0.1%; I^2: 79.6%; 11 studies; 1,318 patients; very low certainty) or hypoglycemic episodes.

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Conclusions Compared with SMBG, isCGM reduces HbA1c, enhances patient satisfaction, and reduces TBR. However, it may increase the incidence of mild device-related adverse events. No definitive effects were observed on the TIR or hypoglycemia frequency.

Prospero registration CRD42024562805.

Keywords Diabetes mellitus, type 1, Diabetes mellitus, type 2, Continuous glucose monitoring, Intermittently scanned continuous glucose monitoring, Blood glucose self-monitoring

Background

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycemia caused by defects in insulin secretion, insulin action or a combination of both [1]. In 2021, the estimated number of people with diabetes globally was 537 million, with a relevant prevalence of 10.5% and high associated mortality. Projections point to a progressive increase in the incidence of this disease, especially in middle-income countries, along with significant expenses for healthcare systems [2]. Additionally, chronic hyperglycemia in DM patients results in severe complications, including renal insufficiency, blindness, neuropathy and cardiovascular disease [1].

DM can be classified into general categories, the most common of which are type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM is characterized by the autoimmune destruction of insulin-producing beta cells, leading to absolute insulin deficiency [3]. T2DM accounts for 95% of all diabetes cases and is one of the major epidemics of this century, mostly in adults, despite reports of an increasing incidence in children [4]. The etiology of T2DM is complex and multifactorial, involving genetic and environmental components associated with metabolic syndrome and insulin resistance [3].

In the management of DM, intensive glycemic control has been associated with a reduction in diabetes-related complications, emphasizing the importance of lowering hyperglycemia as a key treatment goal for this disease [5, 6]. In addition, glycemic variability—defined as fluctuations in glucose levels over time—has emerged as a significant risk factor for the development of chronic DM-related complications and for an increased incidence of severe hypoglycemic episodes, which are associated with adverse cardiovascular events and higher mortality rates [7–9]. Therefore, treatment targets for individuals with DM should encompass the three primary components of dysglycemia: persistent hyperglycemia, hypoglycemia, and glycemic variability [7].

Furthermore, monitoring glucose levels is essential for assessing glycemic control in individuals with DM. The conventional approach to monitoring blood glucose involves using a glucometer for self-monitoring (SMBG). This method requires individuals to perform fingerstick tests to obtain blood samples, which can be both uncomfortable and time-consuming, which can affect patient compliance, reducing adherence rates [10, 11]. Moreover, recent studies have revealed that many marketed devices do not meet minimum regulatory requirements [12]. In addition, this method may not detect episodes of low blood glucose that occur during sleep or without symptoms [13]. As an alternative, continuous glucose monitoring (CGM) systems provide real-time measurements of glucose levels in the interstitial fluid and transmit the data to a display device [13, 14]. CGM systems include a sensor, transmitter, and display device, such as a receiver or smartphone. There are two main types: real-time CGM (rtCGM), which provides continuous automatic readings, and intermittently scanned CGM (isCGM), which records glucose data but requires active scanning to view results [13]. The rtCGM involves a subcutaneous sensor that provides real-time glucose data, allowing for immediate adjustments, especially when integrated with insulin pumps; however, it often involves higher costs and the need for periodic calibration [15]. isCGM measures glucose in the interstitial fluid and offers data through scanning with a reader or smartphone app, providing convenience and potentially improving adherence. Its use is approved for patients over four years of age [16].

Some studies suggest that the use of isCGM can improve glycemic control, reduce the incidence of hypoglycemia, and enhance patients' quality of life. It also provides a comprehensive overview of glycemic patterns and daily fluctuations, enabling more precise and individualized treatment adjustments [16]. Therefore, a systematic review was conducted through randomized controlled trials (RCTs) to evaluate the efficacy of isCGM compared with SMBG in individuals with T1DM or T2DM receiving insulin therapy. The review focused on outcomes related to glycemic control, treatment satisfaction, and safety, including the incidence of adverse events.

Methods

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [17] and has been reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [18]. The study protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024562805.

Eligibility criteria

We selected RCTs in which the 'PICO' structure met the following inclusion criteria:

Participants (P)

Individuals over four years of age diagnosed with T2DM or T1DM, on the basis of the criteria of the American Diabetes Association (ADA) [3], regardless of sex or disease duration and whose treatment involved multiple insulin injections, were included.

Interventions (I)

The intermittently scanned continuous glucose monitoring (isCGM).

Comparison (C)

The self-monitored blood glucose (SMBG) method.

Outcomes (O)

The outcomes considered in this review included glycemic control, measured by HbA1c (%) and assessed ≥ 12 weeks postintervention; time below target glucose range (TBR), defined as blood glucose levels below 70 mg/dL; patient-reported outcome using the Diabetes Treatment Satisfaction Questionnaire (DTSQ); target glucose range (TIR), defined as glucose levels within 70 to 180 mg/dL [19]; hypoglycemic event level 1 (≥ 54 to < 70 mg/dL) and level 2 (glucose < 54 mg/dL) [20]; isCGM-associated cutaneous adverse events; and the frequency of participants who ceased using the isCGM due to cutaneous adverse events.

Exclusion criteria

We excluded studies in which participants did not use insulin, studies in which the control group did not use SMBG, studies lacking the outcomes of interest for this review, conference papers, nonrandomized studies, and studies on other types of diabetes not classified as T2DM or T1DM.

Identification of studies

Electronic databases

The search strategies were conducted on June 26, 2024, and were developed for the main electronic health databases: Embase (Elsevier), Medline (PubMed), and the Cochrane Collaboration's Controlled Clinical Trials (CENTRAL). These strategies included index terms and synonyms related to T2DM, T1DM, continuous glucose monitoring, and blood glucose self-monitoring. In PubMed, the filter for RCTs, supported by the Cochrane Library, was applied, and a similar embedded filter was used in Embase. The complete search strategies for each database are detailed in the supplementary file. No restrictions were imposed regarding language or publication year.

References were managed via EndNote, in which duplicates were removed. The initial screening of titles and abstracts was performed via the free web application Rayyan [21].

Study selection and data extraction

Two reviewers (MSB and VSNN) independently screened titles and abstracts to identify potentially eligible studies for inclusion in the review. The studies selected for full-text review were then evaluated for alignment with the proposed 'PICO' framework. In cases of disagreement, a consensus meeting was held between the reviewers to reach a final decision.

All reviewers independently used a standardized form to extract relevant data from the selected studies, including year of publication; sample size; follow-up duration; eligibility criteria (type of intervention and comparison, outcomes); baseline characteristics of patients (mean age, duration of diabetes diagnosis, and average HbA1c at baseline); means and standard deviations (SDs) of the last follow-up visit for each group; differences in means between groups regarding HbA1c, TIR, and TBR; and the number of device-related adverse events and hypoglycemia events classified as level 1 and level 2.

Data collection was primarily conducted via an intention-to-treat analysis whenever feasible.

Assessment of risk of bias in included studies

From each selected RCT, the risk of bias was assessed via the revised Cochrane Risk-of-Bias Tool for Randomized Controlled Trials (RoB 2), which examines five domains for each outcome: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result [22]. Each item was independently and collaboratively evaluated by two reviewers and classified as "low risk," "some concerns," or "high risk" of bias. In cases of disagreement, a consensus meeting was conducted to reach the final decision.

Studies in which investigators were aware of the group assignments in advance of allocating the next patient were considered to have a high risk of selection bias in domain 1. For attrition bias (domain 3), studies that employed intention-to-treat analysis with appropriate data imputation or those that did not use intention-to-treat but had losses less than 5% with similar dropout rates between the intervention and control groups were considered to have a low risk. Conversely, studies that used intention-to-treat analysis based only on data from the last follow-up or had losses exceeding 10% or

unbalanced dropout rates between groups were classified as having an uncertain risk of bias in this domain.

Determination of the intermittently scanned continuous glucose monitoring effect

For dichotomous data, the relative risk (RR) with a 95% confidence interval (CI) was used as the measure of the intervention effect. For continuous outcomes, the difference in mean (MD) values between groups at the end of each follow-up, accompanied by the 95% CI, was employed as the estimate of effect. Many studies did not report means and standard deviations (SDs) but instead provided the adjusted mean difference between groups at the last follow-up visit.

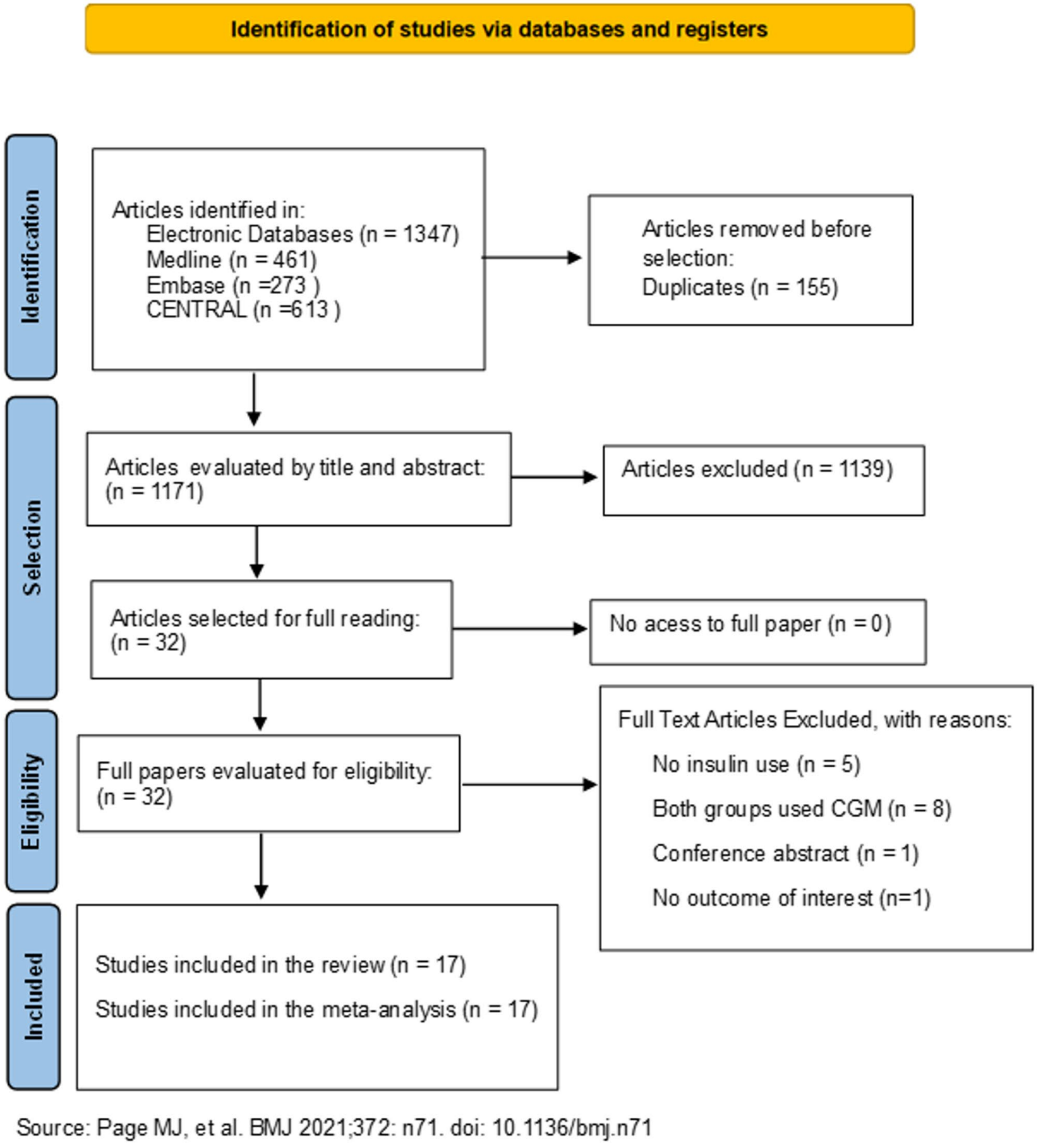

Fig. 1 Flow diagram of the study selection process

Synthesis and data analysis

The unit of analysis was the data published in the included studies. The outcome data were plotted in the meta-analysis via Stata Statistical Software 18 (Stata Statistical Software: Release 18; StataCorp LLC, College Station, TX, USA). The random effects model was chosen as the analytic model in the meta-analysis. This decision was based on our preliminary assumption that there would be heterogeneity among the populations and studies included in the analyses.

To avoid unit analysis error, we treated the number of hypoglycemic events as count data, recognizing that hypoglycemia is a common occurrence in DM patients receiving multiple insulin injections. Consequently, it was analyzed as a continuous outcome variable [23].

Proportional meta-analysis was performed to calculate the overall frequency of participants discontinuing isCGM due to cutaneous adverse events.

Heterogeneity assessment

Variability in the exposure or intervention effects is known as statistical heterogeneity and is a consequence of clinical or methodological variety, or both, among the studies [24]. In this review, statistical heterogeneity between the results of the studies included was ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of individual studies), by Higgins or I^2 statistics, in which $I^2 > 50\%$ indicated a moderate probability of heterogeneity, and by chi-square tests (Chi2), where $p < 0.10$ indicated heterogeneity [24]. In the case of statistical heterogeneity among the studies and if more than ten studies were included in a meta-analysis, a meta-regression was performed to explore potential sources of variability and better understand the relationships between the study characteristics and the outcomes evaluated. The mean age of the participants, the average time since DM diagnosis, the mean HbA1c at baseline, and the duration of intervention were used as covariates. The Knapp–Hartung correction was used to calculate the significance of the meta-regression coefficients [25].

Sensitivity analysis

For HbA1c, TBR, and treatment satisfaction, we performed sensitivity analyses stratifying studies on the basis of their risk of bias (separating those with "high risk" from those with "some concerns" and "low risk"). This allowed us to evaluate whether the exclusion of high-risk studies altered the observed intervention effect.

Assessment of publication bias

When >10 studies were included in the meta-analysis, a funnel plot was used to investigate the presence of publication bias [26].

Quality of evidence

The quality of evidence for estimating the effect of isCGM on DM outcomes that could be plotted in the meta-analysis was generated following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group [27, 28].

The precision domain was evaluated via the confidence interval and optimal information size (OIS), which were calculated with Stata software. For the HbA1c outcome, a difference of 0.5% was considered clinically significant. With an alpha value of 0.05 and a beta value of 0.20, the OIS was determined to be 118 participants per group [29]. For the DTSQ, the sample size was calculated assuming a mean difference of 0.5 in overall satisfaction between treatment groups, with a standard deviation of 0.8. Under these assumptions, a sample size of 41 participants per group would be required to achieve 80% power [30]. With respect to the duration of hypoglycemia, a sample size of 178 participants was calculated to provide 80% power to detect a 30% difference between groups, with a significance level of 0.05 [31].

Results

Selection of studies

The search strategy yielded 1,347 references, and after removing duplicates, 1,171 studies remained (Fig. 1), 32 of which were selected for full reading. Seventeen studies met our eligibility criteria after these studies were completely reviewed and were therefore included in this review [16, 31–46]. The reasons for the exclusion of the 15 studies reviewed are detailed in Table S1 in the supplementary file [47–61].

Characteristics of the included studies

The studies included in this review primarily investigated individuals with T1DM, all of whom used isCGM as the intervention, with SMBG serving as the comparator. In all intervention groups, the device employed was the FreeStyle Libre system, developed by Abbott Diabetes Care.

The primary study populations are adults, although some include adolescents and children. The participants were predominantly from European and Asian countries. The follow-up duration varies, but most studies have implemented interventions for at least 24 weeks. HbA1c values were the most frequently evaluated outcome. In RCTs that evaluated TIR and TBR, participants in the control groups used blinded CGM devices during predefined study phases. Typically, all participants underwent a masked baseline isCGM period, followed by further blinded isCGM use in the control groups near the end of the intervention period (two weeks before data collection). TIR and TBR were collected during comparable time frames for both intervention and control

Table 1 Characteristics and summary of findings of studies evaluating the effect of the intermittently scanned continuous glucose monitoring versus self-monitoring of blood glucose in individuals with type 1 or type 2 diabetes on insulin therapy

Author/Year	Study Design	Country	DM Type	Intervention (nº participants)	Treatment time	Comparator (nº participants)	Outcomes
Ajjam 2019	RCT Cluster	UK	T2DM	FGMS 4 (50)	30 weeks	SMBG (52)	-HbA1c -TIR -TBR -DTSQ -Adverse event
Bolinder 2016 and Oskarsson 2018	RCT	Multicenter (Europe)	T1DM	FGMS (120)	26 weeks	SMBG (121)	-HbA1c -TBR - HFS, DTSQ - Adverse event
Boucher 2020	RCT	New Zealand	T1DM	FGMS (33)	26 weeks	SMBG (31)	-HbA1c -DTSQ
Davis 2019	RCT	Australia		FGMS (30)	24 weeks	SMBG (29)	-HbA1c
Haak 2017	RCT	Multicenter (Europe)	T2DM	FGMS (149)	26 weeks	SMBG (75)	-HbA1c -Hypoglycemia frequency - Frequency of hypoglycemia -TIR -TBR - DTSQ - Adverse event
Jefferies 2023	RCT	New Zealand	T1DM	FGMS (49)	12 weeks	SMBG (51)	-HbA1c -Hypoglycemia frequency -TIR -TBR - Adverse event
Kim 2024	RCT	South Korea	T2DM	FGMS (52)	24 weeks	SMBG (52)	-HbA1c -TIR -TBR -DTSQ (data could not be extracted)
Leelarathna 2022	RCT	UK	T1DM	FGMS (78)	24 weeks	SMBG (78)	-HbA1c -Hypoglycemia frequency -Ketoacidosis frequency -TIR -TBR -DTSQ - Adverse event
Marsters 2020	RCT	New Zealand	T1DM	FGMS (33)	26 weeks	SMBG (31)	- Adverse event
ISCHIA 2023	RCT crossover	Japan	T1DM	FGMS (51)	12 weeks	SMBG (51)	-TIR -TBR
Piona 2018	RCT	Slovenia	T1DM	FGMS (25)	2 weeks	SMBG (20)	-TIR
Secher 2021	RCT	Denmark	T1DM	FGMS (grupo C = 48) FGM + CHO (39)	26 weeks	SMBG (grupo A = 42) SMBG + CHO (41)	-HbA1c -TIR -TBR -DTSQ -Adverse event
Wang 2021	RCT	China	T2DM	FGMS (40)	2 weeks	SMBG (40)	-General Comfort Questionnaire
Xu 2021	RCT	China	T1DM	FGMS (25)	26 weeks	SMBG (30)	-HbA1c -DTSQ
Zhang 2021	RCT	China	T1DM	FGMS (71)	48 weeks	SMBG (75)	-HbA1c -TIR -TBR

Table 1 (continued)

Author/Year	Study Design	Country	DM Type	Intervention (nº participants)	Treatment time	Comparator (nº participants)	Outcomes
Yan 2023	RCT	China	T1DM	FGMS (54)	24 weeks	SMBG (50)	-HbA1c -Hypoglycemia frequency -TIR - Adverse event
Yaron 2019	RCT	Israel	T2DM	FGMS (53)	10 weeks	SMBG (48)	DTSQ

RCT: Randomized Controlled Trial, T2DM: Type 2 Diabetes Mellitus, T1DM: Type 1 Diabetes Mellitus, FGMS: Flash Glucose Monitoring System, SMBG: Self-Monitored Blood Glucose, TIR: Time in Range, TBR: Time Below Range, DTSQ: Diabetes Treatment Satisfaction Questionnaire, and HFS: Hypoglycemia Fear Survey

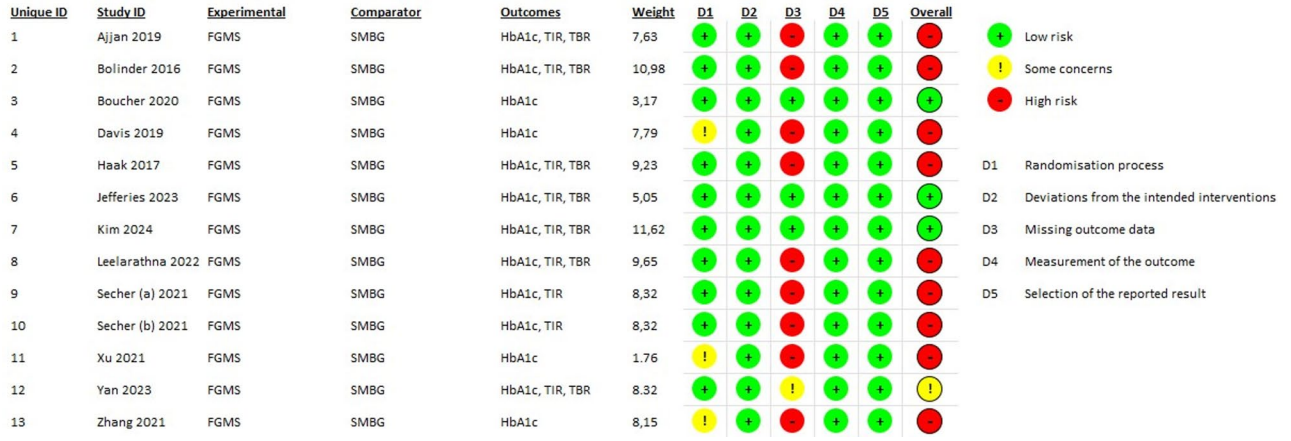

Fig. 2 Risk of bias assessment for HbA1c outcomes

Fig. 3 Risk of bias assessment for treatment satisfaction measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ); FGMS: Flash Glucose Monitoring System (FGMS; *FreeStyle Libre*); SMBG: self-monitored blood glucose

groups [16, 31, 32, 35–37, 41, 45]. One of the RCTs maintained the use of isCGM in both study arms throughout the intervention period, employing blinded isCGM in the control group [40]. Few articles reported hypoglycemic events, patient-reported outcomes were considered in a small number of analyzed studies, and a minority indicated the number of device-related adverse events. The characteristics regarding the eligibility criteria of the included studies are presented in Table 1.

Risk of bias of the included studies

Figure 2 presents the risk of bias for the included studies concerning the outcomes of HbA1c, TIR, and TBR. Figure 3 shows the risk of bias related to patient satisfaction as measured by the DTSQ questionnaire. For most of the studies included, these outcome results were assessed as having a high risk of bias due to missing data and the absence of intention-to-treat analysis.

Meta-analysis

Regarding glycemic control, the meta-analysis of HbA1c measured at the last follow-up visit favored the intervention (MD: -0.25%, CI 95%: -0.39 – -0.10%, 13 studies, 1,482 participants, I^2: 82.6%, Fig. 4; moderate certainty of evidence, Table 2). Using meta-regression, only the duration of the intervention emerged as a significant

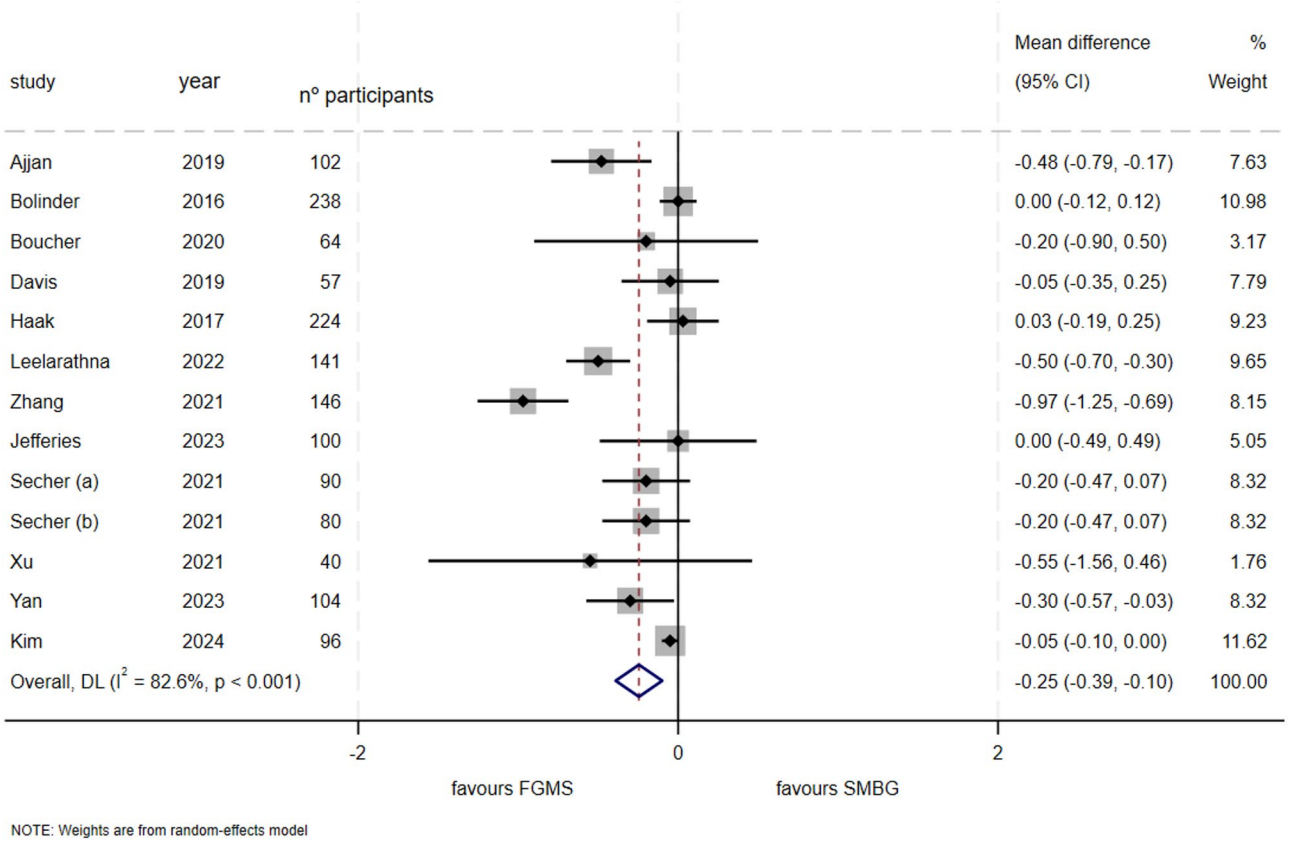

Fig. 4 Meta-analysis of glycemic control assessed by HbA1c (%)

moderator ($p = 0.003$; adjusted R-squared = 67.91%; see Fig. 5). These findings indicate that studies with an intervention duration of 24 weeks or more are expected to demonstrate an HbA1c reduction closer to -0.5%. Conversely, studies with less than 24 weeks of intervention are anticipated to have an effect close to zero. The subgroup and sensitivity analyses did not change the direction of the isCGM effect size (supplementary file).

Regarding patient satisfaction, the results of the meta-analysis favored the intervention, with an MD of 4.5 (95% CI: 2.18–6.82; I^2: 92.9%; 10 studies; 1,150 patients; Fig. 6), and the certainty of evidence was rated as moderate (Table 2). The quality of evidence was downgraded by one level because the majority of included studies were classified as having a high risk of bias. Although the CIs did not overlap, the inconsistency between studies was not considered clinically significant, as all intervals pointed in the same direction, supporting a consistent trend in favor of the isCGM.

With respect to the percentage of time with blood glucose levels less than 70 mg/dL (TBR), the meta-analysis favored the intervention, with an MD of -0.15% (95% CI: -0.23– -0.07%; I^2: 96.7%; 8 studies; 1,094 patients; see Fig. 7; Table 2). However, the quality of evidence was rated as low because of the presence of statistical heterogeneity that could not be explained by meta-regression—primarily because the number of studies included in the meta-analysis was less than 10—and not by subgroup analysis on the basis of the type of DM (supplementary file). Additionally, the evidence was downgraded because of the high risk of bias identified in the studies analyzed (Fig. 2).

For the TIR, no significant difference was found between groups (MD: 0.02%; 95% CI: -0.05–0.1%; I^2: 79.6%; 11 studies; 1,318 patients; Fig. 8; Table 2); however, the certainty of the evidence was classified as very low, owing to the inconsistency and the interval crossing the line of no effect.

With respect to isCGM-associated cutaneous adverse events, seven studies assessed this outcome, although only one actively searched for adverse events using a self-reported cutaneous adverse event via an electronic safety questionnaire. Severity was graded as mild, moderate, or severe. Compared with SMBG, the meta-analysis revealed a greater risk of mild adverse events in the intervention group (RR: 2.69, 95% CI: 1.5– 4.81; I^2: 0%, 7 studies, 991 participants; Fig. 9, moderate certainty of evidence; Table 2), while revealing no difference between groups for other skin reaction grades despite the wide confidence interval. The most frequent adverse events

Table 2 Summary of the quality of evidence, assessed via the GRADE approach, for the comparison of the intermittently scanned continuous glucose monitoring with self-monitoring of blood glucose in individuals with type 1 or type 2 diabetes on insulin therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SMBG	Risk with FGM				
HbA1c (%) Mean follow-up: 24 weeks	Mean HbA1c (%) was **0**%	Mean **0.25% lower** (0.39 lower to 0.1 lower)	-	1482 (13 RCTs)	⨁⨁⨁◯ Moderate[a]	FGMS improves HbA1c levels
Percentage of readings (time/day) within TIR	The average percentage of glucose readings (time/day) within TIR was **0**%	Mean **0.02% higher** (0.05 lower to 0.1 higher)	-	1318 (11 RCTs)	⨁◯◯◯ Very Low[a, b,c]	The evidence regarding the effect of FGMS on TIR is very uncertain.
DTSQ	Mean DTSQ was **0**	**4.5 higher** (2.18 higher to 6.8 higher)	-	1150 (10 RCTs)	⨁⨁⨁◯ Moderate[a]	FGMS appears to enhance DTSQ
Percentage of readings (time/day) in TBR	The average percentage of readings (time/day) TBR was **0**	**0.15 lower (**0.23 lower to 0.07 lower)	-	1094 (10 RCTs)	⨁⨁◯◯ Low[a, b]	FGMS may improve TBR
Mild adverse events associated with FGMS	17 per 1.000	**30 more per 1.000** (9 more to 67 more)	**RR 2.69** (1.5 to 4.81	991 (7 RCTs)	⨁⨁⨁◯ Moderate[a]	FGMS is associated with mild skin reactions

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR**: Risk ratio; **DTSQ**: Treatment Satisfaction Questionnaire; **TIR**: Target glucose range (glucose: 70 to 180 mg/dL); **FGMS**: Flash glucose monitoring system; **TBR**: Time below target glucose range (glucose ≤ 70 mg/dL).

GRADE levels of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. In the majority of the included studies, there were losses to follow-up of patients, some with losses greater than 10%, and these were not balanced across the groups.

b. The causes of this heterogeneity could not be explained by metarregression.

c. The confidence interval crosses the line of no effect

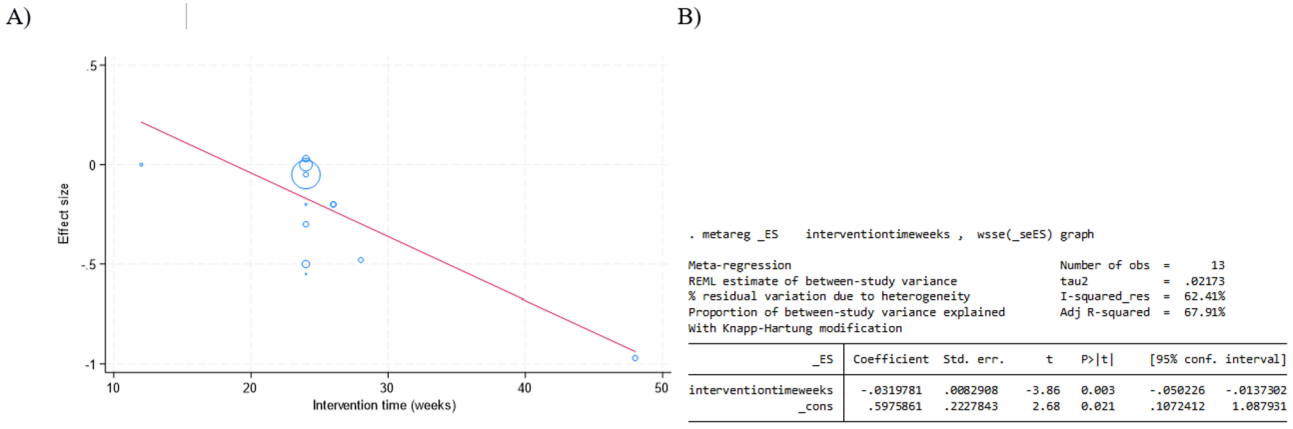

Fig. 5 (**A**) Bubble plot of the meta-regression analysis of the effect of intervention duration on HbA1c reduction. This finding indicates that studies with an intervention length of 24 weeks or more are likely to show an HbA1c decrease close to -0.5%, whereas shorter interventions tend to have effects near zero. (**B**) The residual heterogeneity (I^2 residual) was 62.41%, with 37.59% attributable to sampling variability across studies. The proportion of variance explained by the covariate (intervention duration) was 67.91%

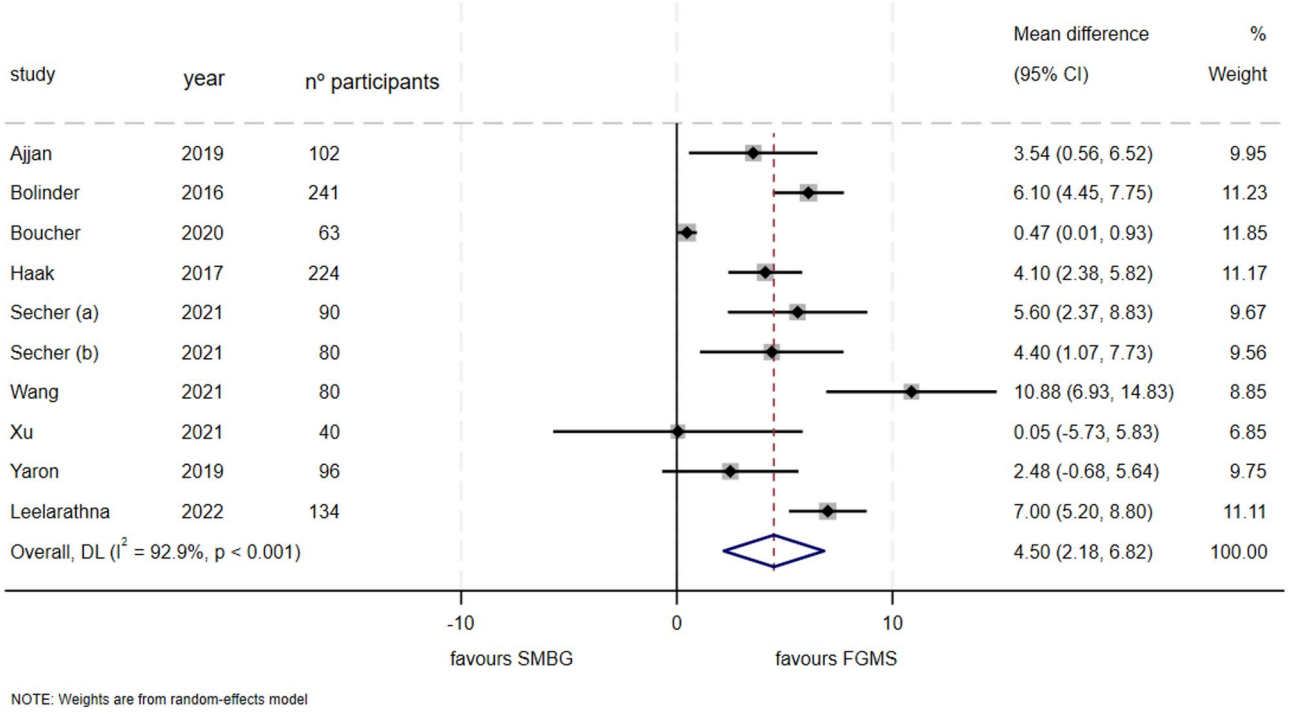

Fig. 6 Meta-analysis of patient satisfaction with diabetes treatment measured by the DTSQ

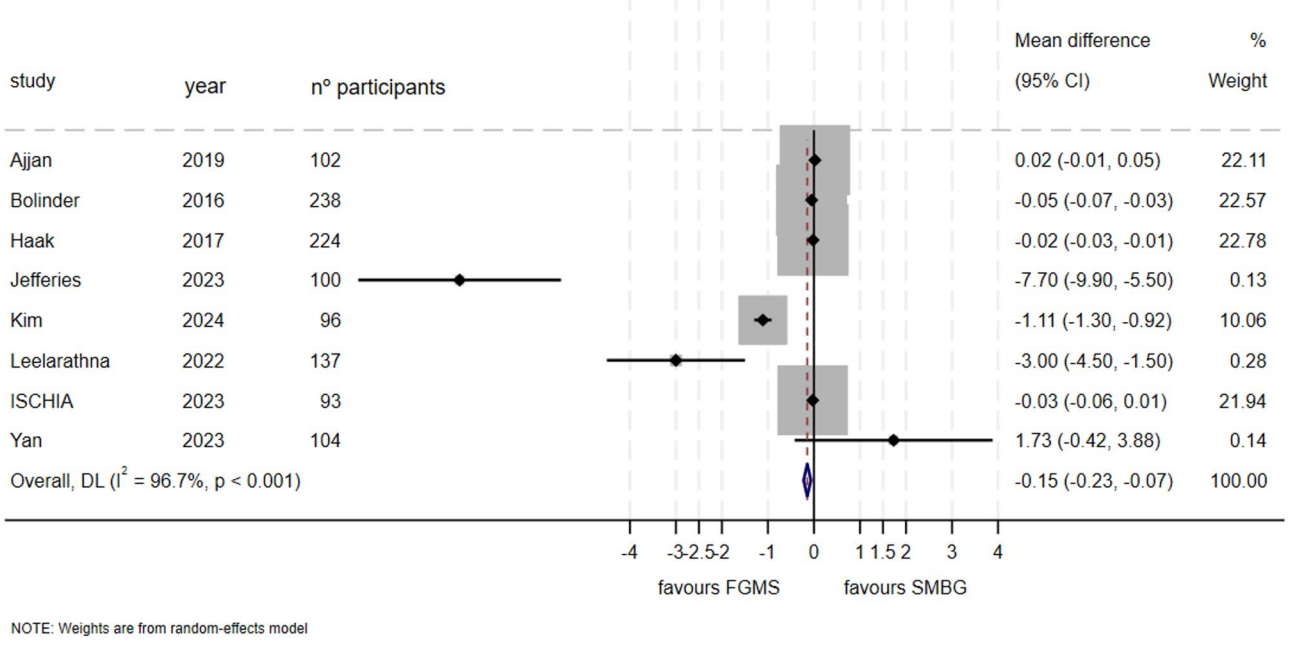

Fig. 7 Meta-analysis of the percentage of time below 70 mg/dL blood glucose level (TBR)

were mild and resolved with local treatment. Supplementary file provides a list of isCGM-related adverse events described in the studies, along with the actions taken for their management. The overall frequency of participants who ceased using isCGM due to cutaneous adverse events was 1% (95% CI: 0– 6%, 7 studies, 533 participants; supplementary file).

Regarding hypoglycemic events, the meta-analyses did not reveal a significant difference between the groups for either level 1 (MD: -0.19, 95% CI: -0.45–0.08; 3 studies; 564 patients) or level 2 (MD: -0.24, 95% CI: -0.50–0.01; 2 studies; 462 patients), as detailed in the supplementary file.

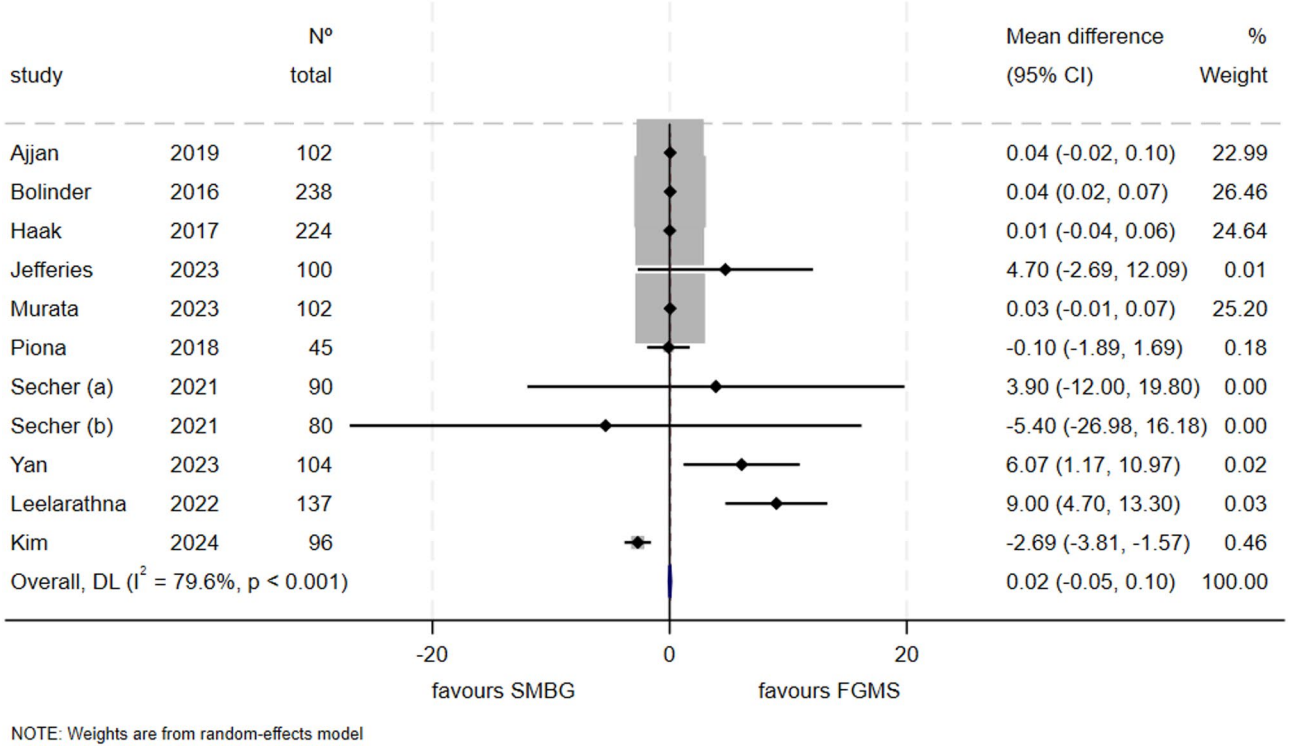

Fig. 8 Meta-analysis of time in the target glucose range (TIR)

Sensitivity analysis

The sensitivity analysis results are presented in the supplementary file. However, because most studies were classified as having a high risk of bias, the results of the two studies classified as low risk were limited by their small sample size. Consequently, we were unable to adequately assess whether the inclusion of studies with a lower risk of bias would maintain the same overall results. In any event, during the assessment of the quality of evidence, all results had their evidence quality reduced by one level, precisely owing to the high risk of bias in the majority of the included studies.

Publication bias

Publication bias was investigated for HbA1c and DSTQ outcomes. In the confunnel plots, asymmetry was not observed in any of the plots (supplementary file).

Discussion

This review included 17 RCTs comprising 1,860 participants. Compared with SMBG, the use of the isCGM reduced HbA1c levels, improved TBR and patient satisfaction, as measured by the DTSQ. However, it is important to consider that, although isCGM led to a statistically significant reduction in HbA1c in this review, the magnitude of this reduction (-0.25%, 95% CI: -0.39 – -0.10%) not represent a clinically relevant impact on glycemic control, considered 0.5% [62]. Although isCGM is associated with device-related adverse events, the vast majority of cases are mild, resulting in the discontinuation of isCGM in only 1% of patients due to skin reactions. Owing to loss to follow-up and statistical heterogeneity, no clear effect of isCGM on the TIR or the frequency of hypoglycemic events was observed.

There are at least six published systematic reviews on this topic [63–68], but none of them met the eligibility criteria for this review. Castellana et al. included 13 studies, of which only five were RCTs [68]. Cowart et al. included five RCTs but did not perform meta-analyses [63]. Elbalshy et al. evaluated various continuous glucose monitoring devices, but only four RCTs assessed isCGM [64]. Evans et al. and Gordon et al. included exclusively observational studies [65, 67]. Gao et al. reviewed 19 RCTs; however, most studies on T2DM involved patients who were not receiving insulin therapy [66]. Liang et al. included five RCTs, but two involved patients without insulin, and the remaining studies were included in our review [69].

This systematic review is particularly important because it focuses exclusively on RCTs involving patients using insulin, a population at high risk for hypoglycemic events. By concentrating on this group, this review provides more precise and clinically relevant evidence to inform treatment strategies for individuals most vulnerable to hypoglycemia. From the perspective of government policymakers adhering to high-quality synthesis

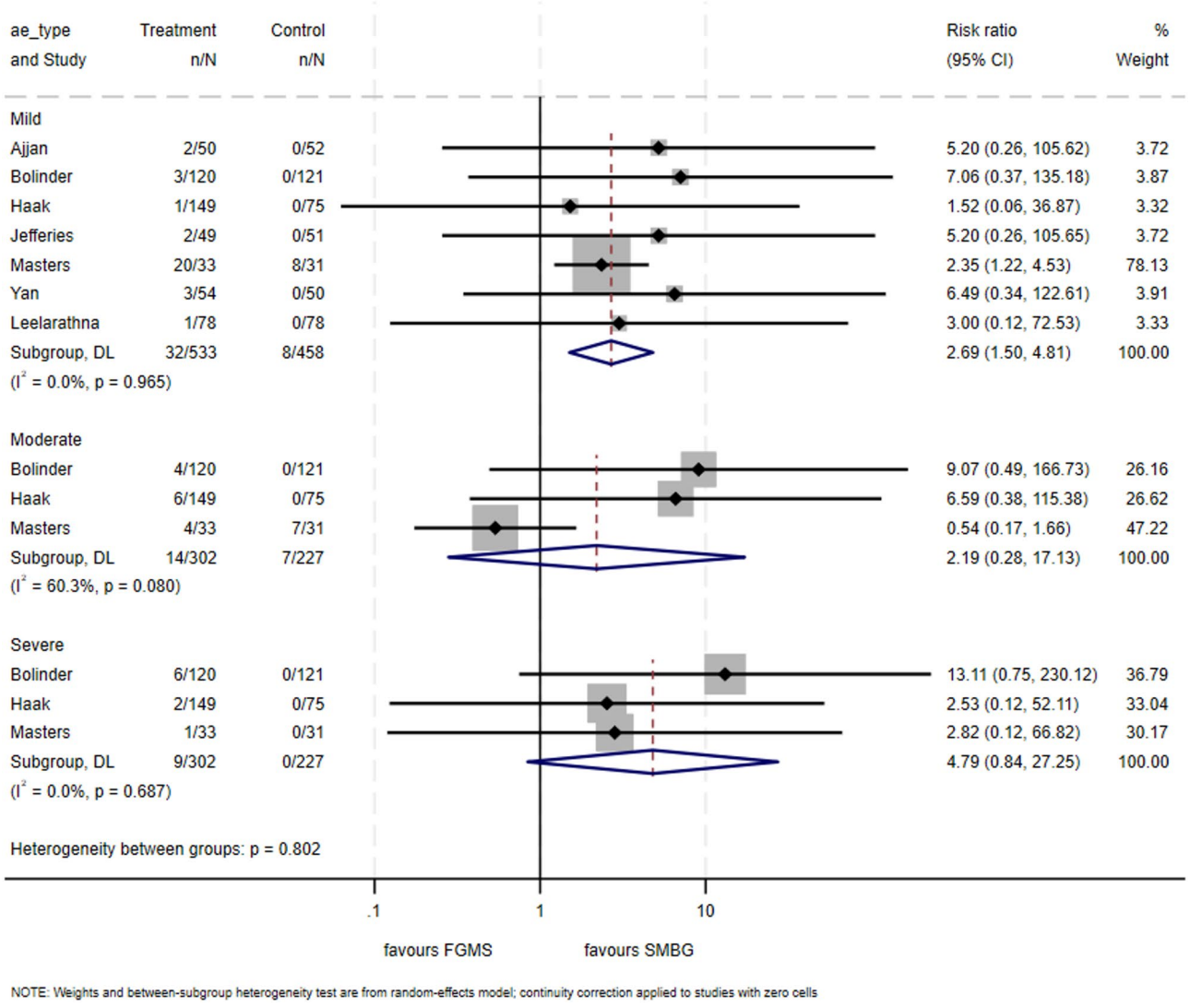

Fig. 9 Meta-analysis of device-related cutaneous adverse events associated with FGMS (Flash Glucose Monitoring System (FGMS; *FreeStyle Libre*)

guidelines, this review offers a robust and reliable evidence base. These findings can support the integration of intermittently scanned continuous glucose monitoring devices into health systems worldwide, helping to improve patient outcomes and optimize resource allocation in diabetes care. Ultimately, the review's methodological rigor and targeted focus enhance its potential to influence policy and expand access to innovative monitoring technologies globally.

One of the main limitations of this systematic review is the presence of significant statistical heterogeneity in some meta-analyses, which could not be fully explained by the variables included in the meta-regression. This variability may have affected the precision of the pooled estimates and underscores the need for cautious interpretation of the results. Additionally, none of the included studies evaluated important clinical outcomes, such as cardiovascular events or chronic diabetes complications, which are critical for understanding long-term benefits and risks. Another limitation is the variability in study design and intervention duration across the included trials, which may have contributed to heterogeneity and limited the comparability of the results. Regarding the finding, based on meta-regression, that studies with a longer intervention time obtained greater reductions in HbA1c, it may be related to survivorship bias, especially since most of the included studies had a high risk of bias due to losses and the lack of intention-to-treat analysis [70]. Furthermore, the overall quality of the evidence was rated as low to moderate, reflecting methodological differences and potential biases within the primary studies.

Time Above Range (TAR), defined as glucose levels > 180 mg/dL, is considered a useful parameter for insulin titration and treatment reassessment [71].

However, this parameter was not included as an outcome in the present systematic review, primarily due to insufficient and inconsistent data reporting across the included studies. Instead, we focused on TIR, as it provides a more comprehensive assessment of glycemic control and shows stronger correlations with both HbA1c—a well-established monitoring parameter—and the risk of chronic diabetes complications, such as retinopathy and microalbuminuria [19, 71].

Our findings should be interpreted in the context of the rapid evolution of glucose monitoring and insulin delivery technologies. isCGM has represented an important step forward from traditional SMBG, offering patients more comprehensive glycemic information and improving several clinically relevant outcomes. However, diabetes care is increasingly moving toward integrated automated insulin delivery systems, which combine real-time CGM with insulin pumps under algorithmic control, particularly for individuals with T1DM [72]. Although these systems are not yet fully "closed-loop" due to the need for pre-prandial bolus administration, they have become the standard of care in many high-resource settings. Nevertheless, isCGM remains highly relevant, given its reasonable cost, broader accessibility, and applicability in both T1DM and T2DM. Our review therefore provides important evidence for patients and clinicians who continue to rely on isCGM as a practical alternative to SMBG.

Conclusion

In conclusion, on the basis of the findings of this systematic review, compared with SMBG, isCGM enhances patient satisfaction, as assessed by the DTSQ questionnaire, and reduces the TBR. However, it may be associated with a higher incidence of mild device-related adverse events. For glycemic control, although isCGM reduced HbA1c, its clinical relevance remains uncertain, particularly given the lack of significant improvement in TIR. No definitive effect was observed in the frequency of hypoglycemic events.

Supplementary Information

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Supplementary Material 1

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Author contributions
VSNN conceptualized and designed the study. VSNN developed the search strategies. VSNN, MSB and MAFMN independently screened eligible studies and extracted data from the included studies. MSB and VSNN were used to assess the individual risk of bias. VSNN and JSCG performed the meta-analyses. VSNN supervised all the phases of this review and referred to any disagreements to avoid errors. All authors participated in data synthesis and assessment of the quality of evidence. All the authors critically revised the manuscript and approved its final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
As no primary data collection was performed, no formal ethical evaluation is required by our institution.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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