Impact of continuous glucose monitoring on improving emotional well-being among adult people with type 1 diabetes mellitus: a systematic review and meta-analysis

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Short title: Impact of CGM on well-being among people with TD1

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Key words: adults, continuous glucose monitoring, quality of life, self-monitoring of blood glucose, type 1 diabetes

What's new?

Studies showed that continuous glucose monitoring (CGM) among people treated with a continuous subcutaneous insulin infusion (CSII) led to reduction in HbA1c compared with self-monitoring of blood glucose (SMBG). Users of CGM retrospectively report more hypoglycemia safety and positive impact on their quality of life due to the CGM and audible alarms that either predict or signal low glucose levels. However, results of randomized controlled trials (RCTs) have not been consistent in demonstrating effects of CGM on quality of life and other patient-reported outcomes such as fear of hypoglycemia or hypoglycemia awareness. It is important to learn why retrospective reports and personal experience of users suggest positive impact of CGM on daily living with diabetes while RCTs fail to demonstrate it. This is the first quantitative meta-analysis of adults with T1D exclusively that provides further evidence for CGM systems' ability to reduce fear of hypoglycemia and improve emotional well-being.

ABSTRACT

Introduction: Real-time continuous glucose monitoring (CGM) has changed the way people with type 1 diabetes mellitus (T1DM) and health care providers perceived diabetes management and glucose control.

Objectives: The purpose was to compare emotional well-being between adult people with type 1 diabetes who used CGM or conventional self-monitoring of blood glucose (SMBG).

Patients and methods: The MEDLINE/PubMed, the Cochrane Library/Embase, CINAHL, Scopus, Web of Science, ProQuest databases were searched. Primary outcomes were health-related quality of life, glycemic control and fear of hypoglycemia. The inclusion criteria were: adults, RCTs, CGM, SMBG, survey studies on quality of life, fear of hypoglycemia.

Results: The meta-analysis was based on 11 studies with a total of 1228 T1DM. HFS worry domain analysis indicated reduction of hypoglycemia fear in CGM user compared with SMBG users: Cohen's d equaled -0.24 (95% CI: -0.41 to -0.07), mean difference: -3.15 (95% Cl: -5.48 to - 0.82). The outcome analysis for the DTSQ brought about Cohen's d at 0.23 (95% CI: -0.18; 0.63). The overall Cohen's d value equaled -0.24 (95% CI: -0.57; 0.09) indicating a lack CGM effect on improving HbA1c, however excluding one study from the calculations made HbA1c reduction significantly higher in CGM users (Cohen's d = -0.33; 95% CI: -0.66 to -0.00; *P*=0.047).

Conclusions: The first quantitative meta-analysis of adults T1DM exclusively that provides further evidence for CGM systems' ability to reduce fear of hypoglycemia and improve quality of life. CGM systems have advantage over SMBG in T1DM adults and improve HbA1c levels.

1. INTRODUCTION

Real-time continuous glucose monitoring (rtCGM) has changed the attitude of people with type 1 diabetes mellitus (T1DM) and health care providers towards diabetes management and glucose control [1,2]. The growing body of evidence on efficacy of rtCGM [3-8] led in 2019 the American Diabetes Association (ADA) to recommend the rtCGM to be used daily for maximum results [9].

Patients with T1DM report greater confidence in detecting and managing hypoglycemia, especially in social situations, and believe they can live more freely and safely despite being at risk of hypoglycemia [10]. This risk remains one of the major sources of emotional distress in people with diabetes [11,12]. The HypoDE study results demonstrated that rtCGM reduced emotional distress and specific fear [12,13]. Nevertheless, randomized controlled trials (RCTs) have delivered mixed results about impact of rtCGM on quality of life [4,6,14] and other patient-reported outcomes such as fear of hypoglycemia or hypoglycemia awareness [5,9,15,16].

The 2012 review by Langendam et al. examined effectiveness of continuous glucose monitoring (CGM) systems compared with conventional self-monitoring of blood glucose (SMBG) in patients with diabetes mellitus type 1 [17]. However, it did not focus on issues such as emotional well-being, quality of life or fear of hypoglycemia and the authors emphasized a need for such research.

This meta-analysis concentrates on studies published after 2012 as there had been no such work since then. It is to our best knowledge the first study to meta-analyze impact of CGM on emotional well-being among adult people with type 1 diabetes mellitus.

There are CGM systems integrated with an insulin pump (sensor augmented pump, SAP) and independent ones. The quality of treatment in type 1 diabetes patients is also affected by the

model of insulin therapy: multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII). The newer insulin pumps integrated with CGM have additional functions and automatic features such as close-loop-systems that protect patients against hypoglycemia. It is important to learn why retrospective studies and personal experience of users indicate positive effect of rtCGM on their daily life while RCTs fail to demonstrate a significant effect on patient-reported outcomes [12]. We decided to analyze effect sizes for patient-reported outcome measures in order to investigate more precisely the impact of rtCGM on T1DM reported outcomes. The control group included T1DM who used conventional self-monitoring of blood glucose (SMBG). SMBG and CGM measure glucose differently, the former in blood directly, while the latter in subcutaneous tissue. Thus, such measurements of glucose in blood may not necessarily be in line with each other and the largest differences refer to low value levels. Nevertheless, CGM is considered appropriate for evaluating trends in glucose level. SMBG may also be performed occasionally in CGM groups, e.g. for calibration of systems that require it or when a sensor needs to be changed [14-17].

The aim of this meta-analysis was to compare differences in emotional well-being (including fear of hypoglycemia) among adults with T1DM who used CGM and SMBG. The additional objective was to compare HbA1c levels between T1DM using CGM and patients with diabetes using SMBG. This was the only clinical parameter common for the studies included in the meta-analysis.

2. PATIENTS AND METHODS

2.1. Inclusion criteria

Type of studies, participants and interventions

The study inclusion criteria included randomized controlled trials and survey studies comparing emotional well-being, including health-related quality of life and fear of hypoglycemia. The participants were individuals aged 18 or older classified as having type 1 diabetes mellitus (DM) with glycated hemoglobin (HbA1c) of at least 7.5% (58 mmol/mol) and using any type of CGM and SMBG.

Intervention: Continuous glucose monitoring systems (invasive retrospective and real-time systems).

Control: Conventional SMBG defined as self-measurements of blood glucose using glucometers and finger sticks (glucose level measured with a blood glucose meter).

Types of outcome measures

Primary outcomes:

- emotional well-being, including quality of life: diabetes-specific, measured with a validated instrument such as the 'Hypoglycemia Fear Survey' or the 'Diabetes distress' or generic, measured with a validated instrument like the 'WHO-5 Well-Being Index'; or other;

- glycemic control: change in glycated hemoglobin A1c level (HbA1c).

We were not able to analyze secondary outcomes such as complications and adverse effects, CGM derived glycemic control, deaths, costs, covariates, effect modifiers or confounders because data from each study were presented in differently and thus incomparable. The same referred to episodes of hypoglycemia (<70 mg/dL, <3.9 mmol/L) or ketoacidosis.

Search methods

The MEDLINE/PubMed, the Cochrane Library/Embase, CINAHL, Scopus, Web of Science, ProQuest databases were searched with a time restriction of January 1, 2013 to October 30,

2019 and using various combinations of key terms: continuous glucose monitoring, adults, quality of life, hypoglycemia fear survey. Reference lists of selected studies were hand-searched. Additional information is described in the Supplementary material 1, *Search strategies*. We analyzed articles in English only. Reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports were checked to identify additional studies.

2.2. Data collection and analysis

Selection of studies

Two authors independently scanned the titles or abstracts of every record retrieved in order to identify studies for further assessment. All potentially relevant articles were investigated as full text. We tried to find the final publication of the trial whenever only abstracts were available. Studies without a final publication were considered separately. In case of duplicate publications and accompanying reports of a primary study, we tried to maximize yield of information by simultaneous evaluation of all available data.

The full text articles were examined for compliance with eligibility criteria. We included studies in the review if they:

- were RCTs or survey studies;

- included adults (> 18 years of age), patients with type 1 DM;

- lasted > 8 weeks;

- included a CGM system and emotional well-being.

We excluded studies if:

- they included children, adolescents, pregnant women, exclusively patients with type 2 diabetes;

- CGM system was not compared with conventional SMBG levels or with another type of CGM system;

- none of the preferred outcomes were reported.

Two researchers performed study selection independently. Differences in opinion were resolved through discussion. The Figure 1 presents the adapted PRISMA flow-chart of study selection [18]. The study was registered to the PROSPERO (ID: CRD42020155077).

Data extraction and management

Two researchers independently abstracted relevant population and intervention characteristics using standard data extraction templates for studies that met the inclusion criteria (Table 1). Additional data are described in Supplementary material, *Table S1*. Disagreements were resolved by discussion. Any missing relevant information was sought from the original author(s) of the article. Extracted data are presented in Table 1.

Risk of bias

Two authors assessed each study independently using the Cochrane Collaboration's tool [19]. Disagreements were resolved by consensus. Additionally, the online study [20] included in the review was checked according the to the EQUATOR Network's guidelines [21] and the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [22,23] to verify its quality. Additional data are described in the Supplementary material, *Table S2 and Table S3*.

Reporting biases

We used funnel plots with Begg-Mazumdar and Egger tests to assess the potential asymmetry of results and small study bias. Potential sources of asymmetry on funnel plots are publication bias, poor methodological quality of smaller studies and true heterogeneity in effect associated with study size [19].

Data synthesis

The following comparisons were included in the analyses: CGM system versus conventional self-monitoring and between different types of CGM systems.

Heterogeneity and sensitivity

The heterogeneity of the studies was evaluated using the I^2 inconsistency index (0%-100%) and between study variance of true effects T^2. The higher the I^2, the greater the heterogeneity. The I^2 value higher than 50% indicates substantial heterogeneity, the value higher than 75% indicates high heterogeneity [24]. The $T^2 > 0$ is considered substantial. The sensitivity analysis was performed by removing individual studies from the overall result.

Statistical analysis

The effect size expressed by Cohen's d and pooled mean difference with a 95% confidence interval between CGM and SMBG users were estimated using random effect model. The p-value of <.05 was considered statistically significant. Statistical analyses were performed with STATISTICA software (version 13.1; Dell Inc. 2016).

3. RESULTS

3.1. Studies included

Eleven studies were eventually included in the review with a total of 1228 T1DM [10,12,14,16,20,25-30]. Nine studies were randomized trials[10,12,14,16, 26 – 30], one was quasi-experimental comparative design pilot study [25] and one was an online survey [20]. The average age ranged from 42.6 [25] to 70.7 [20]. The participation of women in study groups varied between 45% [14] and 64% [16]. The percentage of people using an insulin pump varied significantly between studies and ranged from 3% [16,27] to 100% [26]. Three

studies [10,12,28] included participants that did not use an insulin pump and one study did not provide such information [30]. The characteristics of studies are described in Table 1.

We included 7 studies [14,16,20,25-28] in the quantitative synthesis and 4 studies [10,12,29,30] in the qualitative synthesis. Studies included in the qualitative synthesis had outcomes reported as: median and interquartile range [30], mean difference [29] and baseline-adjusted means [12]. The study by Olafsdottir et al. [10] was excluded from the quantitative analysis because it replicated results of the study by Lind et al. [28].

3.2. Excluded Studies

Three studies with a total of 931 T1DM [31-33] were excluded because they lacked control groups. The methodological characteristics of the excluded studies are described in *Table S1*.

3.3. Quality Assessment

Of the 11 studies, one was conducted using the questionnaire method. Among the suggested guidelines we found CHERRIES to be the most suitable for a web-based survey. The scoring system and outcomes are summarized in *Table S2*. Out of the ten randomized studies, eight had a low risk of bias, one study had a moderate risk of bias and one study had a high risk of bias (*Table S3*). Two studies were conducted with intention to treat. The risk of bias in individual studies is presented in *Table S4*. Eight studies had pre-protocols with three of them being individually-randomized parallel-group trials and five being individually randomized cross-over trials. Figure 2a and 2b show in detail risk of bias for individual studies.

3.4. Qualitative Synthesis

The outcomes of the qualitative synthesis are shown in *Table S5*. Only one study reported higher level of HbA1c in the CGM group after intervention (compared with the control group) [12]. The studies using the HFS-II total score, HFS Worry, HFS Behavior / Avoidance

reported a higher score in the control group after follow-up [12,29]. The only exception was Reddy et al. 2018 [30] which had a higher score for CGM on HFS-II total score, HFS Worry, HFS Behavior / Avoidance and PAIDS. Likewise, in the study by Reddy et al. 2018, the PAIDS score was significantly higher for the CGM group (compared with the control group) from baseline to follow-up. No differences were observed for DDS score [12]. One study (Olafsdottir AF, et al., 2018) analyzed [10] Hypoglycemic Confidence Questionnaire (HCQ) and had a higher score in the CGM group compared with the SMBG group. The WHO-5 Well-Being Index was analyzed by van Beers CAJ et al. 2017, however authors did not disclose their data [29].

3.5. Quantitative Synthesis

3.5.1. Hypoglycemia Fear Survey II (HFS-II)

3.5.1.1. Hypoglycemia Fear Survey – total

Four studies were included in the outcome analysis for the HFS-II total questionnaire [16,24,26,27]. The Cohen's d value (95% CI) for HFS-II total equaled -0.04 (-0.32; 0.24), P=0.78, indicating a lack of CGM effect in reducing fear of hypoglycemia. Additional data are described in Supplementary material (*Figure S1*).

3.5.1.2. Hypoglycemia Fear Survey – worry

Six studies were included in the outcome analysis for the HFS worry questionnaire [14,16,20,25,26,27]. The Cohen's d value (95% CI) equaled -0.24 (-0.41; -0.07) and the result was statistically significant: P=0.005 (*Figure S2*). The mean difference analysis indicated that using CGM reduced the level of fear of hypoglycemia by approximately 3 points: -3.15, P = 0.008; 95% Cl -5.48 to - 0.82 (Figure 3).

3.5.1.3. Hypoglycemia Fear Survey – behavior

Four studies were included in the outcome analysis for the HFS behavior questionnaire [16,25,26,27]. Cohen's d (95% CI) value for HFS behavior equaled -0.03 (-0.30; 0.24) indicating a lack CGM effect in reducing fear of hypoglycemia (*Figure S3*).

3.5.2. Diabetes Treatment Satisfaction Questionnaire (DTSQ)

Four studies were included in the outcome analysis for the DTSQ total (status version) [16,26,27,28]. Cohen's d value equaled 0.23 (95% CI: -0.18; 0.63), indicating a lack CGM effect on higher treatment satisfaction (*Figure S4*).

3.5.3. Change in HbA1c

The reduction of HbA1c in CGM intervention groups varied between 0.43 and 1.0 percentage points in three of the studies [14,25,28]. Little et al. found no differences in the 2018 study in HbA1c level between intervention and control groups (7.7%) [27]. Meanwhile, Little et al. in 2014 as well as Kropff, et al. in 2016 observed minor reduction of HbA1c for control groups (both by 0.1% percentage points) [16,26]. Changes in HbA1c levels for each study are presented in Table 2. The overall Cohen's d value equaled -0.24 (95% CI: -0.57; 0.09) indicating no impact of CGM on HbA1c level (*Figure S5*).

3.6. Sensitivity Analysis and publication bias assessment

3.6.1. Hypoglycemia Fear Survey II (HFS-II)

3.6.1.1. Hypoglycemia Fear Survey – total

The studies using the HFS-II total questionnaire [16,25,26,27] demonstrated low heterogeneity with $I^2 = 0$ % (95% CI: 0 – 63 %) and $T^2 = 0$ (95% CI: 0.00 – 0.16). The sensitivity analysis showed that excluding individual studies did not change the result significantly. The Cohen's d values ranged from -0.07 (95% CI: -0.44; 0.31) to -0.00 (95% CI; -0.29; 0.28) (Table 3). The relationship between effect size and study size is presented in the funnel plot (*Figure S6*). The Egger test did not indicate association between effect size and

standard error ($P = 0.06$), however the Begg-Mazumdar test indicated an association between effect size and standard error ($P = 0.04$).

3.6.1.2. Hypoglycemia Fear Survey – worry

The studies using a HFS worry subscale [14,16,20,25,26,27] demonstrated low heterogeneity with $I^2 = 0\%$ (95% CI: 0 – 48 %) and $T^2 = 0$ (95% CI: 0.00 – 0.04). The sensitivity analysis showed that excluding individual studies did not significantly change the result. The Cohen's d values ranged from -0.27 (95% CI: -0.45; -0.09) to -0.20 (95% CI: -0.40; -0.01) (Table 3). The relationship between effect size and study size is presented in the funnel plot (*Figure S7*). The Begg-Mazumdar and the Egger tests did not indicate associations between effect size and standard error ($P = 0.85$ and $P = 0.86$, respectively).

3.6.1.3. Hypoglycemia Fear Survey - behavior

The studies using a HFS - behavior questionnaire [16,25,26,27] demonstrated low heterogeneity $I^2 = 0\%$ (95% CI: 0 – 62%), $T^2 = 0$ (95% CI: 0.00 – 0.14). The sensitivity analysis showed that excluding individual studies did not significantly change the result. The Cohen's d values ranged from -0.08 (95% CI: -0.39; 0.23) to 0.02 (-0.34; 0.37) (Table 3). The relationship between effect size and study size is presented in the funnel plot (*Figure S8*). The Begg-Mazumdar test and the Egger test did not indicate association between effect size and standard error ($P = 1$ and $P = 0.45$, respectively).

3.6.2. Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The studies using DTSQ [16,26,27,28] demonstrated high heterogeneity of $I^2 = 74.5\%$ (95% CI: 29.0 – 90.9%) and $T^2 = 0.12$ (95% CI: 0.02 – 0.42). The Lind et al. 2017 [28] distinguished substantially from other studies in terms of the effect size of 0.67 (*Figure S4*). The sensitivity analysis showed that exclusion of this study lowered the effect size to almost zero; d=0.03 (95% CI: -0.25; 0.30). Cohen's d value from 0.03 (95% CI: -0.25; 0.30) to 0.30

(-0.18; 0.78) (Table 3). The relationship between effect size and study size is presented in the funnel plot (*Figure S9*). The Begg-Mazumdar test did not indicate association between effect size and standard error ($P = 0.12$), however such association was indicated by the Egger ($P = 0.04$).

3.6.3. Change in HbA1c

The studies analyzing HbA1c levels [14,16,25-28] demonstrated high heterogeneity of $I^2 = 71.7\%$ (95% CI: 34.5 – 87.8%) and $T^2 = 0.11$ (95% CI: 0.02 – 0.31). The sensitivity analysis showed that excluding Kropff et al. 2016 [26] had significant impact on the Cohen's d changing it to -0.33 (95% CI: -0.66; -0.00). The values ranged from -0.24 (95% CI: -0.57; 0.09) to -0.33 (95% CI: -0.66; -0.00) (Table 3). The relationship between effect size and study size is presented in the funnel plot (*Figure S10*). Begg-Mazumdar test and Egger test did not indicate an association between effect size and standard error ($P = 0.77$ and $P=1$, respectively).

4. DISCUSSION

This systematic review and meta-analysis examined 11 studies comparing head-to-head the CGM and SMBG interventions for T1D in adult populations. This is, to our best knowledge, the first quantitative meta-analysis of adults with T1D exclusively that provides further evidence for CGM systems' ability to reduce fear of hypoglycemia and improve emotional well-being. Our calculations show that using CGM may reduce a level of hypoglycemia fear by approximately 3 points: -3.15. This may not be considered a substantial reduction as HFS-W scores range between 0 – 72 points with a higher score indicating a higher level fear [34]. The sensitivity analysis showed that CGM was able to improve HbA1c levels, however it did not affect scores for HFS – II total, HFS – behavior domain or DTSQ.

The studies that were included in the HFS worry subscale analysis [14,16,20,25,26,27] demonstrated low heterogeneity while the Cohen d value indicated that using CGM increased patient satisfaction compared with control groups. As heterogeneity of these studies was low while the Cohen d value significant, the reliability of this result is rather high. Nevertheless, studies using DTS [16,26,27,28] had high heterogeneity with a single large effect size 0.67 for Lind et al. [28].

Out of the seven studies, six investigated a change in HbA1c [14,16,25-28] and one by Polonsky WH, et al., 2016 used questionnaires only [20]. The value of Cohen d also suggested the positive effect of CGM on HbA1c levels. Excluding the Kropff et al. [26] in the sensitivity analysis showed that HbA1c level improvement was statistically significant with a larger effect size. The possible explanation is that the control group in the Kropff's et al. study [26] consisted of T1DM with a closed-loop glucose control system (artificial pancreas). Therefore, it was excluded from the analysis. The studies by Polonsky et al. [14] and Lind et al. [28] had large groups of T1DM (158 and 161, respectively) and their individual effect size was high: -0.70 (95% CI: -1.0; -0.36, $P<0.001$) and -0.49 (95% CI: -0.72; -0.25, $P<0.001$), respectively, suggesting that the two may be considered most reliable. This finding is in line with results of another meta-analysis [17] that looked at both, adult and pediatric population.

4.1. Strengths and Limitations of the Study

Among strengths of our study are narrow inclusion criteria that make calculations more reliable. Unlike other studies, we also investigated a fear of hypoglycemia. This meta-analysis is the first study to analyze emotional well-being including quality of life among adult T1DM using CGM and the first attempt to evaluate the effect of CGM on fear of hypoglycemia in adults with T1DM. The risk of publication bias was found to be low, but due to the small number of included studies this result is not reliable and should be treated with great caution. There is still a need for larger sample sizes to investigate the true effect of rtCGM more

precisely. This issue requires further, insightful examination, also in terms of methodology for randomized clinical trials that investigate emotional well-being of T1DM.

The qualitative meta-synthesis by Messer et al. demonstrated a positive impact of CGM on physical, emotional and relational aspects of life [35]. Our quantitative meta-analysis focused on emotional general well-being that includes some aspects of quality of life and fear of hypoglycemia. The reason was that we did not identify any studies that would quantify quality of life and meet the inclusion criteria. HFS, EQ-5D or DTSQ are not tools for assessing quality of life, but measures of emotional well-being, so available evidence is another limitation.

The limitations include a relatively small number of studies included. Second, we were not able to compare clinical outcomes as each study used different measures or methodology. Various methodologies were the reason for excluding 3 studies with considerable samples [31-33] as they had no control groups. Lind et al. [28] who used the Swedish version of HFS - behavior questionnaire is one of examples. Hence, some studies could only be subject to qualitative analysis [10,12,29,30].

Our meta-analysis covers articles that analyzed the impact of CGM and SMBG on emotional well-being in T1DM adults. Therefore, we were not able to compare details of different methods for treating type 1 diabetes, ex. measurement frequency, differences in insulin doses in CGM groups and SMBG groups or evaluation of hypoglycemia.

4.2. Implications for Current Clinical Practice and Future Research

This systematic review suggests minor superiority of CGM systems in controlling glycaemia among adults. However, it is important to note that there are also other treatments methods for type 1 diabetes and other CGM systems used in clinical practice. Our results are in line with Ehrmann's et al. [12] conclusions that CGM has significant impact and medium effect size on

fear of hypoglycemia at d = 0.32 (95% CI: 0.01-0.66). This suggests that larger samples of patients could result in larger effect sizes and differences in outcomes. The greater number of studies could also result in more significant Cohen's d values. However, substantial differences in methodology of studies addressing the subject of life quality and fear of hyperglycemia were the reason for including only 7 studies using the same research tool (questionnaires) [14,16, 20, 25-28].

Larger sample sizes may be essential to better investigate the true effect of rtCGM. Large-scale clinical trials with longer follow-up periods are necessary to thoroughly investigate how quality of life benefits from different CGM systems and how it affects glucose variability, hypoglycemia risk, HbA1c levels as well as on acute and chronic diabetes complications.

This study suggests that CGM systems have advantages over the SMBG as they significantly reduce fear of hypoglycemia and improve HbA1c levels. However, more studies with larger samples are necessary to investigate associations between CGM and quality of life or fear of hypoglycemia. It is also essential to standardize methods, measures and results for clinical trials that examine quality of life and fear of hypoglycemia in adults with TD1.

Comparing effect sizes demonstrated that the effect of CGM on patient reported outcomes was considerably small. This should be taken into account when future RCTs on the effect of CGM on T1DM reported outcomes are planned.

Contribution statement: AK and RO conceived of the study concept and developed the study design. AK, JO and MM were responsible for data collection and analysis. AK, MM and JO drafted the manuscript. AK and MM were responsible for the data interpretation. AK and RO revised the final draft. All authors approved the final version to be published.

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Table 1. Characteristics of included studies

Source	Population	Year	Country	Study design	Sample	Women %	Age, mean (SD)	Type of CGM	Duration of interventions and follow-up	Control group (e.g. SMBG or blinded CGM)	HbA1c inclusion criterion	Baseline HbA1c	Insulin pump users	Duration of disease, years	Quality of life, measure, questionnaire	Funding source
									Studies included in the quantitative synthesis							
Polonsky WH, et al., 2017 [14]	adults	ND	USA	prospective randomized trial	158	45.0	48.0	Dexcom G4 Platinum	24 weeks	SMBG	7.5–10.0%	8.6% (0.6)	NO	12.0 (14)	WHO-5, EQ-5D-5L, DDS, HFS-II Worry, HCQ	Dexcom, Inc. provided funding for the study to the Behavioral Diabetes Institute and to the Jaeb Center for Health Research
Walker TC, et al., 2014 [25]	adults	ND	USA	quasi-experimental comparative design pilot study	10	60.0	42.6 (9.6)	Dexcom SEVEN PLUS™ CGM system (Dexcom Inc, San Diego, CA)	12 weeks	CGM units modified to obscure the numerical glucose value	ND	7.68 (1.56)% CGM, 7.24 ± 1.05% control	40%	20.0 (13.6)	HFS-II, QLI-D	This study was completed with the assistance of an unrestricted equipment grant from Dexcom Inc.
Polonsky WH, et al., 2016 [20]	≥ 65	2016	USA	online survey	285	48.1	70.7 (5.0)	Dexcom, Inc	4 months	RT-CGM hopefuls	NO	NO	56.5%	36.1 (18.5)	WHO-5, HFS-II, DDS	This work was funded by Dexcom, Inc.
Kropff J, et al. 2016 [26]	adults	ND	France, Italy, the Netherlands	multicenter, randomized crossover trial	32	56.3	47.0 (11.2)	continuous glucose monitoring	8 weeks	closed-loop glucose control using an artificial pancreas	7.5–10.0%	8.2 (0.6)%, 66 (5) mmol/mol	100%	28.6 (10.8)	HFS-II, DTSQ,	The study was supported by the European Community Framework Programme 7 (FP7-ICT-2009-4 grant number 247138).

Little SA, et al., 2018 [27]	adults	ND	UK	multicenter, randomized, 2 x 2 factorial study	96	63.0	49.0 (12)	RT-CGM, Medtronic iPRO	24 weeks	SMBG	< and ≥ 8%, [< and ≥ 64 mmol/mol]	66 (12) mmol/mol	3%	29.0 (12)	HFS-II, DTSQ	The study was funded by a peer-reviewed grant from Diabetes UK (07/0003556). The National Institute for Health Research and the Cambridge National Institute for Health Research Biomedical Research Centre funded data entry and trial support.
Little SA, et al., 2014 [16]	adults	ND	UK	multicenter, randomized, 2 x 2 factorial study	96	64.0	48.6 (12.2)	Medtronic iPro1	24 week	SMBG	< and ≥ 8%, [< and ≥ 64 mmol/mol]	8.3%, (67 mmol/mol)	3%	29.0	HFS-II, DTSQ	The study was funded by a peer-reviewed grant from Diabetes UK (07/0003556). The National Institute for Health Research and the Cambridge National Institute for Health Research Biomedical Research Centre funded data entry and trial support.
Lind M, et al., 2017 [28]	adults	2014-2016	Sweden	randomized in a cross-over, open-label, controlled	161	45.3	43.7	Dexcom G4 PLATINUM, Dexcom Inc, San Diego, CA	69 weeks	SMBG	≥ 7.5% (58 mmol/mol)	8.6% (70mmol/mol)	NO	22.2 (11.8)	WHO-5, DTSQ, HFS-II, HCQ, PAIDS	The trial was sponsored by the NU Hospital Group, Trollhättan and Uddevalla, Sweden

Studies included in the qualitative synthesis

Ehrmann D, et al., 2019 [12]	adults	ND	German	multicentre, randomised controlled trial	141	31.8 - control group, 46.7 - CGM	47.3 (10.1) - control group, 45.8 (12.0) - CGM	Dexcom Gen 4 Platinum sensor	30 weeks	SMBG	≤9.0%	7.4% (1.0) - control grouo, 7.6% (1.0) - CGM	NO	20.8 (13.1) - control group, 20.9 (14.0) - CGM	GMSS, HFS-II, EQ-5D	Study was funded by Dexcom, Inc., San Diego.
vab Beers CAJ, et al., 2017 [29]	adults	ND	ND	randomized, open-label crossover trial	52	46.2	48.6 (11.6)	ND	16 weeks	SMBG	ND	7.5% (0.8%)	44.2%	30.5 (18.5–40.8)	WHO-5, PAID-5, HFS Worry	This research received funding from Eli Lilly and Sanofi. Medtronic provided continuous glucose monitoring devices.

Study	Population	Years	Country	Design	N			Intervention	Duration	Comparator	Threshold	HbA1c			Outcomes	Funding
Reddy M, et al., 2018 [30]	adults	ND	UK	prospective randomized non masked parallel group study	36	ND	ND	Dexcom G4	16 weeks	flash glucose monitoring (Abbott Freestyle Libre)	<58 or ≥ 58 mmol/mol	54.0 (46.0 to 62.0) CGM, 51.0 (48.5 to 59) control	ND	ND	HFS-II, PAID	This study was funded by Dexcom.
Olafsdottir AF, et al., 2018 [10]	adults	2014-2016	Sweden	open-label multicenter crossover randomized clinical trial	161	46.4	44.6 (12.7)	Dexcom G4 PLATINUM, Dexcom Inc, San Diego, CA	69 weeks	SMBG	≥ 7.5% (58 mmol/mol)	8.7 (0.84)% , 72 (9.1) mmol/mol	NO	22.2 (11.8)	HCQ	The trial was sponsored by the NU Hospital Group, Trollha¨ttan and Uddevalla, Sweden.

Data are mean: SD or n (%); CGM, continuous glucose monitoring; DDS, diabetes distress; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GMSS, Glucose Monitoring Satisfaction Survey; HbA1c, glycated hemoglobin A1c; HCQ, Hypoglycemia Confidence Questionnaire; HFS-II, Hypoglycemia Fear Survey; HFS-II Worry, worry subscale of the Hypoglycemia Fear Survey; ND, no data; NO, none; PAIDS, Problem Areas in Diabetes Scale; QLI-D, Quality of Life Index–Diabetes; SMBG, self-measurements of blood glucose; WHO-5, World Health Organization–5.

Table 2. The outcomes of the glycated hemoglobin A1c (HbA1c)

Source	Study group		Control group	
	Primary end point HbA1c, mean (SD), %	**n**	**Primary end point HbA1c, mean (SD), %**	**n**
Lind M, et al., 2017 [28]	7.92 (0.79) %	142	8.35 (0.97) %	142
Polonsky WH, et al., 2017 [14]	7.7 (0.8) %	105	8.2 (0.5) %	53
Walker TC, et al., 2014 [25]	6.18 (1.14) %	5	7.18 (1.31) %	5
Polonsky WH, et al., 2016 [20]	questionnaire survey			
Kropff J, et al. 2016 [26]	8.0 (0.4) %	32	7.9 (0.5)%	32
Little SA, et al., 2018 [27]	7.7 (3.1) %	36	7.7 (3.2) %	36
Little SA, et al., 2014 [16]	8.2 (1.1) %	46	8.1 (0.9)%	43

HbA1c, glycated hemoglobin A1c; SD, standard deviation.

Table 3. Sensitivity analysis for: Hypoglycemia Fear Survey – II total, worry, behavior,

Diabetes Treatment Satisfaction Questionnaire, glycated hemoglobin A1c (HbA1c).

Cohen's d analysis

Excluded study	d	Lower 95% CI	Upper 95% CI	*P*	Weight	Standard Error of Cohen's d	Standard Error of Cohen's d change
HFS – II total, HFS worry and HFS behavior							
HFS – II total							
Little 2014	-0.07	-0.44	0.31	0.73	55.96%	0.19	33.68%
Walker 2014	-0.00	-0.29	0.28	0.96	95.22%	0.15	2.48%
Kropff 2016	-0.05	-0.38	0.28	0.76	72.63%	0.17	17.34%
Little 2018	-0.04	-0.36	0.28	0.79	76.19%	0.16	14.56%
Without excluding	-0.04	-0.32	0.24	0.79	100.00%	0.14	0.00%
HFS worry							
Little 2014	-0.27	-0.45	-0.09	0.003	84.46%	0.09	8.81%
Walker 2014	-0.23	-0.40	-0.07	0.006	98.30%	0.09	0.86%
Polonsky 2016	-0.21	-0.42	0.00	0.06	60.76%	0.11	28.29%
Kropff 2016	-0.26	-0.44	-0.09	0.003	90.34%	0.09	5.21%
Polonsky 2017	-0.20	-0.40	-0.01	0.04	75.37%	0.10	15.18%
Little 2018	-0.24	-0.42	-0.07	0.007	90.76%	0.09	4.96%
Without excluding	-0.24	-0.41	-0.07	0.005	100.00%	0.08	0.00%

HFS behavior							
Little 2014	0.02	-0.34	0.37	0.93	58.11%	0.18	31.18%
Walker 2014	-0.01	-0.29	0.27	0.96	95.34%	0.14	2.41%
Kropff 2016	-0.06	-0.38	0.27	0.74	70.08%	0.17	19.46%
Little 2018	-0.08	-0.39	0.23	0.63	76.48%	0.16	14.35%
Without excluding	-0.03	-0.30	0.24	0.82	100.00%	0.14	0.00%
DTSQ							
Little 2014	0.30	-0.18	0.78	0.23	75.03%	0.24	17.83%
Kropff 2016	0.28	-0.21	0.77	0.27	77.52%	0.25	21.33%
Lind 2017	0.03	-0.25	0.30	0.85	69.29%	0.14	-31.66%
Little 2018	0.27	-0.23	0.77	0.29	78.16%	0.25	22.85%
Without excluding	0.23	-0.18	0.63	0.27	100.00%	0.21	0.00%
HbA1c							
Little 2014	-0.32	-0.67	0.03	0.07	81.73%	0.18	6.56%
Walker 2014	-0.21	-0.55	0.14	0.24	94.84%	0.18	5.02%
Kropff 2016	-0.33	-0.66	-0.00	0.05	83.64%	0.17	0.16%
Polonsky 2017	-0.12	-0.48	0.23	0.49	79.73%	0.18	7.93%
Lind 2017	-0.17	-0.60	0.26	0.43	77.17%	0.22	30.12%

Little 2018	-0.29	-0.66	0.08	0.13	82.90%	0.19	13.86%
Without excluding	-0.24	-0.57	0.09	0.15	100.00%	0.17	0.00%

HbA1c, glycated hemoglobin A1c; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HFS, Hypoglycemia Fear Survey – II total, worry, behavior.
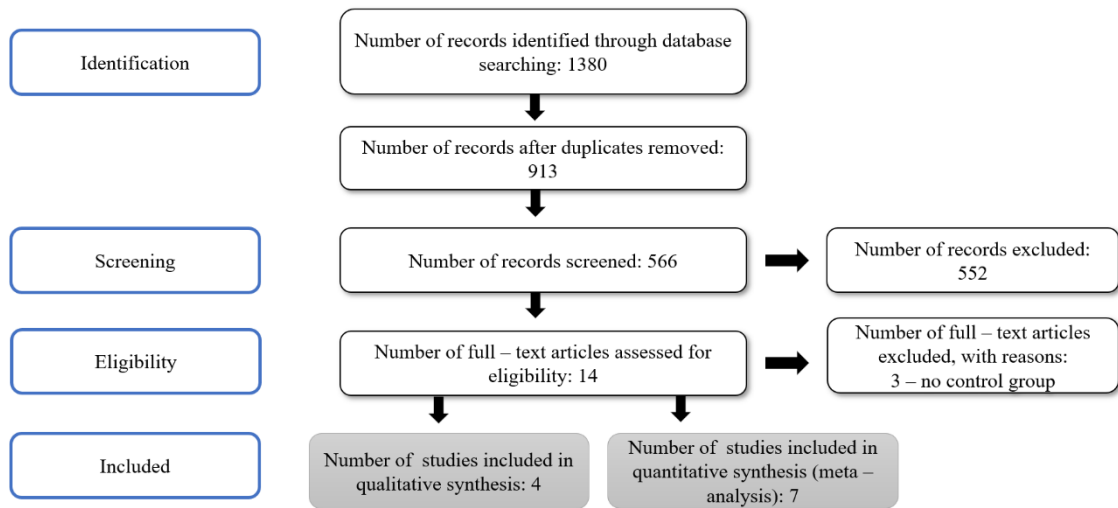
Figure 1. Study flow diagram

Figure 2a. Risk of bias studies with pre - protocol. Individually-randomized parallel-group trial

Individually randomized cross-over trial

Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Lind 2017	CGM	SMBG	fear of hypoglycemia	1	+	+	+	+	−	−
Olafsdottir 2018	CGM	SMBG	hypoglicemic confidence	1	+	?	+	+	+	!
Kropff 2016	closed-loop glucose control using an artificial pancreas	CGM	fear of hypoglycemia	1	+	+	+	+	+	+
Little 2018	CGM	SMBG	fear of hypoglycemia	1	+	+	+	+	+	+
Little 2014	CGM	SMBG	fear of hypoglicemia	1	+	+	+	+	+	+

+ Low risk
? Some concerns
− High risk

Figure 2b. Risk of bias studies with pre - protocol. Individually randomized cross-over trial

HFS worry

study	means difference (D)
Little 2014	-1.00 (-8.15; 6.15)
Walker 2014	-11.00 (-31.82; 9.82)
Polonsky 2016	-4.40 (-8.40; -0.40)
Kropff 2016	-0.10 (-5.43; 5.23)
Polonsky 2017	-4.25 (-8.77; 0.27)
Little 2018	-3.10 (-10.98; 4.78)
overall	-3.15 (-5.48; -0.82)

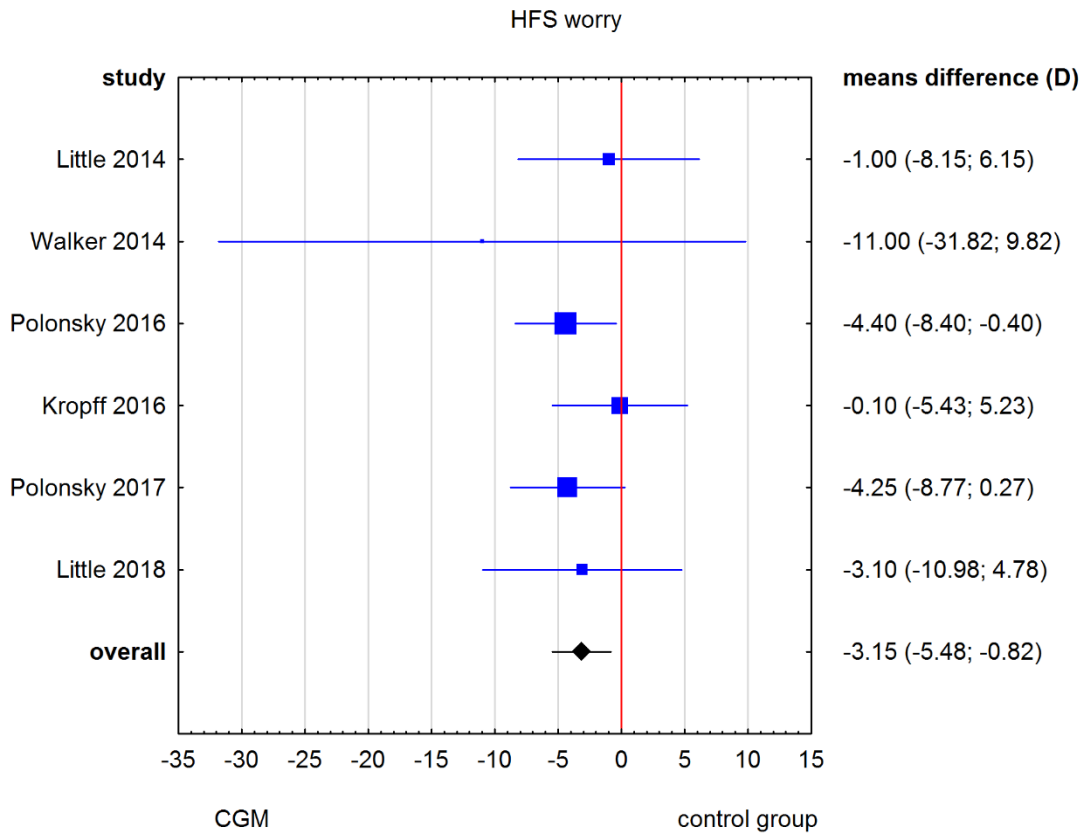CGM   control group

Figure 3. Forest plot for Hypoglycemia Fear Survey worry. Means difference analysis