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Systematic review: self-monitoring of blood glucose in patients with Type 2 Diabetes

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Abstract

Aims

The benefit of self-monitoring of blood glucose (SMBG) in the reduction of HbA_{1c} in non-insulin-treated participants remains unclear. HbA_{1c} may be improved in this population with SMBG. We aimed to investigate this.

Materials and methods

Meta-analyses of randomized controlled trials (RCTs) were performed comparing SMBG versus usual care and structured versus unstructured SMBG; the effect of clinician therapy adjustment based on SMBG readings was examined. Medline, Embase and Cochrane Central were electronically searched to identify articles published from 1 January 2000 to 30 June 2020. Trials investigating changes in HbA_{1c} were selected. Screening was performed independently by two investigators. Two investigators extracted HbA_{1c} at baseline and follow-up for each trial.

Results

Nineteen RCTs, involving 4,965 participants were included. Overall, SMBG reduced HbA_{1c}. Preplanned subgroup analysis showed that using SMBG readings to adjust therapy contributed significantly to the reduction. No significant improvement in HbA_{1c} was shown in SMBG without therapy adjustment). The same difference was observed in structured SMBG compared to unstructured SMBG.

Conclusions

HbA_{1c} is improved with therapy adjustment based on structured SMBG readings. Implications are for clinicians to prescribe structured SMBG with an aim for therapy adjustment based on the readings, and not prescribing unstructured SMBG. Participants with suboptimal glycemic control may benefit most. A SMBG regimen that improves clinical- and cost-effectiveness is presented. Future studies can investigate this regimen specifically.

Keywords

Type 2 Diabetes Mellitus, Systematic Review, Health Care Technology

INTRODUCTION

More than 450 million people live with diabetes worldwide and this is projected to rise to 700 million by 2045; over 90% of these live with type 2 diabetes (International Diabetes Federation (IDF), 2019). Glycemic control is the fundamental part of diabetes management (UKPDS Study Group, 1995), where glycosylated hemoglobin (HbA_{1c}) is the main measure for its evaluation, strongly predicting diabetes complications (Stratton et al., 2000). The American Diabetes Association (ADA), Chinese Diabetes Society (CDS), and European Association for the Study of Diabetes (EASD) (Davies et al., 2018; Jia et al., 2019) recommend maintaining a HbA_{1c} of ≤7% (53 mmol/mol) to significantly improve prognosis and reduce the risk of diabetes complications (Davies et al., 2018; Jia et al., 2019).

Blood glucose is closely linked to glycemic control: blood glucose readings strongly indicate HbA_{1c} (Nathan et al., 2008). However, the effectiveness of self-monitoring of blood glucose (SMBG) on glycemic control in non-insulin-treated participants remains unclear (Davies et al., 2018). Investigating SMBG frequencies, Xu et al. (2019) report that up to 14 SMBG readings a week reduce HbA_{1c}. Two early meta-analyses (Malanda et al., 2012; Zhu et al., 2016) supported this result, however, warned that reductions in HbA_{1c} did not achieve clinical significance, calling for further evidence. A recent meta-analysis investigated SMBG though included participants on insulin (Machry et al., 2018). Another meta-analysis only included trials up to 2015 (Mannucci et al., 2018).

The lack of clarity of SMBG benefit in non-insulin-treated participants may contribute to reluctance by clinicians (e.g., nurses) to prescribe SMBG in this population. This suggests a need for further evaluation of the effects of SMBG on HbA_{1c} in non-insulin-treated participants with type 2 diabetes to prevent disease.

Structured SMBG may afford better glycemic control. Structured SMBG has previously been regarded as testing blood glucose according to a defined regimen, with readings utilized to make appropriate therapy adjustments (participants or clinicians adjusting therapy based on SMBG readings e.g., oral hypoglycemic agents or lifestyle) (Parkin et al., 2012). However, definitions of structured SMBG have evolved and there is no current consensus (Davies et al., 2018; IDF, 2018; Parkin et al., 2012). For example, the ADA, EASD, and IDF do not offer a definition in their latest guidelines nor an optimal regimen, although the IDF provides examples for the latter: five-point or seven-point with paired (pre- and post-prandial) readings and at bedtime, or a "staggered" regimen (paired for alternate meals) (Davies et al., 2018; IDF, 2018). In this review, structured SMBG is considered as a SMBG regimen with times for SMBG readings clearly defined (e.g., three-point [such as pre-prandial for three main meals] twice weekly) which may or may not be "staggered". Furthermore, therapy adjustment is considered as clinicians adjusting therapy based on SMBG readings. The ADA, EASD, and IDF recommend prescribing SMBG with therapy adjustment; however, this is based on expert consensus and not empirical evidence (Davies et al., 2018; IDF, 2018); the IDF calls for further evidence (IDF, 2018). Accordingly, the current review addresses this call and implements an updated tool for assessing the risk of bias, not used in previous SMBG meta-analyses. This review and meta-analysis updates and extends the latest review (Mannucci et al., 2018), to explore if new trials and analysis, and investigating structured readings and therapy adjustment, have new implications for SMBG. Therefore, the aims of this review were to assess the effect of I) SMBG versus usual care and II) structured SMBG versus unstructured SMBG, on glycemic control in non-insulin-treated participants with type 2 diabetes, and extend with further analysis: III) SMBG readings used to adjust therapy versus usual care.

MATERIALS AND METHODS

This review is an update and extension to a recent review (Mannucci et al., 2018), which includes trials up to 2015. The search strategy presented in this paper was first used for studies up to 2015 which resulted in the same trials being identified as in the previous review (Mannucci et al., 2018) along with seven more recent trials. This review is presented according to the statement for preferred reporting items for systematic review and meta-analysis (PRISMA) (Moher et al., 2015). The protocol is not published elsewhere; it is registered with the International Prospective Register of Systematic Reviews (Chircop et al., 2019) – CRD42019157463.

Data Sources and Searches

Multiple initial scoping searches were executed by using preliminary versions of the search strategy, which allowed for both scoping of the literature and refinement of the final search strategy. This allowed the identification of all relevant key-words and to assure that no other reviews existed on what is being investigated. An electronic search was carried out on the databases, namely Medline, Embase, and Cochrane Central; search results up to 18 October 2019 were eligible. Search alerts for newly published articles matching the search were implemented for these databases until 30 June 2020. A search was performed on http://www.clnicaltrials.gov for any unpublished studies up to 18 October 2019. In addition, reference lists of retrieved studies were searched for other relevant studies. Recent journal issues related to the care of diabetes were searched up to 30 June 2020. An electronic search was performed to identify relevant studies that have cited previous reviews (Machry et al., 2018; Malanda et al., 2012; Mannucci et al., 2018; Xu

et al., 2019; Zhu et al., 2016). The search strategy included the following terms: blood glucose self-monitoring, SMBG, blood glucose monitoring, BGM, glycemic control, HbA_{1c}, A_{1c}, glycosylated hemoglobin, type 2 diabetes mellitus, and T2DM. Search terms were combined with Boolean operators. Truncation and wild cards were used to produce an exhaustive search. The search was limited to studies published from the year 2000 onwards because of significant improvements in blood glucose meters (e.g., decreased waiting time and sample size) (Clarke & Foster, 2012).

Study Selection

The inclusion criteria included type 2 diabetes, non-insulin-treated participants, the investigation of HbA_{1c}, and RCTs. For structured SMBG, the inclusion criteria included a SMBG regimen, which is clearly defined, with ≥10 readings every two months. Exclusion criteria included type 1 diabetes, insulin-treated participants, the investigation of parameters other than HbA_{1c}, continuous glucose monitoring, telemonitoring, telecare, observational, retrospective, and single-arm trials, and languages other than English, Italian, and Japanese. Usual care was considered as care that would have otherwise (if not enrolled in a trial) been received and that an intervention group would also be receiving; this may include no SMBG, or SMBG as necessary if considered essential by a clinician (e.g., hypoglycemic episodes). Screening first took place on the titles, then abstracts, and lastly full-text articles. Screening of the full-text articles and data extraction were performed independently by JC and DS. Disagreements (6.8%) were addressed through discussion; after clarifying the selection criteria, there was a 100% agreement eliminating the need to consult YK.

Data Extraction and Quality Assessment

The following data were extracted from each trial: i) authors and year of publication, ii) trial duration, iii) number of participants and age, iv) type of analysis, v) type of SMBG, vi) education or support provided, vii) health setting, viii) clinician who adjusted therapy, ix) baseline HbA_{1c}, x) HbA_{1c} at follow-up, and xi) funding. JC and DS independently extracted and compared data, and any disagreements were addressed through discussion. The quality of the trials was assessed independently by JC, DS and YK with Cochrane Risk of Bias 2 (RoB2) (Sterne et al., 2019). This tool permits a more accurate risk of bias assessment compared to RoB1: when blinding of participants is not possible (such as when a placebo is not possible), this considers whether allocation concealment (blinding of outcome assessors) would likely affect the outcome of an intended intervention (Sterne et al., 2019). Discrepancies (5.6%) and disagreements (33%) with the data extraction and quality assessment respectively were addressed through discussion. Consensus was reached without the need for YK to make a final decision.

Data Synthesis and Analysis

The outcome for all analyses was the difference in HbA_{1c} between intervention and control groups. Data from intention-to-treat analysis were used; if these were unavailable, per-protocol data were used. All data were reported with ±1.96 standard deviation (SD) or 95% confidence intervals (CI). Mean changes in HbA_{1c} were analyzed as continuous variables using mean difference changes between baseline and the last follow-up group available, and their CI as summary measures. The last follow-up groups available included at three, six, nine, 12, and 24 months. For each trial, the mean changes from baseline within the groups and their SD were extracted; if not available, the

mean differences between groups and their SD were extracted; if not available, SD of the mean difference between groups was estimated by standard formulae from the reported standard error, CI or probability value (Higgins et al., 2019). If the median was available but not the mean, the latter was transformed from the former (Luo et al., 2018); SD was estimated from the interquartile range when only this was available (Wan et al., 2014). If trials had more than one intervention group, the data for each were combined (Higgins et al., 2019). Heterogeneity was examined using I^2 statistics (Higgins & Thompson, 2002). To address heterogeneity (Higgins et al., 2019), a random-effects model was implemented for the meta-analyses if overall heterogeneity was ≥30%; otherwise, a fixed effect model was used (Higgins & Thompson, 2002). Publication bias was investigated by asymmetry testing: funnel plots were examined visually if 10 or more trials were included in the analyses (Egger et al., 1997; Sterne et al., 2011). Meta-analyses, aggregated effect sizes, CI, degree of heterogeneity, and funnel plots were computed using Review Manager (RevMan), version 5.3 (Higgins et al., 2019).

Meta-analyses planned in the protocol (Chircop et al., 2019) compared (I) SMBG versus usual care and (II) structured SMBG versus unstructured SMBG, on HbA_{1c}. Subgroup meta-analyses planned in the protocol (Chircop et al., 2019) were comparing (i) SMBG readings used to adjust therapy versus usual care, (ii) SMBG with nursing education versus usual care, (iii) SMBG with nursing education versus SMBG without nursing education and (iv) unstructured SMBG versus usual care. As per the protocol (Chircop et al., 2019), a minimum number of three trials were required for the data to be synthesized. The interpretation of the analyses was made by JC and DS independently. No disagreements (0%) arose requiring discussions, eliminating the need for a final decision being made by YK.

RESULTS

Study Selection

The electronic search resulted in the identification of 76 studies. Forty-seven studies were identified through other sources. Of 123 studies in total, five duplicates were identified. This resulted in 118 titles and abstracts being screened, with 86 being excluded. This resulted in 32 full-text articles being screened for eligibility, with 11 being excluded. Reasons for exclusion include: not RCTs (n = 5), no control arm (n = 2), telemonitoring (n = 2), telecare (n = 1), and SMBG part of trial not being randomized and controlled (n = 1). In total, 18 trials reported in 21 articles are included in this review (Barnett et al., 2008; Bosi et al., 2013; Davidson et al., 2005; Durán et al., 2010; Farmer et al., 2009; Franciosi et al., 2011; García de la Torre et al., 2013; Guerci et al., 2003; Kan et al., 2017; Kleefstra et al., 2010; Malanda et al., 2016; Nishimura et al., 2017; O'Kane et al., 2008; Parsons et al., 2019; Polonsky et al., 2011; Schwedes et al., 2002; Shen et al., 2019; Sodipo et al., 2017; Suriyawongpaisal et al., 2016; Williams et al., 2020; Young et al., 2017); all trials are included in the meta-analyses. The inclusion process flowchart is presented in Figure 1.

<Figure1>

Study Characteristics

Table 1 shows the characteristics of the included trials with the number of participants, duration, and participants' baseline HbA_{1c}. The articles were published between 2002 and 2020. Thirteen trials investigated structured SMBG versus usual care, four trials compared structured SMBG with unstructured SMBG, and one trial compared unstructured SMBG with usual care (Guerci et al.,

158 2003). Almost all trials had a duration of six (8 trials) or 12 (8 trials) months; one trial (Sodipo et
159 al., 2017) had a duration of three and another (Durán et al., 2010) of 36. Thirteen trials
160 implemented an intention-to-treat analysis, four implemented a per-protocol analysis, and one
161 implemented both (Bosi et al., 2013). In trials investigating structured SMBG versus usual care,
162 participants received care in diabetes, endocrinology, or specialist settings (six trials), primary
163 settings not specific to diabetes (five trials), a range of these (Parsons et al., 2019), and a medical
164 center (Malanda et al., 2016). In trials investigating structured SMBG versus unstructured SMBG,
165 most participants received care in diabetes settings (Bosi et al., 2013) or primary settings
166 (Nishimura et al., 2017; Polonsky et al., 2011) not specific to diabetes. No trials investigated
167 SMBG with nursing education versus SMBG without nursing education, only one (Franciosi et
168 al., 2011) investigated SMBG with nursing education versus usual care and only one (Guerci et
169 al., 2003) investigated unstructured SMBG versus usual care; therefore, meta-analyses were not
170 performed for these comparisons, as per the protocol (Chircop et al., 2019). Almost half (44%) of
171 the trials investigated SMBG with readings used to adjust therapy. The therapy adjusted was
172 pharmacotherapy, by nurses and physicians, except for two trials where investigators, whose
173 professions were not reported, adjusted this (Barnett et al., 2008; Sodipo et al., 2017), and one trial
174 where therapy adjusted was diet, by dietitians (Suriyawongpaisal et al., 2016). Most trials
175 investigated participants who are not newly diagnosed (diabetes duration: > 1 year), except for
176 four (Durán et al., 2010; Kan et al., 2017; O'Kane et al., 2008; Sodipo et al., 2017).

177 <Table 1.>

178

179 No trials reported only the median or interquartile range, eliminating the need for transformations
180 and estimations of values by formulae respectively (Luo et al., 2018; Wan et al., 2014). Two trials

included two SMBG groups: one trial (Farmer et al., 2009) with less-intensive and more-intensive monitoring and another trial (Suriyawongpaisal et al., 2016) with a seven-point and a five-point SMBG. Therefore, the intervention groups for these were combined (Higgins et al., 2019). Only data for the planned comparisons were extracted; other data, e.g. from a telemonitoring arm (Parsons et al., 2019), participants receiving insulin (Kan et al., 2017), and participants undertaking a supervised exercise program (Durán et al., 2010) were not included in meta-analyses. Overall heterogeneity (I^2) was ≥30% for each analysis so random effects meta-analyses were used. One meta-analysis included ten or more trials and was investigated by asymmetry testing for publication bias (Egger et al., 1997; Sterne et al., 2011).

Risk of Bias

According to RoB2 (Sterne et al., 2019), eight of the 18 trials had an overall high risk of bias due to deviations from the intended interventions (Parsons et al., 2019; Polonsky et al., 2011; Suriyawongpaisal et al., 2016), missing outcome data (Barnett et al., 2008; Guerci et al., 2003; Schwedes et al., 2002), issues with randomization (Guerci et al., 2003; Kleefstra et al., 2010) and issues with reporting the result (Kan et al., 2017). No trials had a risk of bias for measuring the outcome, HbA_{1c}. The method of measuring the outcome was appropriate: this was measured by reliable and strongly valid measurement instruments (automated blood analyzer machines) (Higgins et al., 2019; Nathan et al., 2008). Blinding was appropriate: the use of placebo and blinding of participants was not possible due to the intervention being a test carried out by themselves, therefore allocation concealment (blinding of outcome assessors) was considered (Sterne et al., 2019). (Figure 2).

<Figure 2.>

Analysis (I): SMBG versus usual care

Fourteen trials compared SMBG to usual care. At baseline, the mean HbA_{1c} was 8.2% (8.1, 8.3) (66 mmol/mol (65, 67), n = 1752) in the intervention and 8.2% (8.2, 8.3) (66 mmol/mol (66, 67), n = 1524) in the control groups. Almost half of the trials (43%, 6 trials) had a mean HbA_{1c} of ≤ 8% (64 mmol/mol) at baseline in both groups. The mean difference change was negative for almost all trials (86%, 12 trials), indicating improvement in HbA_{1c}. The weighted mean difference (WMD) was -0.3% (-0.4, -0.2) (-3 mmol/mol (-5, -2), n = 3276) with moderate heterogeneity (I^2 = 57%). The forest plot is presented in Figure 3. By way of visual inspection, no outliers were noted. Asymmetry testing indicated a low probability of publication bias (Egger et al., 1997; Sterne et al., 2011). As there was moderate heterogeneity, we also examined only those trials with a high baseline HbA_{1c} (Barnett et al., 2008; Davidson et al., 2005; Guerci et al., 2003; O'Kane et al., 2008; Parsons et al., 2019; Schwedes et al., 2002; Sodipo et al., 2017; Suriyawongpaisal et al., 2016). In congruence with previous reviews (Machry et al., 2018; Zhu et al., 2016), this was defined as > 8% (64 mmol/mol). In those eight trials (n = 2186), there was a significant reduction in HbA_{1c} of -0.4% (-0.5, -0.2), -4 mmol/mol (-6, -3), and heterogeneity was reduced (I^2 = 21%).

<Figure 3>

Analysis (II): Structured SMBG versus unstructured SMBG

Four trials compared structured SMBG to unstructured SMBG. At baseline, the mean HbA_{1c} was 8.0% (7.9, 8.2) (64 mmol/mol (61, 66), n = 847) in the intervention and 7.9% (7.7, 8.1) (63 (61, 65), n = 842) in the control group. Half of the trials (Bosi et al., 2013; Nishimura et al., 2017) had a mean HbA_{1c} of ≤ 8% (64 mmol/mol) at baseline in both the intervention and control groups. The mean difference change was negative for all trials, indicating improvement in HbA_{1c}. The WMD was that of -0.2% (-0.3, -0.1) (-2 mmol/mol (-3, -1), n = 1689) with mild heterogeneity (I^2 = 30%). The forest plot is presented in Figure 4. By way of visual inspection, no outliers were noted. An accurate assessment of publication bias was not possible: asymmetry testing was not performed as there were fewer than ten trials included in this analysis (Sterne et al., 2011).

<Figure 4>

Subgroup analysis (III): SMBG readings used to adjust therapy versus usual care

In the preplanned subgroup analysis, eight trials compared SMBG readings used to adjust therapy, versus usual care. More than half (Durán et al., 2010; Farmer et al., 2009; Franciosi et al., 2011; Young et al., 2017) had a mean HbA_{1c} of ≤ 8% (64 mmol/mol) at baseline in both the intervention and control groups. The mean difference change was negative for all trials, indicating improvement in HbA_{1c}. The WMD was that of -0.4% (-0.5, -0.2) (-4 mmol/mol (-6, -2), n = 1935) with moderate heterogeneity (I^2 = 64%). The forest plot is presented in Figure 3.

DISCUSSION

This present systematic review of SMBG effects on HbA_{1c} is the most comprehensive to date; it includes RCTs up to 30 June 2020. The review compared the effect of I) SMBG versus usual care

II) structured SMBG versus unstructured SMBG and III) SMBG readings used to adjust therapy versus usual care, on glycemic control in non-insulin-treated participants with type 2 diabetes. In the primary analysis of 14 trials, SMBG resulted in significant decreases in HbA_{1c} compared to usual care (-0.3%, -3 mmol/mol). This accords well with previous reviews of fewer participants (Mannucci et al., 2018; Zhu et al., 2016). There was moderate heterogeneity though most trials (12 trials) showed decreases in HbA_{1c} compared to usual care. Secondary analyses examining those trials with high baseline HbA_{1c} revealed significant reductions (-0.4%, -4 mmol/mol) with good heterogeneity. Thus, the effect of SMBG may be influenced by the initial value of HbA_{1c}, and SMBG may be more important in participants with suboptimal control. Taken together, these analyses suggest that SMBG results in moderate improvements in HbA_{1c}, which are larger if participants have suboptimal glycemic control.

The analysis comparing structured SMBG with unstructured SMBG showed a decrease in HbA_{1c} in the structured group compared to the unstructured group (-0.2%, -2 mmol/mol) with good heterogeneity. Thirteen of the 14 trials included in the primary analysis (I) used structured SMBG. There was only one trial that compared unstructured SMBG with usual care so meta-analysis was not possible; it reported greater reductions in HbA_{1c} in the unstructured SMBG group than usual care (Guerci et al., 2003). Thus, a structured approach appears to improve the efficacy of SMBG.

In the preplanned subgroup analysis, eight trials compared structured SMBG readings used to adjust therapy, with usual care. Using readings to adjust therapy resulted in greater reductions in HbA_{1c} (-0.4%, -4 mmol/mol) though heterogeneity was moderate suggesting differences in

participant populations influence benefits observed, e.g., health literacy and behavior (Cook et al., 2018; Kim et al., 2020). However, trials included in this analysis all had therapy adjusted by clinicians, and in seven of the eight trials, pharmacotherapy was adjusted; in the other trial, diet was adjusted (Suriyawongpaisal et al., 2016). If sustained long-term (Stratton et al., 2000), this improvement in HbA_{1c} would significantly reduce diabetes-related morbidity and mortality. Secondary analyses that compared SMBG without therapy adjustment to usual care revealed no significant HbA_{1c} improvement (-0.2% (-2 mmol/mol). Together, these analyses show structured readings better therapy adjustment.

Our meta-analyses provide similar estimates of benefit to Manucci et al. (2018) in larger corpuses of trials, with seven more trials included. It is worth noting that this review did not include one of the trials (Durán et al., 2010) in the structured versus unstructured SMBG meta-analysis as, in the control group, SMBG was only initiated when it was considered appropriate and always if insulin was started (Durán et al., 2010); the use of insulin is an exclusion criterion. No previous review compared structured SMBG readings used to adjust therapy versus usual care. Our analyses show that structured SMBG readings with therapy adjustment improve HbA_{1c} and so support expert consensus (Davies et al., 2018). Suriyawongpaisal et al. (2016) offer an explanation for this: over-reliance on participant education and a lack of clarity on therapy goals. Their findings support clinicians reviewing SMBG readings and providing appropriate therapy, this is congruent with current IDF guidance and our findings (IDF, 2018; Suriyawongpaisal et al., 2016). The IDF identifies that the use of SMBG can encourage timely action, avoiding clinical inertia (a failure of initiating or intensifying therapy when indicated) (IDF, 2018; Phillips et al., 2001). The IDF

recommends the prescription of SMBG only when healthcare providers can adjust therapy (i.e., have the appropriate knowledge, skills and willingness); our findings support this (IDF, 2018).

These analyses show that structured SMBG with therapy adjustment leads to clinically significant improvements in HbA_{1c}. Secondary analyses show that reductions in HbA_{1c} are greater with higher initial HbA_{1c} levels. Consideration should be given for SMBG as part of a wider multifactorial approach (Ji et al., 2020; Moreira et al., 2015). However, implications are for clinicians to prescribe SMBG if readings are structured with an aim for therapy adjustment based on the readings, and not prescribing unstructured SMBG. Additionally, our results suggest that participants with suboptimal glycemic control benefit most from SMBG prescription.

The structured SMBG regimen to prescribe has not been established in clinical practice. The IDF offers several examples such as five-point, seven-point and 'staggered' (IDF, 2018). Nishimura et al. (2017) offer a less-frequent seven-point regimen: seven readings on three consecutive days once every two months without daily readings. This seven-point regimen is simple (only three days of SMBG in two months); it is easily modifiable according to participants' and clinical needs (e.g., days which are convenient can be chosen and risk of hypoglycemia respectively), supporting individual considerations as suggested by the ADA, IDF and CDS (Davies et al., 2018; Jia et al., 2019). Only one study included investigates less-frequent SMBG versus usual care; more significant decreases in HbA_{1c} are reported (-0.6%, -6 mmol/mol) (Franciosi et al., 2011). SMBG carries significant financial burden in diabetes (participants who perform SMBG incur 80% more costs) (Grimes et al., 2016), and by reducing the number of readings with this seven-point SMBG

regimen e.g., by 65% and 83% compared to daily and twice daily SMBG respectively, leads to significantly improved cost-effectiveness. Therefore, this less-frequent SMBG regimen is presented as a favorable structured SMBG regimen, both in terms of clinical- and cost-effectiveness; though evaluation of this specific regimen may be merited.

Strengths of this review include the systematic literature search, the use of RoB2 to assess bias, the inclusion of trials with different technical and clinical factors, and the low risk of publication bias for the trials of SMBG versus usual care. Limitations within the review include not investigating glycemic variability and health-related quality of life, funding sources (ten trials were funded by industry and three trials did not provide funding information), variability in the risk of bias with eight of the included trials having a high risk of bias, moderate heterogeneity (I^2) for the SMBG versus usual care analysis, and a low number of trials (four trials) for the structured versus unstructured analysis.

Conclusion

This review with meta-analyses found that glycemic control is improved in non-insulin-treated participants with type 2 diabetes mellitus when clinicians adjust therapy based on structured SMBG readings. Clinicians can prescribe structured SMBG to adjust therapy based on the readings, and not prescribe unstructured SMBG. This review supports focusing on participants with suboptimal glycemic control. A SMBG regimen that significantly improves convenience and cost-effectiveness while maintaining clinical benefit is presented. Future studies can be aimed at investigating this regimen specifically.

Originality

The authors declare that this work nor any part of it is not published, submitted or being considered elsewhere.

Contribution Statement

JC conceived, designed, and led the research, conducted the literature search, led the statistical analyses, and wrote the manuscript.

JC and DS developed the search strategy and conducted the literature screening and data extraction.

JC, DS, and YK revised the manuscript, assessed the quality of trials and reviewed the final manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Figure Legends

Figure 1.

Flowchart of the included studies. Template from: Moher et al. (Moher et al., 2015).

Figure 2.

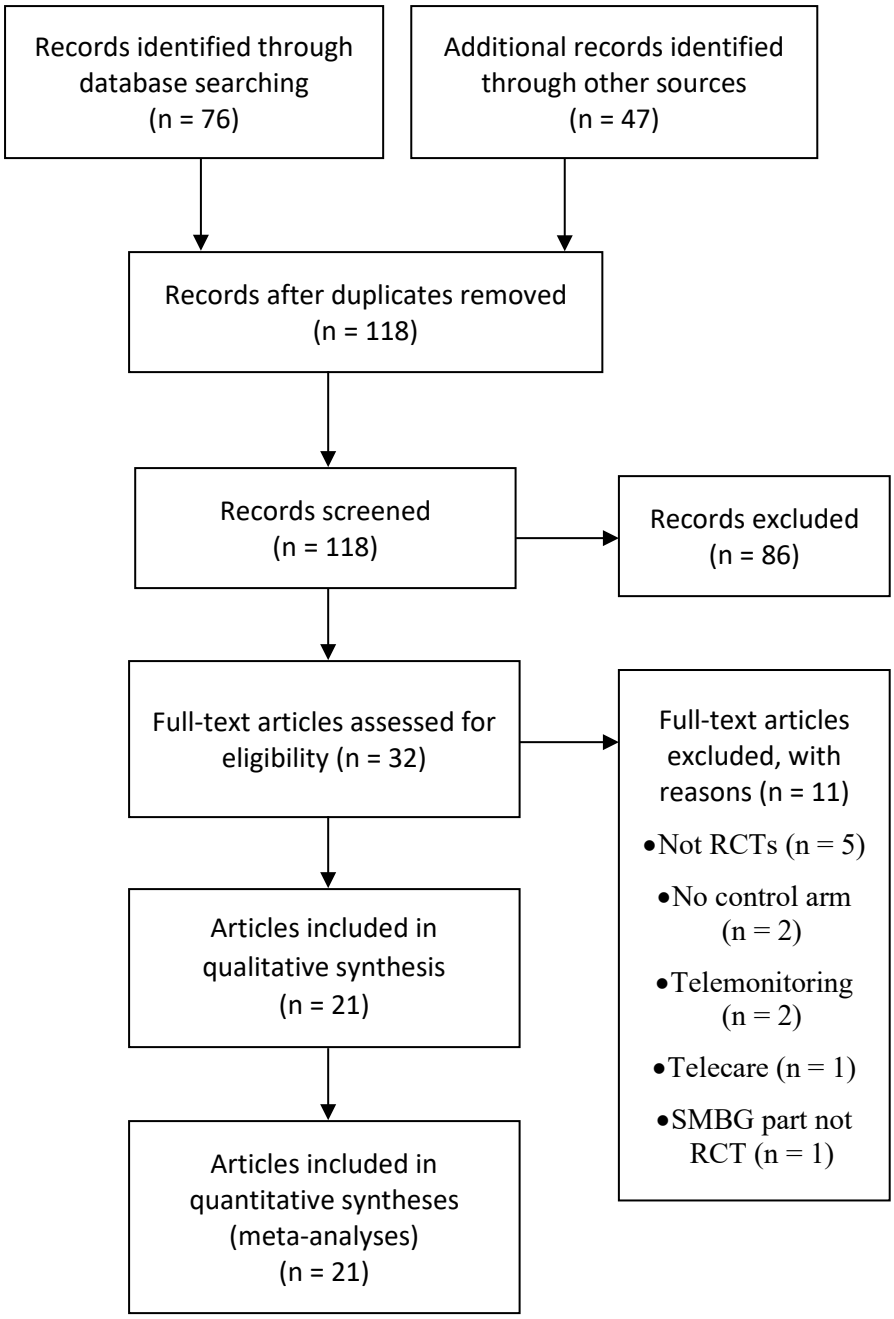
Cochrane Risk of Bias 2 Traffic Light Plot: SMBG versus usual care.

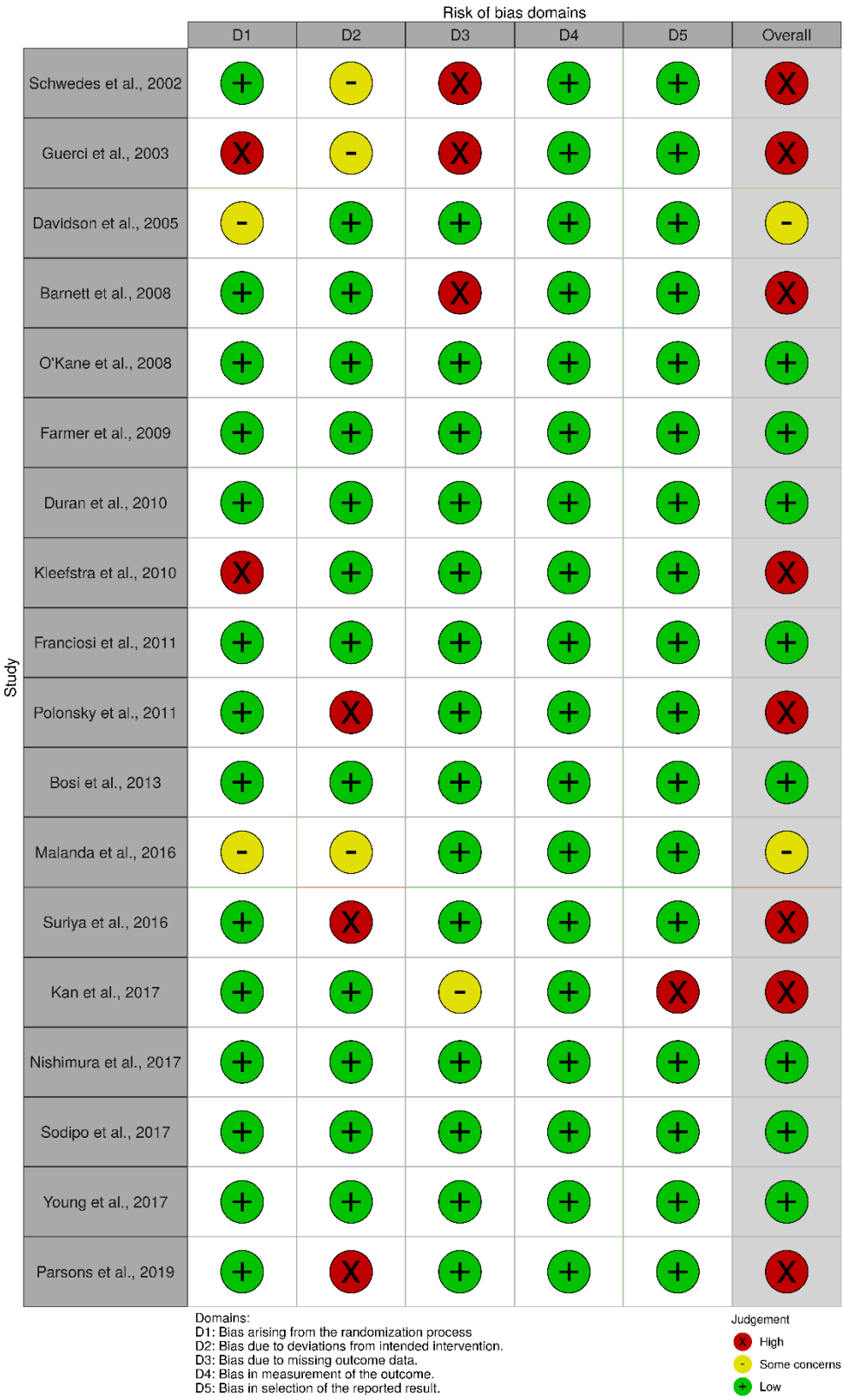
Figure 3.

Forest plot of meta-analysis for SMBG versus usual care including SMBG readings used to adjust therapy versus usual care. Mean differences between intervention and control groups from baseline are presented for all 12 trials. The data are quantitively synthesized and presented as weighted mean difference.

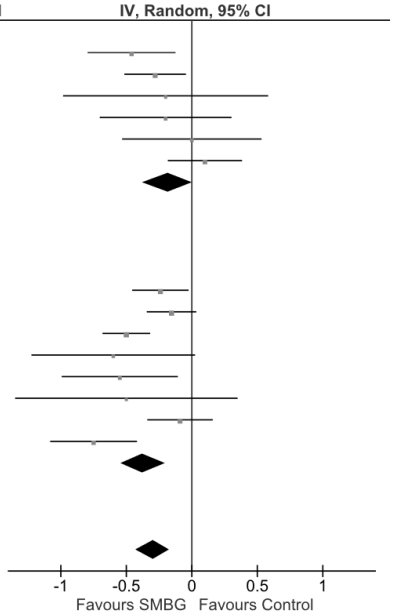
Figure 4.

Forest plot of meta-analysis for Structured SMBG versus unstructured SMBG. Mean differences between intervention and control groups from baseline are presented for all four trials. The data are quantitively synthesized and presented as weighted mean difference.


Records identified through database searching (n = 76)
Additional records identified through other sources (n = 47)
Records after duplicates removed (n = 118)
Records screened (n = 118)
Records excluded (n = 86)
Full-text articles assessed for eligibility (n = 32)
Full-text articles excluded, with reasons (n = 11)
•Not RCTs (n = 5)
•No control arm (n = 2)
•Telemonitoring (n = 2)
•Telecare (n = 1)
•SMBG part not RCT (n = 1)
Articles included in qualitative synthesis (n = 21)
Articles included in quantitative syntheses (meta-analyses) (n = 21)


Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Schwedes et al., 2002
Guerci et al., 2003
Davidson et al., 2005
Barnett et al., 2008
O'Kane et al., 2008
Farmer et al., 2009
Duran et al., 2010
Kleefstra et al., 2010
Franciosi et al., 2011
Polonsky et al., 2011
Bosi et al., 2013
Malanda et al., 2016
Suriya et al., 2016
Kan et al., 2017
Nishimura et al., 2017
Sodipo et al., 2017
Young et al., 2017
Parsons et al., 2019
Domains:
D1: Bias arising from the randomization process
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
High
Some concerns
Low

Study or Subgroup	SMBG Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 SMBG versus usual care								
Schwedes et al., 2002	-1	1.08	113	-0.54	1.41	110	7.6%	-0.46 [-0.79, -0.13]
Guerci et al., 2003	-0.88	1.54	345	-0.6	1.54	344	10.1%	-0.28 [-0.51, -0.05]
Davidson et al., 2005	-0.8	1.6	43	-0.6	2.1	45	2.4%	-0.20 [-0.98, 0.58]
O'Kane et al., 2008	-1.9	1.589	96	-1.7	1.834	88	4.7%	-0.20 [-0.70, 0.30]
Kleefstra et al., 2010	-0.1	0.9	22	-0.1	0.8	18	4.3%	0.00 [-0.53, 0.53]
Malanda et al., 2016	-0.1	0.9	57	-0.2	0.6	60	8.8%	0.10 [-0.18, 0.38]
Subtotal (95% CI)			**676**			**665**	**37.9%**	**-0.18 [-0.37, 0.01]**
Heterogeneity: Tau² = 0.02; Chi² = 7.82, df = 5 (P = 0.17); I² = 36%								
Test for overall effect: Z = 1.86 (P = 0.06)								
1.1.2 SMBG, readings used to adjust therapy, versus usual care								
Barnett et al., 2008	-1.15	1.14	271	-0.91	1.29	248	10.7%	-0.24 [-0.45, -0.03]
Farmer et al., 2009	-0.155	0.775	301	0	1.02	152	11.4%	-0.15 [-0.34, 0.03]
Duran et al., 2010	-0.4	0.4743	65	0.1	0.5524	65	11.6%	-0.50 [-0.68, -0.32]
Franciosi et al., 2011	-1.3	0.959	46	-0.7	1.131	16	3.4%	-0.60 [-1.22, 0.02]
Suriyawongpaisal et al., 2016	-0.93	1.3296	98	-0.38	1.42	63	5.5%	-0.55 [-0.99, -0.11]
Sodipo et al., 2017	-1.5	2.149	55	-1	2.298	52	2.1%	-0.50 [-1.34, 0.34]
Young et al., 2017	-0.05	1	141	0.04	1.12	147	9.7%	-0.09 [-0.33, 0.15]
Parsons et al., 2019	-1.05	1.2033	99	-0.3	1.2336	116	7.7%	-0.75 [-1.08, -0.42]
Subtotal (95% CI)			**1076**			**859**	**62.1%**	**-0.37 [-0.54, -0.20]**
Heterogeneity: Tau² = 0.03; Chi² = 19.61, df = 7 (P = 0.006); I² = 64%								
Test for overall effect: Z = 4.21 (P < 0.0001)								
Total (95% CI)			**1752**			**1524**	**100.0%**	**-0.30 [-0.43, -0.17]**
Heterogeneity: Tau² = 0.03; Chi² = 30.31, df = 13 (P = 0.004); I² = 57%								
Test for overall effect: Z = 4.46 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.07, df = 1 (P = 0.15), I² = 51.8%								



Study or Subgroup	SMBG Mean	SMBG SD	SMBG Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Polonsky et al., 2011	-1.2	1.018	256	-0.9	1.065	227	27.5%	-0.30 [-0.49, -0.11]
Bosi et al., 2013	-0.39	0.735	501	-0.27	0.735	523	54.6%	-0.12 [-0.21, -0.03]
Kan et al., 2017	-1.91	1.9	60	-1.35	1.82	60	3.2%	-0.56 [-1.23, 0.11]
Nishimura et al., 2017	-0.28	0.616	30	-0.11	0.527	32	14.7%	-0.17 [-0.46, 0.12]
Total (95% CI)			**847**			**842**	**100.0%**	**-0.19 [-0.31, -0.07]**

Heterogeneity: Tau² = 0.00; Chi² = 4.32, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 3.08 (P = 0.002)

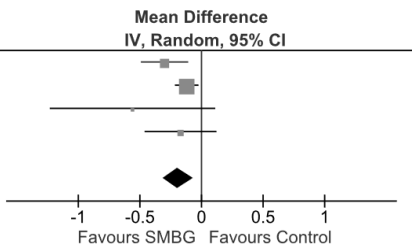


Table 1. Characteristics of trials.

Author, year	Trial Duration (months)	Participants (I - C) and age	Analysis	Type of SMBG	Education or support	Health setting	SMBG used to adjust therapy	Baseline HbA_{1c} I:C % (mmol/mol)	Difference in HbA_{1c} (mmol/mol) (95% CI)	Funding
Structured SMBG versus usual care										
Schwedes et al., 2002	6	113 – 110, 45-70	PP	6-point twice weekly	SMBG interpretation I	Health centers	No	8.5:8.4 (69:68)	-5 (-9, -1)	Industry
Davidson et al., 2005	6	43 – 45, 38-62	ITT	6-point six times weekly	Diabetes program, dietary counselling I C	Community clinic	No	8.5:8.4 (70:68)	-2 (-11, 6)	Industry
Barnett et al., 2008	6	271 – 248, 40-80	ITT	5-point twice weekly	Hypoglycemia education I C	Specialist centers	Inv	8.1:8.1 (65:65)	-3 (-5, 0)	Industry
O'Kane et al., 2008	12	96 – 88, <70	ITT	Eight readings weekly	Structured education program I C	Diabetes OP	No	8.8:8.6 (73:71)	-2 (-8, 3)	Non-industry
Farmer et al., 2009	12	301 – 152, ≥25	ITT	3-point twice weekly	SMBG interpretation MI	Rural/suburban GP centers	GP	7.5:7.5 (58:58)	-2 (2, 0)	Non-industry
Durán et al., 2010 (Durán et al., 2010; García et al., 2013)	36	65 – 65, 18-80	ITT	6-point every three days	Lifestyle session I	Endocrinology OP	Phy	6.6:6.7 (49:50)	-6 (-7, -4)	Non-industry
Kleefstra et al., 2010	12	22 – 18, 18-70	ITT	4-point twice weekly	No	Diabetes OP	No	7.6:7.7 (60:61)	0 (-6, 6)	Industry
Franciosi et al., 2011	6	46 – 16, 45-75	ITT	2-point thrice weekly	SMBG interpretation I	Diabetes OP	Nur,Diab	8.0:7.9 (64:63)	-7 (13, 0)	Industry
Malanda et al., 2016	12	57 – 60, 45-75	PP	6-point twice weekly	SMBG interpretation I	Medical Center	No	7.5:7.4 (59:58)	1 (-2, 4)	Industry
Suriyawongpaisal et al., 2016	6	98 – 63, >30	PP	7-point & 5-point, thrice weekly	Diet counselling I	Diabetes clinic	Diet	8.7:8.4 (72:69)	-6 (-11, -1)	Not reported
Sodipo et al., 2017	3	55 – 52, ≥18	ITT	2-point thrice weekly	Structured education program I C	General OP clinic	Inv	8.7:8.7 (72:72)	-6 (-15, 4)	Not reported
Young et al., 2017	12	141 – 147, ≥30	ITT	One reading daily	No	Primary care practices	Cli	7.6:7.5 (59:59)	-1 (-4, 2)	Non-industry
Parsons et al., 2019 (Parsons et al., 2019; Williams et al., 2020)	12	99 - 116, 18-80	PP	4-point twice weekly	General diabetes education I C	Diabetes, GP or hospital clinic	Nur, GP	8.5:8.7 (70:72)	-8 (-2, -5)	Industry
Unstructured SMBG versus usual care										
Guerci et al., 2003	6	345 - 344, 40-75	ITT	Six readings weekly	Dietary advice	GP	No	9.0:8.9 (75:74)	-3 (-6, -1)	Non-industry
Structured SMBG versus unstructured SMBG										
Polonsky et al., 2011	12	256 - 227, ≥25	ITT	7-point[a]	SMBG interpretation I	Primary care practices	Phy I	8.9:8.9 (74:74)	-3 (-5, -1)	Industry

Bosi et al., 2013	12	501 – 523, 35-75	ITT, PP	4-point[b]	SMBG interpretation I	Diabetes clinics	Cli I	7.4:7.3 (57:56)	-1 (-2, -0)	Industry
Kan et al., 2017 (Kan et al., 2017; Shen et al., 2019)	6	60 - 60, 47-70	ITT	2-point[c]	30 min teaching[d] I C	Investigation center	N,Phy I C	9.6:9.5 (81:81)	-6 (-13, 1)	Non-industry
Nishimura et al., 2017	6	30 - 32, ≥20	ITT	7-point[e]	SMBG interpretation video I C	Outpatient department	Phy I C	7.2:7.2 (55:55)	-2 (-5, 1)	Industry

Data are presented as number.

Abbreviations: C, control group; CI, confidence interval; Diab, diabetologist; Diet, dietitian; GP, general practitioner; I, intervention group; Inv, investigators; ITT, intention-to-treat analysis; MI, more-intensive monitoring group; Nur, nurse; OP, outpatients; Phy, physician; PP, per-protocol analysis; SMBG, self–monitoring of blood glucose.

a. I: 7-point on three consecutive days prior to scheduled visit. C: To follow physicians' SMBG recommendations.

b. I: 4-point thrice weekly. C: 4-point once at baseline, six months, and 12 months.

c. I: 2-point daily. C: usual care.

d. Antidiabetic drugs, glycemic targets and healthy lifestyle.

e. I: 7-point for three consecutive days once every two months. C: Thrice weekly.