

1 Efficacy of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin: a systematic review and meta-analysis

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11Abstract

12Background: Self-monitoring of blood glucose (SMBG) is commonly performed by patients with diabetes mellitus. There is debate surrounding the clinical utility and cost-effectiveness of SMBG in patients with type 2 diabetes who do not use insulin. We conducted a systematic review and meta-analysis to determine: 1) the effect of SMBG versus no self-monitoring; 2) the effect of patient education regarding self-interpretation and application of SMBG results; and 3) the optimal frequency of self-monitoring.

13Methods: Electronic databases, conference proceedings, and grey literature sources were searched up to March 2009 to identify randomized controlled trials (RCTs) and observational studies investigating the use of SMBG in patients not using insulin. Where appropriate, data related to clinical, surrogate, and patient-reported outcomes were pooled using random-effects meta-analysis.

14Results: SMBG was associated with a statistically significant improvement in hemoglobin A1c (weighted mean difference -0.25%, 95% CI -0.36%, -0.15%). There was no significant difference between studies that employed education for self-interpretation and application of results and those that did not. Based on limited evidence, SMBG failed to demonstrate consistent benefits in terms of quality-of-life, patient satisfaction, hypoglycemia, long-term complications of diabetes, or mortality. There was insufficient evidence pertaining to the optimal frequency of SMBG.

15 Interpretation: SMBG was associated with a clinically modest, statistically significant reduction in hemoglobin A1c, regardless of whether subjects were provided with education on interpreting and using results. Further studies are required to determine whether self-monitoring reduces the risk of long-term complications of diabetes, and to identify patients most likely to benefit from SMBG.

Introduction

Diabetes mellitus is associated with serious long-term complications and premature death.^{1,2} In 2004/05, diabetes was diagnosed in about 5.5% (1.8 million) of Canadians aged 20 years and older.³ Type 2 diabetes accounts for approximately 90% of all diabetes cases.⁴ Maintaining a hemoglobin A1c (HbA_{1c}) concentration of 7.0% or less is recommended for all patients with diabetes to reduce the risk of long-term complications.²

Self-monitoring of blood glucose (SMBG) may contribute to glycemic control by allowing for adjustments in diet, physical activity, and pharmacotherapy in response to meter readings. While the need for SMBG for patients treated with insulin is well-established,² the utility of the practice for patients with type 2 diabetes managed without insulin is controversial.⁵⁻⁸ Nevertheless, SMBG use is highly prevalent in this population. In a recent study, blood glucose test strip claimants covered by the Ontario Public Drug Program who did not use insulin claimed, on average, more than 1 test strip per day.⁹ Apart from the economic costs, SMBG may be associated with patient discomfort and inconvenience. Hence, there is a need for evidence-based information to guide optimal use of this technology in patients with type 2 diabetes who do not use insulin.

Existing systematic reviews in this area have reported marginal advantages of SMBG in terms of HbA_{1c}, but have not usually assessed other outcomes of interest such as hypoglycemia, long-term complications of diabetes, or quality of life.¹⁰⁻¹⁶ Furthermore, previous reviewers have not accounted for differences across trials in the degree to which subjects were educated on how to interpret and act

upon SMBG results. This is a key limitation since users must be able to act appropriately in response to abnormal readings if SMBG is to be effective. In this article, we report the results of a systematic review and meta-analysis of a number of patient-relevant outcomes associated with the use of SMBG in patients with type 2 diabetes not treated with insulin. Detailed methods and complete results are reported elsewhere.¹⁷

Methods

Literature Search

Medline, Medline In-Process & Other Non-Indexed Citations, EMBASE, Biosis Previews, CINAHL and PsycINFO were searched for studies published in English from 1990 to March 2009. The search was restricted to studies published after 1990 to increase the likelihood that study conditions were reflective of current practices for managing diabetes. Parallel searches were also run in the Cochrane Library and the Centre for Reviews and Dissemination databases. The search strategy was comprised of both controlled vocabulary, such as Medical Subject Headings, and keywords. The main search concepts were ‘blood glucose test strips’ and ‘type 2 diabetes mellitus’. Additional citations were obtained through internet searching, conference proceedings, and from stakeholder feedback.

Outcomes of interest

This report presents results for HbA_{1c}, hypoglycemia, health-related quality-of-life, patient satisfaction, and long-term complications of diabetes. Results for other clinical outcomes are presented elsewhere.¹⁷

Selection Criteria

Full-text articles and conference abstracts reporting controlled clinical trials and observational studies (i.e., cohort, case-control, time series) were selected for inclusion if they compared either SMBG versus no self-monitoring, or different frequencies of SMBG, in patients with type 2 diabetes. We excluded studies that did not report outcomes by type of diabetes or type of therapy, were of less than four weeks duration, or demonstrated substantial differences between treatment groups in terms of management practices other than SMBG.

Quality assessment

Two reviewers independently assessed the methodological quality of included studies using modified Scottish Intercollegiate Guideline Network-50 instruments for RCTs and cohort studies.¹⁸ Disagreements were resolved by consensus or a third reviewer.

Data extraction

Two reviewers independently extracted data from each included article using a form designed *a priori*.¹⁷ Disagreements were resolved by consensus or a third reviewer. Study authors were contacted in case data were missing.

Data analysis

Data were pooled across RCTs using random effects meta-analysis.^{19,20} Sensitivity analyses tested the effect of removing studies of poor quality, and those that presented pooled results for patients using oral antidiabetes agents or no pharmacotherapy. Subgroup analyses were conducted based on: provision of education regarding interpretation and application of SMBG results; medication class; SMBG frequency; SMBG duration; and patient characteristics. Heterogeneity was assessed using the I^2 statistic.²¹ Data from observational studies were not pooled due to a high degree of methodological heterogeneity.

Results

Study selection

The literature search identified 1624 citations, of which 324 were reviewed as full text articles, and 9 RCTs and 16 observational studies were selected for inclusion (Figure 1).^{8,22-47}

Study characteristics and methodological quality

Sample sizes ranged from 28³⁴ to 689²³ in the included RCTs, and from 115³⁷ to 12786²⁶ in the observational studies. Study duration ranged from 6 to 12 months for RCTs, and from 3 months⁴⁴ to 6.5 years³³ for observational studies. The frequency of SMBG in RCTs varied from one strip per week^{29,45} to 6 strips per day on 6 days per week⁸.

Four RCTs,^{31,36,45,47} were rated as being of good methodological quality, and four^{8,23,24,34} as poor quality (Appendix A). (One RCT²⁹ was reported as an abstract and could not be assessed for quality.) Reasons for assigning ratings of poor quality were: inadequate descriptions of randomization and allocation concealment procedures; high dropout rates; and failure to conduct an intention-to-treat analysis. All included observational studies were rated as being of poor quality except for three time series studies,^{25,35,42} which could not be assessed for quality (Appendix B).

Meta-analysis Results

Patients using oral antidiabetes drugs

Effect of self-monitoring on HbA_{1C}

Seven RCTs (N = 2,270) reported the effect of SMBG versus no self-monitoring on change in HbA_{1C} from baseline.^{8,23,24,31,34,36,47} Meta-analysis yielded a statistically significant difference in HbA_{1C} in favour of SMBG (weighted mean difference -0.25%, 95% CI -0.36% to -0.15%) (Figure 2a, Table 1). Results were similar when the analysis was restricted to good quality studies,^{31,36,47} or to studies in which all subjects used oral antidiabetes agents (Table 1).^{23,31,47}

We conducted a subgroup analysis based on whether study participants were instructed on interpretation and application of results from SMBG (figure 2b). The pooled differences in HbA_{1c} were similar regardless of whether trials implemented such an educational component (Table 1). In the Diabetes Glycaemic Education and Monitoring (DiGEM) trial, the only RCT³¹ that directly compared the effect of SMBG with either less intensive or more intensive education, there was no statistically significant difference in HbA_{1c} [mean difference 0.03%, 95% CI -0.15% to 0.21%].

Additional subgroup analyses were conducted to determine whether the HbA_{1c} estimate was affected by differences across studies in frequency or duration of SMBG, baseline HbA_{1c}, time of diabetes diagnosis, and type of oral antidiabetes agent used (Table 1). Results were generally similar to the overall analysis across all subgroups, although the pooled estimate across the two trials employing a SMBG frequency of more than twice daily was somewhat higher than trials testing lower frequencies. Also noteworthy is the finding that there was no statistically significant effect of SMBG on HbA_{1c} in the only RCT that enrolled newly-diagnosed patients [mean difference -0.40%, 95% CI -0.96% to 0.16%].³⁶

The only RCT directly comparing one SMBG frequency with another reported no significant difference in HbA_{1c} at six months between a frequency of one per week versus four per week.⁴⁵

Results from observational studies were mixed with respect to the effect of SMBG on HbA_{1C} levels (Table 2).^{26,32,37,39,43,44,48} In general, mean HbA_{1C} levels were lower in patients performing SMBG, and higher daily SMBG frequencies were associated with incremental reductions in HbA_{1C}. However, effect sizes varied considerably across studies.

Effect of self-monitoring on other outcomes

The pooled relative risk of overall hypoglycemia across three RCTs^{23,31,47} (N=1752) reporting this outcome was significantly higher with SMBG compared with no SMBG [RR (95% CI) = 1.99 (1.37, 2.89)] (Table 3), although the rate of overall hypoglycemia was significantly lower [rate ratio (95% CI) = 0.73 (0.55, 0.98)].^{36,47} There were no statistically significant differences in severe or nocturnal hypoglycemia (Table 3). However, Barnett *et al* reported a statistically significant reduction in the number of symptomatic hypoglycemic events reported by patients using a sulfonylurea who were performing SMBG versus no SMBG [rate ratio (95% CI) = 0.57 (0.38, 0.85)].⁴⁷

Five RCTs reported the effect of SMBG on health-related quality of life and patient satisfaction^{22,23,36,40,41} (Table 4). There were no statistically significant differences between SMBG and no SMBG in terms of patient scores on the Well-being Questionnaire,^{22,40} the Diabetes Treatment Satisfaction Questionnaire,^{22,24} or the overall EuroQol-5D utility score. Interestingly, quality of life measured using the EuroQol-5D was significantly lower in the arm of the DiGEM trial in which patients who were using SMBG were provided with intensive education (mean difference -0.072, 95% CI -0.127 to -0.017), due primarily to increased levels of anxiety and depression.⁴¹

However, results from two studies reporting subscale scores from the Well-being Questionnaire were conflicting with respect to the effect of SMBG on depression.^{36,40}

Two observational studies^{30,33} that compared the effect of SMBG versus no self-monitoring reported mixed results for mortality. A retrospective cohort study of newly-diagnosed patients reported that SMBG was associated with significantly decreased risks for all-cause mortality and non-fatal diabetes-related events at 6.5 years.³³ Conversely, a prospective cohort study of previously-diagnosed patients reported no change in all-cause mortality with SMBG at 10 years.³⁰

Patients not using diabetes pharmacotherapy

One RCT³¹ and two observational studies^{26,32} compared SMBG with no SMBG in patients managed without diabetes pharmacotherapy. In the subgroup of subjects in the DiGEM trial not treated with antidiabetes agents, there were no significant differences in HbA_{1c} between users and non-users of SMBG, regardless of whether or not users were educated to interpret SMBG results.³¹ In contrast, a large retrospective cohort study reported statistically significant differences in HbA_{1c} favouring SMBG versus no testing.²⁶ A second retrospective cohort study reported a 0.35% reduction ($p < 0.0001$) in HbA_{1c} for every additional test strip dispensed per day in new users of SMBG, but not in patients who had used SMBG for at least 3.5 years.³²

Interpretation

Our systematic review identified seven RCTs that compared SMBG with no self-monitoring in patients with type 2 diabetes managed without insulin. Meta-analysis of study results indicated that SMBG is associated with a statistically significant improvement in HbA_{1C} of 0.25%, a result that is consistent with findings of previous systematic reviews.^{10-14,16} The clinical relevance of this effect is questionable in light of published minimal clinically important differences in HbA_{1C}.^{49,50} For patients who were not using diabetes pharmacotherapy, the improvement in HbA_{1C} was even smaller and statistically non-significant.

Data from observational studies were not pooled due to the presence of substantial methodological variation. Compared with evidence from RCTs, the greater likelihood of selection bias in observational studies and the inability to adjust fully for the effect of confounders rendered it difficult to isolate the effects of SMBG on glycemic control.

This review also examined whether SMBG is more effective when used in conjunction with patient education regarding the interpretation of results and appropriate responses.^{11,15,51} We found that results from studies that provided such education were similar to those that did not. Our findings are consistent with the results of the DiGEM trial, which also reported no significant difference in glycemic control between patients instructed in self-interpretation and those who were directed to have a health professional interpret SMBG results.³¹ These results appear to indicate that SMBG offers little benefit regardless of whether education is also provided. However, the failure to observe an added benefit of patient education could also be related to study factors such as poor compliance

with the study protocol, or the lack of a specific algorithm for patients and clinicians to use SMBG results to make therapeutic decisions.

According to the *Diabetes in Canada Evaluation* study, the average HbA_{1c} of patients with type 2 diabetes in Canada is 7.5%, and only 20% of patients have a HbA_{1c} in excess of 8.5%.⁵² Six of the seven RCTs included in our meta-analysis enrolled patients with mean baseline HbA_{1c} ranging from 8.1% to 10.5%. Therefore, our results may be more applicable to patients with poorly controlled diabetes. The DiGEM study, the only RCT that included subjects with a baseline HbA_{1c} less than 8.0%, reported a statistically non-significant benefit of SMBG.³¹

Improvements in quality of life due to SMBG are typically attributed to a greater level of self-efficacy and control,^{53,54} while pain, discomfort, and inconvenience associated with SMBG may reduce quality of life.⁵³⁻⁵⁸ In our analysis, there were no significant differences between SMBG and no SMBG in terms of overall health-related quality of life, patient satisfaction, or patient well-being, although evidence for these outcomes was sparse and analysis was complicated by the use of different scales. Analysis of sub-scales related to psychological well-being demonstrated discrepant findings across studies with respect to the effect of SMBG on anxiety and depression. The available data on the effects of SMBG on quality of life and patient satisfaction are thus inconclusive. Further studies employing standardized instruments are required to determine the benefits, if any, of SMBG on these outcomes.

The relative risks for severe and nocturnal hypoglycemia were not significantly affected by SMBG, but the risk of overall hypoglycemia was significantly higher with SMBG. This may have been due to greater detection of asymptomatic hypoglycemia^{10,14,23,47}. Interestingly, the number of events of overall hypoglycemia was significantly lower with SMBG. The reason for this apparently counter-intuitive result is unclear, although it may be that increased detection of hypoglycemia with SMBG soon after initiation of self-monitoring (which results in a higher relative risk) ultimately produces behavioural changes that reduce future hypoglycemic events (resulting in a lower rate ratio). The finding by Barnett *et al* that rates of symptomatic hypoglycemia are lower in patients treated with a sulfonylurea using SMBG may indicate that self-monitoring prevents asymptomatic hypoglycemia from progressing. However, it should be noted that this is a highly subjective outcome that is significantly prone to ascertainment bias. Further studies employing more rigorous methods are therefore required to confirm this possible benefit of SMBG.

Data regarding long-term clinical endpoints were infrequently reported in observational studies; no such data were reported in RCTs. Given the many possible confounders and likelihood of selection bias in observational studies, further RCTs of adequate size and duration are required to determine whether SMBG reduces long-term complications of diabetes in patients with type 2 diabetes not using insulin.

Strengths and Limitations

Our review is the first to systematically evaluate the available RCT and observational evidence related to SMBG in patients with type 2 diabetes not using insulin across a wide range of outcomes, and over numerous clinically relevant subgroups. However, certain limitations of our analysis warrant mention. In terms of the literature search strategy, potentially relevant studies may have been overlooked by excluding non-English language articles. However, a number of methodological reviews have suggested that this practice has minimal impact on the results of systematic reviews and meta-analyses.⁵⁹⁻⁶² Furthermore, previous systematic reviews in this area did not identify additional RCTs published in a language other than English,^{10-14,16} hence the likelihood of bias arising from the imposed language restriction is minimal. Another limitation is the relatively low statistical power to detect differences within some subgroups, although it is reassuring that the HbA_{1C} point estimates across subgroups were generally similar.

Possible limitations in the internal validity and generalizability of the RCTs included in this review should also be noted. The lack of blinding may have resulted in overestimation of SMBG-related benefits because subjects randomized to SMBG may have been more motivated to perform other behaviours that resulted in better glycemic control. However, it could be argued that any effects of SMBG in terms of increased patient motivation are important ancillary benefits that may also be realized in clinical practice, hence they do not necessarily limit the internal validity of studies. Perhaps more importantly, only one RCT⁴⁷ described a treatment algorithm in which SMBG results were used to adjust antidiabetes treatments. The remaining studies either based therapeutic decisions upon HbA_{1C} levels^{8,23,31,36} or did not specify how treatments were modified in response to SMBG results.^{24,34} Furthermore, the degree to which subjects acted appropriately in response to SMBG results was not documented in studies, even when education regarding

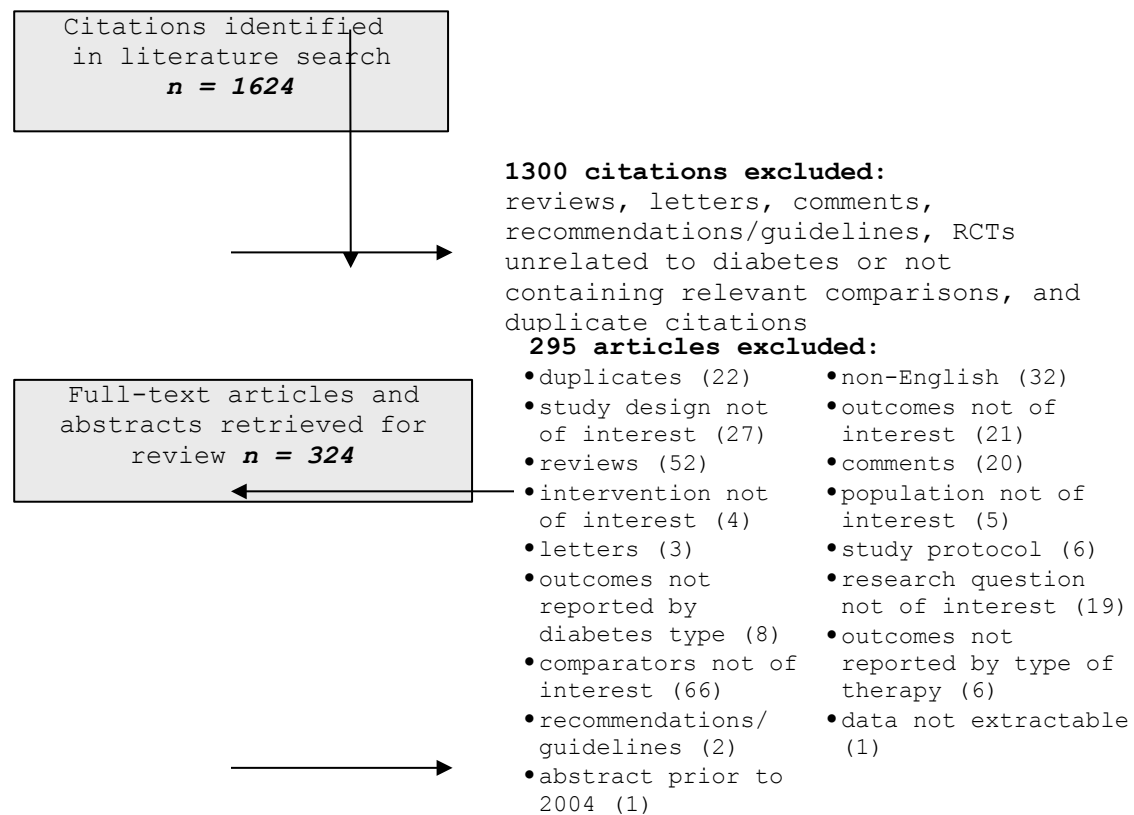
interpretation and application was provided. It is therefore possible that the benefits of SMBG, particularly in combination with patient education, were underestimated. However, results of qualitative research indicate that SMBG results are not often reviewed by physicians,⁶³ hence the manner in which SMBG was employed in RCTs may be reflective of clinical practice.

The remaining limitations stem from the paucity of studies addressing key issues pertaining to self-monitoring in patients with type 2 diabetes not using insulin. Much of the evidence of SMBG efficacy relates to HbA_{1c} levels rather than prevention of complications related to diabetes. Whether HbA_{1c} is an adequate surrogate endpoint for clinically relevant outcomes in patients with type 2 diabetes is controversial, especially in terms of the risk for cardiovascular events.^{64,65} There was also insufficient evidence regarding optimal frequency or timing of self-monitoring. Although some studies implemented patient education regarding interpretation of results from self-monitoring, there was considerable heterogeneity in both the format and intensity of education and co-interventions provided. Therefore, specific educational components that are of value in conjunction with SMBG could not be identified. Finally, patients with type 2 diabetes not using insulin represent a heterogeneous clinical population. It is therefore possible that certain subgroups are more likely to benefit from self-monitoring, for example, patients undergoing significant changes in medication regimen. Further studies are needed to adequately define the place of SMBG in these subgroups.

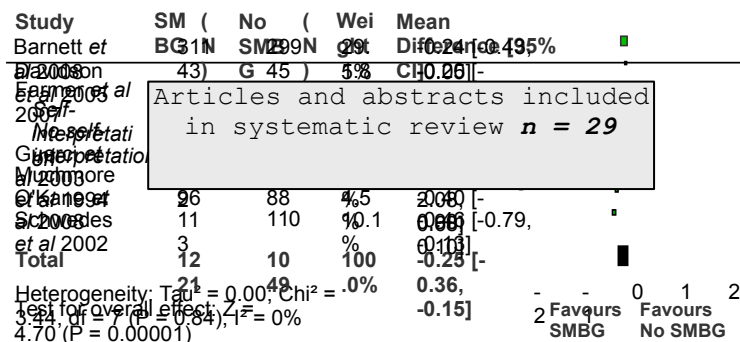
Conclusion

Our findings suggest that SMBG is associated with modest improvements in glycemic control among patients with non-insulin treated type 2 diabetes. The provision of education to help patients translate results from SMBG into appropriate responses appeared to result in no greater benefit than self-monitoring without education, although studies may have been limited in their ability to adequately assess the effects of education. There was little evidence to suggest that SMBG confers benefits in terms of health-related quality-of-life, patient satisfaction, long-term complications, or mortality. Additional high-quality RCTs of sufficient size and duration are required to determine whether self-monitoring reduces the burden of diabetes complications, and to identify the patient subgroups and clinical scenarios in which SMBG is most likely to provide benefit.

Figure 1: Study selection process



a



b

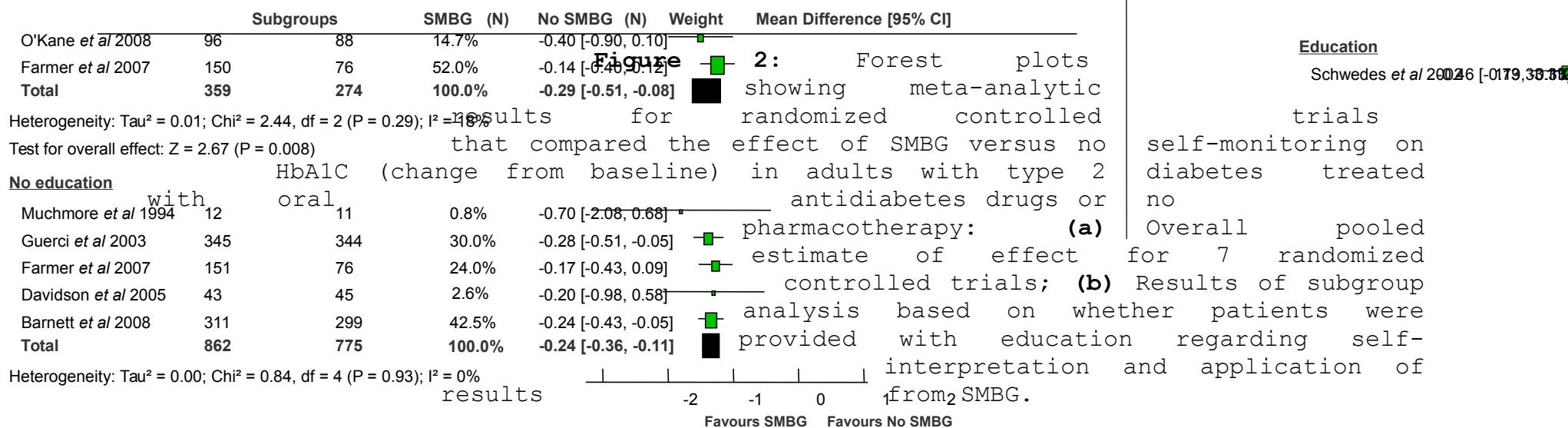
Test for overall effect: $Z = 3.70$ ($P = 0.0002$)

Table 1: Summary of meta-analytic results for HbA1C from randomized controlled trials comparing SMBG with no self-monitoring, or various frequencies of SMBG, in adults with type 2 diabetes treated with oral antidiabetes drugs or no antidiabetes therapy.

Analysis	Number of studies (sample size)	WMD (%) (95% CI)	I ² (%)
SMBG compared with no SMBG			
Overall	7 RCTs ^{8,23,24,31,34,36,47} (n = 2270)	-0.25 (-0.36, -0.15)	0
<i>Sensitivity and subgroup analyses</i>			
Good quality RCTs only	3 RCTs ^{31,36,47} (n = 1247)	-0.21 (-0.34, -0.08)	0
Studies in which all subjects used oral antidiabetes agents	3 RCTs ^{23,31,47} (n = 1628)	-0.24 (-0.36, -0.11)	0
<u>Education regarding application of SMBG results</u>			
Education	3 RCT ^{24,31,36} (n = 710)	-0.28 (-0.47, -0.08)	17.8
No education	5 RCTs ^{8,23,31,34,47} (n = 1712)	-0.22 (-0.34, -0.10)	0
<u>Testing frequency*</u>			
< 1 test per day	3 RCTs ^{8,23,31} (n = 1230)	-0.20 (-0.35, -0.06)	0
1-2 tests per day	2 RCT ^{36,47} (n = 794)	-0.26 (-0.44, -0.07)	0
> 2 tests per day	2 RCTs ^{24,34} (n = 246)	-0.47 (-0.79, -0.15)	0
<u>Duration of self-monitoring</u>			
SMBG for 6 months	5 RCTs ^{8,23,24,36,47} (n = 1794)	-0.28 (-0.41, -0.15)	0
SMBG for > 6 months	3 RCTs ^{31,34,36} (n = 660)	-0.19 (-0.36, -0.01)	0
<u>Proximity to diagnosis</u>			
Previously diagnosed	6 RCTs ^{8,23,24,31,34,47} (n = 2086)	-0.25 (-0.35, -0.14)	0
Newly diagnosed	1 RCT ³⁶ (n = 184)	-0.40 (-0.96, 0.16)	N/A
<u>Baseline glycemic control</u>			
A1c < 8.0%	1 RCT ³¹ (n = 453)	-0.16 (-0.34, 0.03)	N/A

Analysis	Number of studies (sample size)	WMD (%) (95% CI)	I ² (%)
A1c ≥ 8.0%	6 RCTs ^{8,23,24,34,36,47} (n = 1817)	-0.30 (-0.43, -0.17)	0
<u>Type of oral antidiabetes agent</u>			
Sulfonylurea	1 RCT ⁴⁷ (n = 610)	-0.24 (-0.43, -0.05)	
Various	2 RCTs ^{23,31} (n = 1018)	-0.24 (-0.40, -0.07)	0
Frequency comparison			
1 SMBG per week vs. 4 SMBG per week	1 RCT ⁴⁵ (n = 178)	-0.08 (-0.41, 0.25)	N/A

Note: CI - confidence interval, RCT - randomized controlled trial, WMD - weighted mean difference, N/A - not applicable, OADs - oral antidiabetes drugs

* Average daily use of blood glucose test strips is based upon actual testing frequency, when reported. Otherwise, we assumed that patients in the RCT adhered to testing frequencies outlined in the study protocol.

Table 2: Mean differences in HbA1C reported in retrospective cohort studies comparing SMBG with no self-monitoring, or various frequencies of SMBG, in adults with type 2 diabetes treated with oral antidiabetes drugs or no antidiabetes therapy.

Comparison		Number of studies (n)	Mean difference in A1C (%) (95% CI)
SMBG compared with no SMBG			
≥ 1 strip/day vs. no SMBG		1 R. cohort ²⁶ (n = 8735)	-0.68 (-0.77, -0.59)
< 1 strip/day vs. no SMBG		1 R. cohort ²⁶ (n = 10243)	-0.21 (-0.30, -0.12)
Prescription of 2-4 strips per week vs. no prescription of strips		1 R. cohort ³⁷ (n = 115)	-0.20 (-0.77, 0.37)
Prescription of 0.56 strips per day vs. no prescription of strips		1 R. cohort ⁴³ (n = 299)	-0.13 (-0.28, 0.02)
SMBG vs. no SMBG for patients with baseline A1c ≥10%		1 time-series ⁴² (n = 133)	-0.63 (-1.14, -0.12)
Frequency comparisons			
SMBG once per day vs. less than once per day		1 R. cohort ²⁶ (n = 6594)	-0.47 (-0.57, -0.37)
SMBG increased by one strip per day	Patients using OADs	1 R. cohort ³⁹ (n = 1795)	0.09 (p = 0.5392)
	Patients using sulfonylureas	1 R. cohort ⁴⁴ (n = 216)	0.02 (p > 0.50)
	New users of SMBG	1 R. cohort ³² (n = 5546)	-0.42 (p < 0.0001)
	Prevalent users of SMBG	1 R. cohort ³² (n = 7409)	-0.16 (p < 0.0001)
SMBG increased by 10 test strips per week		1 R. cohort ⁴⁸ (n = 5862)	-0.06 (p = 0.38)

Note: CI - confidence interval, R. cohort - retrospective cohort, OADs - oral antidiabetes drugs

Table 3: Summary of meta-analytic results for overall, severe, and nocturnal hypoglycemia from RCTs comparing SMBG with no self-monitoring, or various frequencies of SMBG, in adults with type 2 diabetes treated with oral antidiabetes drugs or no antidiabetes therapy.

Analysis	Number of studies (sample size)	Effect Estimate (95% CI)	I ² (%)
SMBG vs. no SMBG			
Overall hypoglycemia	3 RCTs ^{23,31,47} (n = 1752)	RR: 1.99 (1.37, 2.89)	33.8
	2 RCTs ^{36,47} (n = 794)	Rate ratio: 0.73 (0.55, 0.98)	0
Severe hypoglycemia	3 RCTs ^{24,31,47} (n = 1752)	RR: 0.17 (0.01, 4.12)	N/A
Nocturnal hypoglycemia	1 RCT ⁴⁷ (n = 610)	RR: 0.41 (0.11, 1.58)	N/A
Frequency comparison (1 SMBG per week vs. 4 SMBG week)			
Overall hypoglycemia	1 RCT ⁴⁵ (n = 202)	RR: 0.28 (0.11, 0.73)	N/A
Severe hypoglycemia	1 RCT ⁴⁵ (n = 202)	No events	N/A

95% CI - 95% confidence intervals; SMBG - self-monitoring of blood glucose; RR - relative risk; RCT - randomized controlled trial; N/A - not applicable

Table 4: Mean differences in patient satisfaction with diabetes treatment, well-being, and quality of life reported in randomized controlled trials comparing SMBG with no self-monitoring in adults with type 2 diabetes treated with oral antidiabetes drugs or no antidiabetes therapy.

Analysis	Number of studies (n)	WMD (95% CI)
DTSQ	2 RCTs ^{22,23} (n = 562)	-0.26 (-1.38, 0.86)
WBQ-12	1 RCT ²² (n = 339)	-0.85 (-2.27, 0.56)
WBQ-22	1 RCT ⁴⁰ (n = 223)	1.83 (-0.05, 3.71)
<u>EQ-5D</u>		
SMBG overall	1 RCT ⁴¹ (n = 453)	-0.06 (-0.13, 0.02)
SMBG + education	1 RCT ⁴¹ (n = 302)	-0.029 (-0.084, 0.025)
SMBG w/o education	1 RCT ⁴¹ (n = 301)	-0.072 (-0.127, -0.017)

Note: CI - confidence interval, DTSQ - diabetes treatment satisfaction questionnaire, EQ-5D - EuroQoL-5D, RCT - randomized controlled trial, WBQ - well being questionnaire, WMD - weighted mean difference

Contributors: All of the authors contributed to the conception and design of the study.

Avtar Lal, Changhua Yu, Brendan McIntosh, Kristen Chelak, and Chris Cameron extracted data from primary studies and analyzed and interpreted the results. Sumeet Singh provided oversight for the extraction, analysis and interpretation of the data. Brendan McIntosh with the help of Sumeet Singh, Chris Cameron, and Dr. Marshall Dahl drafted the manuscript. All of the authors critically reviewed the manuscript, and approved the final version submitted for publication.

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APPENDIX A: Results of Quality Assessment of RCTs

Study	SIGN-50 elements (RCT checklist)										Overall quality rating
	Appropriate and clearly focused question	Randomized assignment	Adequate concealment	Blinding of subjects and investigators	Groups are similar at baseline	The only difference between groups is treatment under investigation	Standard, valid, and reliable measurement of outcome(s)	The drop-out rate is acceptable and is comparable between the groups	ITT analysis performed	Comparable results for multiple study sites	
	AA	AA	NAd	NAd	AA	AA	AA	13% SMBG	AA	NAd	good

Barnett, et al., 2008 ⁵⁰								17% no SMBG			
Davidson, et al., 2005 ⁴	AA	NR	NAd	AA	AA	PA	PA	1	AA	NAp	poor
Farmer, et al., 2007 ³⁴	AA	WC	WC	NAd	AA	AA	AA	7.3 SMBG	AA	AA	good
								11.2 control			
Guerçi, et al., 2003 ²⁸	AA	NR	NAd	NAd	AA	AA	AA	32.2 SMBG	PA	AA	poor
								29.1 control			
Muchmore, et al., 1994 ³⁷	AA	PA	NAd	NAd	PA	PA	NR	~ 10%	NAd	NAp	poor
O’Kane, et al., 2008 ³⁹	WC	WC	PA	PA	PA	AA	PA	2.0 SMBG	WC	NAp	good
								2.2 control			
Scherbaum, et al., 2008 ⁴⁸	WC	AA	AA	NAd	AA	WC	NAd	12% 1/week	PA	NAd	good
								11% 4/week			
Schwedes, et al., 2002 ²⁹	AA	PA	NAd	PA	AA	PA	WC	10.8	PA	PA	poor
Siebolds, et al., 2006 ⁴³	AA	PA	NAd	NAd	AA	PA	AA	10.8	PA	PA	poor

AA=adequately addressed; DM=diabetes mellitus; ITT=intention to treat; NAd=not addressed; NAp=not applicable; PA=poorly addressed; QA=quality assessment; WC=well-covered

16APPENDIX B: Results of Quality Assessment of observational studies

Study	SIGN-50 elements (Cohort study checklist)					
	Appropriate and clearly focused question	Groups are comparable other than the factor under investigation	Recruitment rate reported	Likelihood that subjects have the outcome at the time of enrollment is assessed	The dropout rate is acceptable and is comparable between the groups	Comparison is made between full participants and those lost to follow-up, by exposure status
Aydin et al., 2005 ³¹	AA	AA	NAd	AA	NR	NAp
Bajkowska-Fiedziukiewicz et al., 2008 ⁴⁹	AA	PA	PA	NAd	NR	NAd
Davis et al., 2007 ³³	AA	AA	NAd	AA	1.08	NAd
Evans et al., 1999 ²⁵	AA	AA	NAd	NAd	63	NAd
Karter et al., 2001 ²⁴	WC	AA	AA	NAd	NR	NAd
Karter et al., 2006 ³⁵	AA	AA	NAd	PA	NR	NAd
Martin et al., 2006 ³⁶	WC	AA	NR	PA	0.2	NAd
Murata et al., 2009 ⁵⁴	AA	AA	NAd	NAd	NR	NAd
Rindone et al., 1997 ⁴⁰	AA	AA	NAd	NAd	0	NAd

Schneider et al., 2007 ⁴¹	WC	AA	NR	AA	0.52	NAd
Secnik et al., 2007 ⁴²	AA	AA	NAd	NAd	29 insulin	PA
					26 OAD	
Wen et al., 2004 ⁴⁶	AA	AA	NAp	AA	NAp	NAp
Wieland et al., 1997 ⁴⁷	AA	AA	NAp	NAd	NR	NAp

AA=adequately addressed; DM=diabetes mellitus; ITT=intention to treat; NAd=not addressed; NAp=not applicable; PA=poorly addressed; QA=quality assessment; WC=well-covered

APPENDIX B (cont'd)

Study	SIGN-50 elements (Cohort study checklist cont'd)							Overall quality rating
	Outcomes are clearly defined	Assessment of outcome is made blind to exposure status	Recognition that knowledge of exposure status could have influenced the assessment	The measure of assessment of exposure is reliable	Evidence used to show the method of outcome assessment is valid and reliable	Exposure level or prognostic factor is assessed more than once	Main confounders are taken into account	
Aydin et al., 2005 ³¹	AA	NAd	NAd	PA	NAd	NAd	PA	poor
Bajkowska-Fiedziukiewicz, et al., 2008 ⁴⁹	AA	NAd	NAd	PA	AA	NAd	NAd	poor
Davis et al., 2007 ³³	AA	NAd	NAp	NAd	NAd	NAd	AA	poor
Evans et al., 1999 ²⁵	PA	NAd	NAp	PA	PA	NAd	AA	poor
Karter et al., 2001 ²⁴	PA	WC	NAp	PA	PA	AA	AA	poor
Karter et al., 2006 ³⁵	AA	NAd	NAp	AA	NAd	PA	AA	poor
Martin et al., 2006 ³⁶	AA	NAp	NAp	PA	AA	NAd	AA	poor
Murata et al., 2009 ⁵⁴	AA	NAd	NAp	PA	NAd	NAd	PA	poor
Rindone et al., 1997 ⁴⁰	AA	NAd	NAp	AA	NAd	PA	PA	poor
Schneider et al.,	AA	NAp	NAp	PA	AA	NAd	AA	poor

2007 ⁴¹								
Secnik et al., 2007 ⁴²	AA	NAd	NAp	AA	AA	PA	AA	poor
Wen et al., 2004 ⁴⁶	AA	NAd	NAp	PA	NAd	PA	AA	poor
Wieland et al., 1997 ⁴⁷	AA	NAd	NAp	PA	AA	NAd	NR	poor

AA=adequately addressed; DM=diabetes mellitus; ITT=intention to treat; NAd=not addressed; NAp=not applicable; PA=poorly addressed; QA=quality assessment; WC=well-covered