

ORIGINAL ARTICLE

# Self-monitoring of glucose in type 2 diabetes mellitus: a Bayesian meta-analysis of direct and indirect comparisons

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## ABSTRACT

*Objective:* To evaluate the relative effectiveness of interventions with self-monitoring blood glucose and self-monitoring of urine glucose, versus interventions without self-monitoring, in terms of HbA<sub>1c</sub> reductions in type 2 diabetes mellitus.

*Methods:* Thirteen published full reports on randomised controlled trials investigating the effects of self-monitoring glucose were identified by a systematic search of Medline, Embase, the Cochrane Library (1966–Nov 2005) and previous reviews. Three types of studies were included: self-monitoring of blood glucose versus no self-monitoring, self-monitoring of blood glucose versus self-monitoring of urine glucose and self-monitoring of blood glucose with regular feedback versus monitoring without feedback. The internal validity of studies was assessed systematically by two reviewers, using 13 criteria of a validated list. Results from the three types of studies were analysed simultaneously with a Bayesian meta-analysis of direct and indirect comparisons.

*Results:* Adjusted for baseline HbA<sub>1c</sub> level and

internal validity, interventions with self-monitoring of blood glucose showed a reduction in HbA<sub>1c</sub> of 0.40 percentage-points (%) (95% credible interval [CrI] 0.07 to 0.70%) in comparison to interventions without self-monitoring. Regular feedback more than doubled the HbA<sub>1c</sub> reduction. Self-monitoring of urine glucose showed comparable results to interventions without self-monitoring (0.02% decrease in HbA<sub>1c</sub>; 95% CrI –0.62 to 0.70%). There is a 88% probability that interventions with self-monitoring blood glucose are more effective than interventions with urine glucose monitoring (relative reduction in HbA<sub>1c</sub> is 0.38%, 95% CrI –0.30 to 1.00%).

*Conclusion:* The randomized clinical trials performed to date provided positive results on the effectiveness of interventions with self-monitoring of blood glucose in type 2 diabetes mellitus. Regular medical feedback of the monitored HbA<sub>1c</sub> levels is important. Furthermore, self-monitoring of blood glucose is likely to be more effective than self-monitoring of urine glucose.

## Introduction

Diabetes mellitus (DM) is a clinical and public health problem. DM can now be found throughout the world and epidemiological evidence suggests that, without effective prevention and control programmes, diabetes will probably continue to increase globally<sup>1</sup>. Type

2 DM is responsible for about 90% of all diabetes in developed countries<sup>2</sup>.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the relation between glycaemic control and the development of complications in Type 2 diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, renal

failure, blindness and amputations, confirming the need for intervention in glycaemic control<sup>3</sup>.

For effective management of glycaemic control in DM, the patient must play an active role. Ninety-five per cent of care is provided by the patients themselves<sup>4,5</sup>. This self-management is not limited to medication adherence (i.e. insulin injections or taking oral hypoglycaemic treatment), but includes lifestyle changes (e.g. diet) and self-monitoring of glucose. Self-monitoring of blood glucose (SMBG) or urine glucose (SMUG) is a tool used to help determine patterns of glucose control and identify problem areas. Understanding glucose levels can help the patients to anticipate situations where they may experience high or low blood glucose and allow them to prevent these situations from occurring.

The Diabetes Control and Complications Trial (DCCT) in type 1 DM, where intensive diabetes mellitus management was compared with conventional care, provided evidence that glycaemic control, by means of a package of care that included SMBG in type 1 DM, is effective in the reduction of diabetes related complications, and this finding had a major impact on health policy<sup>6</sup>.

The effectiveness of SMBG in type 2 DM has been evaluated in several systematic reviews of the literature. Faas *et al.*<sup>7</sup>, Gallichan<sup>8</sup>, Halimi<sup>9</sup> and the NHS health technology assessment by Coster *et al.*<sup>10</sup> summarized the results of randomized studies in this area until 1999. It was concluded that, at that time, the evidence regarding the effectiveness of SMBG in type 2 DM was inconclusive. Recently, several additional randomized controlled trials in this area have been performed<sup>11-15</sup> and were included in the reviews by Sarol *et al.*<sup>16</sup> and by Welschen *et al.*<sup>17</sup>. Their conclusion was that interventions with SMBG seem effective in improving glycaemic control relative to interventions without SMBG.

The review by Coster *et al.*<sup>10</sup> and Welschen *et al.*<sup>17</sup> did not provide evidence that SMBG is more effective than SMUG in terms of falls in HbA<sub>1c</sub>. This finding may be due to the fact that only three relatively small studies were performed where SMBG was compared with SMUG<sup>18-20</sup>. Alternatively, it may be that it is the feedback itself which is important to patients and that whether this is through urine or blood testing may not be important. Further randomized studies observed that regular follow-up and feedback from nurses or physicians, regarding the results of SMBG, are important for compliance with SMBG and to improve glycaemic control<sup>14,21</sup>. Although these two studies were included in the review by Sarol *et al.*<sup>16</sup>, they did not quantify the additional impact of regular feedback for self-monitoring.

Previous systematic reviews focused on pair-wise, direct comparisons of treatments: i.e. SMBG versus no

SMBG, and SMBG versus SMUG. In the absence of large, high quality, randomised trials comparing interventions without self-monitoring, SMUG, SMBG and SMBG with regular feedback, it is difficult to determine the most effective type of intervention. An alternative approach is to rely on indirect comparisons of these treatments. An indirect estimate of the effectiveness of trials A over C can be obtained by comparing trials of A versus B with trials of B versus C<sup>22-24</sup>. Mixed treatment comparison (MTC) meta-analysis is a generalization of standard meta-analysis for pair-wise trials to the simultaneous analysis of A versus B, B versus C and A versus C trials. The advantage of MTC meta-analysis over standard meta-analysis is to strengthen inference concerning the relative effectiveness of treatments, by including both 'direct' and 'indirect' comparisons. Furthermore, when this simultaneous inference of treatments is performed in a Bayesian framework it allows the calculation of the probability of which treatment is best; very appealing to decision-makers<sup>22-24</sup>.

A MTC meta-analysis can be very interesting in evaluating the effectiveness of SMUG, SMBG and the role of feedback in glycaemic control. For example, the simultaneous analysis can quantify the difference between SMUG versus no monitoring, in the absence of pair-wise comparisons. Furthermore, it can help in understanding the additional effect of regular medical feedback on the results of SMBG, even when only a limited number of studies that separate SMBG from SMBG with regular feedback are available.

The objective of this study was to evaluate the effectiveness of interventions with SMBG, SMBG with feedback and SMUG, versus interventions without self-monitoring, in type 2 DM, in terms of glycaemic control.

## Methods

### Identification and selection of studies

In order to identify publications concerning the self-monitoring of glucose in type 2 DM, two reviewers searched computerised bibliographic databases (MEDLINE 1966–November 2005, EMBASE 1988–2004 and Cochrane Library issue 4 until 2004) using the Cochrane Collaboration search strategy for identifying controlled clinical trials<sup>25</sup>. This search strategy was combined with the keywords 'diabetes mellitus', 'self monitoring', 'urine' and 'blood glucose self-monitoring'. In addition, previous systematic reviews were used to identify further studies.

The two reviewers determined, independently of each other, whether the identified studies should be

included, according to the following predetermined conditions:

- Type of design – randomised controlled trials (RCT). Only full, published reports were considered; letters and abstracts were excluded.
- Intervention – the intervention for at least one study group should have been SMBG, as part of the intervention used for the improvement of glycated haemoglobin levels. Comparisons with interventions without SMBG were allowed, as well as comparisons with an intervention that included SMUG. Studies in which SMBG was offered in both the experimental and control group were included, if, in the experimental group, SMBG was combined with regular medical feedback but not in the control groups. Studies in which methods and instruments for SMBG were validated and tested for reliability were excluded.
- Study population – all type 2 DM patients, independent of type of treatment (i.e. with or without insulin or oral treatment).
- Outcome measures – glycated haemoglobin (GHb, HbA<sub>1c</sub>, HbA<sub>1</sub>).
- Language – full-published reports in English, German, French and Dutch were considered.

### Assessment of methodological quality

The internal validity of each trial was evaluated using the 13-items pertaining to internal validity from the quality checklist for randomized and nonrandomized studies by Downs and Black<sup>26</sup>. Two reviewers independently analysed the selected trial reports for completeness of information. For each of the 13 criteria, they checked whether there was enough information in the report to make a judgement. If this was not the case, the criterion was judged as ‘unable to determine’. If there was enough information in the report the criterion was judged positive or negative: that is, positive when the methodological aspect was performed adequately and bias was considered unlikely. Discrepancies between reviewers for assessment of the criteria were identified and discussed in a consensus meeting in order to arrive at a final judgement. Based on the judgements of these items, a total quality score was calculated with a range from 0 to 13. When an item was judged positive a value of 1 was assigned; when an item was judged negative, or unable to be determined, a value of 0 was assigned. The checklist of Downs and Black<sup>26</sup> also includes an item regarding statistical power. We did not include this item to detect statistical significant differences as we are not interested in statistical significant results *per se*, but in the size of the (clinical) effect of each study.

### Data extraction and analysis

Data extraction was performed with an adapted version of the Cochrane Metabolic and Endocrine Disorders Group (Heinrich-Heine-Universität, Düsseldorf) standard data extraction form. The two reviewers independently extracted details on design, quality, selection criteria, study population, interventions, glycated haemoglobin and length of follow-up, for each publication.

If sufficient information regarding the outcome measures of interest (glycated haemoglobin) was available, on both baseline and last follow-up measurement, the change from baseline (CFB) per intervention group was calculated, as well as the corresponding standard deviations. For cross-over studies, this change score was calculated as the difference between baseline and the last follow-up measurement before cross-over.

The identified studies were evaluated regarding the heterogeneity of study populations, baseline characteristics and interventions. Consecutively, it was decided which studies were combined in a meta-analysis. Since the effectiveness of SMBG in type 2 DM may be different for patients that do require insulin and for those that do not, two analyses were performed; one that included studies in type 2 DM independent of treatment, and one among non-insulin requiring patients.

For the interventions of interest (no monitoring, SMUG, SMBG and SMBG with feedback) the results of the individual studies were pooled with a Bayesian random-effects model consisting of two levels. At the first level a likelihood function relates the observed CFB in HbA<sub>1c</sub> per intervention in each study to the unknown (underlying) CFB<sub>*i*</sub><sup>*k*</sup> characterizing that intervention *k* in that study *i*. At the second level a parametric statistical model is constructed to relate the parameters from the separate studies to each other, according to Equation 1<sup>23</sup>.

$$CFB_i^k = \mu_i + \begin{cases} 0 & \text{if}(k = A) \\ \delta_i^{AB} & \text{if}(k = B) \\ \delta_i^{AC} & \text{if}(k = C) \\ \delta_i^{AD} & \text{if}(k = D) \end{cases} \quad (\text{Equation 1})$$

where:

- A = no self-monitoring
- B = SMUG
- C = SMBG
- D = SMBG with regular medical feedback
- CFB<sub>*i*</sub><sup>*k*</sup> = change from baseline with treatment *k* in study *i*
- μ<sub>*i*</sub> = change from baseline with treatment A in study *i*
- δ<sub>*i*</sub><sup>AB</sup> = relative treatment effect of treatment B versus A in study *i*
- δ<sub>*i*</sub><sup>AC</sup> = relative treatment effect of treatment C versus A in study *i*
- δ<sub>*i*</sub><sup>AD</sup> = relative treatment effect of treatment D versus A in study *i*

Based on clinical heterogeneity, as observed from the data-extraction, it was decided to use a random-effects model instead of a fixed effects-model.

Bayesian methods involve, through the use of Bayes's theorem, formal combination of a prior distribution of a quantity of interest with a summary of the information concerning the same quantity available from the data in the study (the likelihood) to obtain a posterior distribution of the quantity of interest. The posterior distribution can be interpreted in terms of probabilities. This is in contrast to findings with a conventional frequentist approach. In order not to influence the observed results by the prior distribution, non-informative (i.e. 'flat') normal distributions were used for the (relative) treatment effects ( $\mu$  and  $\delta$ ): with the defined prior distributions (i.e. normal distributions with mean 0 and variance of 1000) it was assumed that *a priori* the treatment effects can vary from -62 to +62 points with a 95% probability. With such a prior distribution, results with a Bayesian analysis are comparable to a conventional frequentist meta-analysis. The advantage of using a Bayesian meta-analysis is the possibility to calculate probabilities of which treatment is best.

With the MTC meta-analysis the relative CFB (along with a 95% credible interval [95% CrI]) in HbA<sub>1c</sub> of SMUG, SMBG and SMBG with feedback, relative to interventions without self-monitoring, was estimated. Furthermore, differences in CFB between SMUG, SMBG and SMBG with feedback were estimated. CrIs are used instead of 95% confidence intervals to differentiate the uncertainty regarding the point estimate using a Bayesian approach. The following analyses were performed:

- (1) Type 2 DM patients. Studies where some patients were allowed to be treated with insulin were not excluded from the analysis.
- (2) Non-insulin requiring type 2 DM patients. Studies where some patients were treated with insulin were excluded from the analysis.
- (3) Analyses with adjustment for baseline glycaemic level by using a covariate in Equation 1.
- (4) Analyses with adjustment for study quality. Each included study was weighted based on the internal validity score according to Equation 2:

$$w_i = \frac{s_i}{\bar{s}} \quad (\text{Equation 2})$$

where:

$w_i$  = weight of study  $i$

$s_i$  = internal validity score of study  $i$

$\bar{s}$  = average internal validity score

Analyses were performed with WinBUGS v. 1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK).

## Results

The search strategy identified 317 studies in DM. Two hundred and ninety of the studies were excluded because they did not meet the inclusion criteria. These studies were mainly carried out retrospectively, or were patient series without a reference group. The other 27 studies were subjected to quality assessment and data extraction. Among these 27 trials another 14 were excluded because the type of diabetes was not known, a mix of both type 1 and 2 was used, the interventions were not clearly described or the outcomes of interest were not used. Of the remaining, 13 included RCTs<sup>11-15,18-21,27-30</sup>. Three studies compared an intervention that included SMBG with SMUG<sup>18-20</sup>. Nine studies compared an intervention that included SMBG with an intervention without self-monitoring<sup>11,13-20,28-32</sup>. Two studies compared different SMBG with SMBG and feedback programs<sup>14,21</sup>. In the study by Estey *et al.*<sup>21</sup>, intense follow-up and feedback on SMBG testing practices was given by a series of phone calls from a registered nurse. In the study by Kwon *et al.*<sup>14</sup>, an internet-based blood glucose monitoring system was used by which patients recorded results of SMBG and physicians provided recommendations through the system. The study populations in two of the 13 studies were a mixture of patients using and not using insulin<sup>11,30</sup>. In the other eleven studies the type 2 patients did not use insulin, or there was no information on insulin use. An overview of the included studies is provided in Table 1.

### Methodological quality

Table 2 shows the results of the assessment of internal validity. The mean score for internal validity was 8.5 (median = 9, standard deviation [SD] = 1.8, range = 4-10) out of 13 points. As may be expected, considering the nature of the intervention, internal validity shortcomings, defined by criteria scored 'negative' or 'unknown', concerned blinding of the patient for the allocated intervention. Furthermore, concealed allocation of the intervention and blinding those measuring the main outcomes, were problematic criteria. No structural differences in total quality score were observed between studies comparing different interventions.

### Effect of self-monitoring glucose

Twelve of the 13 studies were included in the meta-analysis. The study by Rutten *et al.*<sup>29</sup>, was excluded from the analysis, because the intervention SMBG was confounded with other interventions.



Table 1 (Continued)

Study	n	Inclusion criteria	Interventions	Baseline HbA <sub>1c</sub> (% ± SD)	Length of follow-up	
Jaber <i>et al.</i> <sup>27</sup>	1996	39	<ul style="list-style-type: none"> <li>Urban African-American patients with type 2 DM who were currently attending a university-affiliated, internal medicine outpatient clinic</li> <li>Over-weight type 2 DM, age 40–75 years, NIDDM &gt; 1 year, no SMBG within the previous 3 months, not instructed to count dietary carbohydrate, HbA<sub>1c</sub> 9.5–13.5%, no serious underlying medical or psychiatric illness, drug abuse, or alcoholism</li> </ul>	<ul style="list-style-type: none"> <li>(I) Instruction on diabetes and dietary regulation, medication counselling, exercise, SMBG</li> <li>(C) Usual care</li> </ul>	<ul style="list-style-type: none"> <li>(I) 9.2 ± 2.0</li> <li>(C) 9.7 ± 2.5</li> </ul>	4 months
Muchmore <i>et al.</i> <sup>28</sup>	1994	29	<ul style="list-style-type: none"> <li>Type 2 DM &gt; 6 months, age 40–75 years; no insulin, no treatment by internist for diseases other than DM, obesity or hypertension</li> </ul>	<ul style="list-style-type: none"> <li>(I) A proprietary behavioural weight control program, one-on-one counselling by a diabetes nurse and dietician during a run-in period of 8-weeks, SMBG, carbohydrate counting training, using the blood monitoring</li> <li>(C) A proprietary behavioural weight control program, one-on-one counselling by a diabetes nurse and dietician during a run-in period of 8-weeks</li> </ul>	<ul style="list-style-type: none"> <li>(I) 10.3 ± 1.1</li> <li>(C) 10.5 ± 1.5</li> </ul>	44 weeks
Rutten <i>et al.</i> <sup>29</sup>	1990	149	<ul style="list-style-type: none"> <li>Type 2 DM &gt; 6 months, age 40–75 years; no insulin, no treatment by internist for diseases other than DM, obesity or hypertension</li> </ul>	<ul style="list-style-type: none"> <li>(I) Patients who accepted the opportunity of SMBG were given instructions. The patients contacted the practice nurse monthly to state the level of fasting blood glucose. Patients under GP care (not practising SMBG) consulted their doctors at least four times per year, during which the patient was informed of his current blood glucose level. For all patients in the experimental group a therapeutic scheme was used with fixed targets for weight and regulation and with emphasis on loss of body weight</li> <li>(C) In the control patients, no fixed check-up appointments were used. Patients were not instructed in SMBG</li> </ul>	<ul style="list-style-type: none"> <li>(I) 9.7 ± 2.1</li> <li>(C) 8.9 ± 1.9</li> </ul>	12 months
Schwedes <i>et al.</i> <sup>15</sup>	2002	223	<ul style="list-style-type: none"> <li>Age 45–70 years, BMI &gt; 25 kg/m<sup>2</sup>, with HbA<sub>1c</sub> values between 7.5 and 10%; treated either with diet alone or diet in combination with sulphonylureas or metformin; diabetes known for at least 3 months; participation in a diabetes educational program within the previous 2 years</li> </ul>	<ul style="list-style-type: none"> <li>(I) Patients who underwent SMBG were given instructions on the use of a blood glucose device. Patients were requested to measure blood glucose six times on 2 days per week and to record the values obtained in a diary where documentation of eating and their state-of-well being was also recorded</li> <li>(C) Patients received non standardized counselling with a focus on their diet and lifestyle</li> </ul>	<ul style="list-style-type: none"> <li>(I) 8.5 ± 0.9</li> <li>(C) 8.4 ± 0.8</li> </ul>	12 months
Wing <i>et al.</i> <sup>30</sup>	1986	50	<ul style="list-style-type: none"> <li>Age 35–65 years; &gt; 20% above ideal weight for height; use of oral hypoglycaemic medication or insulin for blood control; development of diabetes after the age of 30</li> </ul>	<ul style="list-style-type: none"> <li>(I) Behavioural weight control treatment program, SMBG and focusing on the weight-blood glucose relationship</li> <li>(C) Behavioural weight control treatment program focused on weight reduction as the goal of therapy</li> </ul>	<ul style="list-style-type: none"> <li>(I) 10.2 ± 2.5</li> <li>(C) 10.7 ± 2.0</li> </ul>	62 weeks
Estey <i>et al.</i> <sup>21</sup>	1990	60	<ul style="list-style-type: none"> <li>Type 2 DM. Treatment with diet and/or oral hypoglycaemic agents, completion of the 3-day education program provided at the Diabetes centre, accessibility by telephone</li> </ul>	<ul style="list-style-type: none"> <li>(I) SMBG with internet-assisted patient consultations without outpatient management visits</li> <li>(C) SMBG and usual care involved monthly visits with two or three visits with senior staff during a 12-week period</li> </ul>	<ul style="list-style-type: none"> <li>(I) 6.3 ± 1.1</li> <li>(C) 6.1 ± 1.4</li> </ul>	3 months
Kwon <i>et al.</i> <sup>14</sup>	2004	101	<ul style="list-style-type: none"> <li>Men and women diagnosed with type 2 DM for &gt; 1 year; age &gt; 30 years</li> </ul>	<ul style="list-style-type: none"> <li>(I) SMBG with internet-assisted patient consultations without outpatient management visits</li> <li>(C) SMBG and usual care involved monthly visits with two or three visits with senior staff during a 12-week period</li> </ul>	<ul style="list-style-type: none"> <li>(I) 7.6 ± 1.4</li> <li>(C) 7.2 ± 1.2</li> </ul>	12 weeks

SD = standard deviation; I = intervention; C = control; SMBG = self-monitoring of blood glucose; SMUG = self-monitoring of urine glucose; NIDDM = non-insulin dependent diabetes mellitus; BMI = body mass index

**Table 2. Results of internal validity quality assessment of included studies (based on Downs and Black<sup>26</sup>) and weight of studies in analysis**

Internal validity criteria	Allen <i>et al.</i> <sup>18</sup>	Brown <i>et al.</i> <sup>11</sup>	Davidson <i>et al.</i> <sup>12</sup>	Estey <i>et al.</i> <sup>21</sup>	Fonthonne <i>et al.</i> <sup>19</sup>	Guerci <i>et al.</i> <sup>13</sup>	Jaber <i>et al.</i> <sup>27</sup>	Kwon <i>et al.</i> <sup>14</sup>	Miles <i>et al.</i> <sup>20</sup>	Muchmore <i>et al.</i> <sup>28</sup>	Rutten <i>et al.</i> <sup>29</sup>	Schwedes <i>et al.</i> <sup>15</sup>	Wing <i>et al.</i> <sup>30</sup>
• Was an attempt made to blind study subjects to the intervention they have received?	No	No	No	No	No	No	No	No	No	No	No	No	No
• Was an attempt made to blind those measuring the main outcomes of the intervention?	?	No	Yes	?	?	?	?	?	?	?	?	?	?
• If any of the results of the study were based on 'data dredging', was this made clear?	?	Yes	Yes	Yes	Yes	?	?	?	?	Yes	Yes	?	Yes
• In the trials, do the analyses adjust for different lengths of follow-up of patients?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes
• Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes
• Was compliance with the intervention/s reliable?	Yes	Yes	No	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes
• Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes
• Were the patients in different intervention groups recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
• Were the study subjects in different intervention groups recruited over the same period of time?	?	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	?	Yes	?
• Were the study subjects randomised to intervention groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
• Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No	?	?	?	?	?	?	?	No	No	?	?	?
• Was there adequate adjustment for confounding in the analysis from which the main findings were drawn?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes
• Were losses of patients to follow-up taken into account?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes
Total internal validity score	8	10	10	10	10	7	7	9	4	9	8	9	9
Weight multiplier of study in meta-analysis based on quality	0.935	1.168	1.168	1.168	1.168	0.818	0.818	1.051	0.467	1.051	NA	1.051	1.051

? = no information ; NA = not applicable

In Table 3 the observed results, in terms of CFB in HbA<sub>1c</sub> (expressed in ‘percentage points’) of the 12 RCTs, are presented, organised by the interventions of interest. When these study results were combined with the random-effects model, the pooled CFB in HbA<sub>1c</sub> for interventions without self-monitoring was -0.47% (95% CrI -0.66 to -0.28%). The pooled CFB for interventions with SMUG was -0.61% (95% CrI -1.20 to -0.05%). The pooled CFB for interventions with SMBG was -0.87% (95% CrI -1.14 to -0.58%). The pooled CFB for SMBG with feedback was -1.48% (95% CrI -2.06 to -0.89%).

**Relative effects among type 2 diabetes patients**

In Table 4 the relative efficacy of interventions with SMUG, SMBG and SMBG with feedback among type 2 DM, as obtained with MTC meta-analysis, are presented.

SMUG is expected to result in an additional reduction of HbA<sub>1c</sub> of 0.13% relative to no self-monitoring. There is a 69% probability that an intervention with SMUG results in a larger reduction in HbA<sub>1c</sub> than an intervention without self-monitoring. Interventions with SMBG result in a relative HbA<sub>1c</sub> reduction of 0.40%; there is 99% probability that the reduction with SMBG is larger than without self-monitoring. Regular feedback resulted in an additional reduction of 0.62%. Relative to SMUG, interventions with SMBG resulted in a relative reduction in HbA<sub>1c</sub> of 0.26%. The probability that interventions with SMBG are more effective than interventions with SMUG in reducing HbA<sub>1c</sub> is 84%.

**Adjustment for baseline HbA<sub>1c</sub> level**

When the estimated relative effects were adjusted for baseline HbA<sub>1c</sub> level, the differences between the interventions increased by between 0.01 and 0.12%, except for the difference between SMBG and SMUG which was reduced to -0.21%.

**Table 3.** Change from baseline (and standard deviation) by intervention as observed in randomised controlled trials included in meta-analysis

Study	No self-monitoring			SMUG			SMBG			SMBG with feedback		
	n	Mean CFB HbA <sub>1c</sub> (% [SD])		n	Mean CFB HbA <sub>1c</sub> (% [SD])		n	Mean CFB HbA <sub>1c</sub> (% [SD])		n	Mean CFB HbA <sub>1c</sub> (% [SD])	
Allen <i>et al.</i> <sup>18</sup>				27	-2.0	(2.4)	27	-2.0	(3.4)			
Brown <i>et al.</i> <sup>11</sup>	126	-0.16	(2.62)				126	-0.92	(2.51)			
Davidson <i>et al.</i> <sup>12</sup>	45	-0.6	(2.1)				43	-0.8	(1.6)			
Estey <i>et al.</i> <sup>21</sup>							25	-0.3	(0.7)	28	-0.7	(0.96)
Fontbonne <i>et al.</i> <sup>19</sup>	68	-0.5	(1.54)	72	-0.13	(2.20)	68	-0.36	(3.14)			
Guerci <i>et al.</i> <sup>13</sup>	344	-0.5	(1.54)				345	-0.9	(1.54)			
Jaber <i>et al.</i> <sup>27</sup>	22	-0.07	(2.12)				17	-1.62	(1.83)			
Kwon <i>et al.</i> <sup>14</sup>							50	0.25	(0.96)	51	-0.59	(1.35)
Miles <i>et al.</i> <sup>20</sup>				82	-1.6	(1.9)	68	-1.5	(2.1)			
Muchmore <i>et al.</i> <sup>28</sup>	11	-0.85	(1.87)				12	-1.54	(1.46)			
Schwedes <i>et al.</i> <sup>15</sup>	110	-0.54	(1.41)				113	-1.0	(1.08)			
Wing <i>et al.</i> <sup>30</sup>	25	-0.24	(1.87)				25	0.0	(2.16)			

CFB = change from baseline; SD = standard deviation; SMUG = self-monitoring of urine glucose; SMBG = self-monitoring of blood glucose

**Table 4.** Relative efficacy of self-monitoring of urine glucose, self-monitoring of blood glucose and self-monitoring of blood glucose with feedback versus interventions without self-monitoring among type 2 diabetes patients

Comparisons	Difference in change in HbA <sub>1c</sub>						
	Crude		Adjusted for baseline HbA <sub>1c</sub>		Adjusted for baseline HbA <sub>1c</sub> and weighted for internal validity		
	Mean (95% CrI)	Pr (%)	Mean (95% CrI)	Pr (%)	Mean (95% CrI)	Pr (%)	
SMUG* vs. NSM†	-0.13 (-0.74; 0.43)	69	-0.19 (-0.80; 0.44)	74	-0.02 (-0.70; 0.62)	54	
SMBG* vs. NSM†	-0.40 (-0.70; -0.09)	99	-0.41 (-0.72; -0.06)	98	-0.40 (-0.70; -0.07)	99	
SMBG + FB* vs. NSM†	-1.01 (-1.61; -0.41)	> 99	-1.13 (-1.87; -0.35)	99	-1.04 (-1.66; -0.36)	> 99	
SMBG* vs. SMUG†	-0.26 (-0.79; 0.31)	84	-0.21 (-0.82; 0.39)	78	-0.38 (-1.00; 0.30)	88	
SMBG + FB* vs. SMUG†	-0.88 (-1.62; -0.08)	98	-0.95 (-1.78; -0.09)	98	-1.01 (-1.77; -0.14)	99	
SMBG + FB* vs. SMBG†	-0.62 (-1.14; -0.09)	99	-0.73 (-1.41; -0.04)	98	-0.63 (-1.22; -0.05)	98	

CrI = credible interval; SMUG = self-monitoring of urine glucose; SMBG = self-monitoring of blood glucose; NSM: No self-monitoring; FB = feedback; Pr = probability that first intervention (\*) results in greater HbA<sub>1c</sub> reductions than second intervention (†)

## Adjustment for baseline HbA<sub>1c</sub> level and weighting for internal validity

When, in addition to baseline HbA<sub>1c</sub> level, the studies were weighted according to their internal validity scores (as outlined in Table 2) the results changed most dramatically for the comparison of SMUG versus no self-monitoring and for SMBG versus SMUG. The probability that interventions with SMUG are more efficacious than interventions without self-monitoring decreased to 54% (relative HbA<sub>1c</sub> reduction 0.02%). However, the pooled relative reduction in HbA<sub>1c</sub> of interventions with SMBG relative to interventions with SMUG increased to 38%; the probability that interventions with SMBG are more effective is 88%. (See Table 4.)

### Relative effects among non-insulin requiring type 2 diabetes patients

In Table 5, the relative efficacy of interventions with SMUG, SMBG and SMBG with feedback among non-insulin requiring type 2 DM are presented. The unadjusted results are comparable to the findings for all type 2 DM patients. With adjustment for baseline HbA<sub>1c</sub>, and weighting for quality, interventions with SMUG are comparable to interventions without self-monitoring. Interventions with SMBG are more effective than interventions without self-monitoring (probability of 98%; relative HbA<sub>1c</sub> reduction of 0.42%), and interventions with SMBG are likely to be more effective than interventions with SMUG (probability of 80%; relative HbA<sub>1c</sub> reduction of 0.28%)

## Discussion

This review and meta-analysis of direct and indirect comparisons of self-monitoring in type 2 DM did not provide evidence that interventions with SMUG are more effective than interventions without

self-monitoring. However, interventions with SMBG do seem more effective than interventions without self-monitoring. An additional reduction in HbA<sub>1c</sub> of about 0.4% was observed. Regular medical feedback more than doubled the reduction seen with SMBG. Such a difference can be very important in the long term. The UKPDS study showed that a difference in glycated haemoglobin of 0.9% was associated with a 25% reduction in micro-vascular endpoints over 10 years<sup>3</sup>. Furthermore, with a 80–90% probability, it is expected that interventions with SMBG are more efficacious than interventions with SMUG. The inclusion of two studies comparing interventions with SMBG and feedback versus SMBG interventions without feedback in the meta-analysis, indicated that regular medical feedback is essential to the effectiveness of SMBG in type 2 DM. Results were comparable for a subset of studies of non-insulin requiring type 2 DM patients.

In 2005 two systematic reviews on SMBG in non-insulin requiring type 2 DM patients were published<sup>16,17</sup>. The added value of the current review is that a meta-analysis of direct and indirect comparisons is performed by which the evidence-base of comparisons of interest is increased<sup>22–24</sup>. The analysis allowed the estimation of the effect of SMUG versus no self-monitoring, in the absence of pair-wise comparisons. The Bayesian approach of the current analysis allowed the assessment of the probability that one type of intervention is better than another, which was not possible with the 2005 meta-analyses<sup>16,17</sup>. For example, Welschen *et al.*<sup>17</sup> concluded that there is no significant difference between interventions with SMBG and SMUG because the 95% confidence interval of the difference included the null, whereas we were able to claim that there is 80% probability that SMBG outperforms SMUG in reducing HbA<sub>1c</sub>. In our opinion, this provides more information for decision-makers, than the claim that there is no significant difference. Furthermore, adjustment for baseline HbA<sub>1c</sub> values, and formal incorporation of internal validity scores in the analysis, was performed. The effect of self-monitoring

**Table 5.** Relative efficacy of self-monitoring of urine glucose, self-monitoring of blood glucose and self-monitoring of blood glucose with feedback versus interventions without self-monitoring, among non-insulin requiring type 2 diabetes patients

Comparisons	Difference in change in HbA <sub>1c</sub>					
	Crude		Adjusted for baseline HbA <sub>1c</sub>		Adjusted for baseline HbA <sub>1c</sub> and weighted for internal validity	
	Mean (95% CrI)	Pr (%)	Mean (95% CrI)	Pr (%)	Mean (95% CrI)	Pr (%)
SMUG* vs. NSM†	-0.12 (-0.79; 0.48)	65	-0.23 (-0.91; 0.44)	77	-0.14 (-0.90; 0.56)	66
SMBG* vs. NSM†	-0.39 (-0.78; -0.04)	98	-0.43 (-0.80; -0.03)	98	-0.42 (-0.76; -0.03)	98
SMBG + FB* vs. NSM†	-1.01 (-1.70; -0.34)	99	-1.24 (-2.07; -0.39)	> 99	-1.19 (-2.00; -0.42)	> 99
SMBG* vs. SMUG†	-0.28 (-0.84; 0.35)	83	-0.19 (-0.80; 0.43)	73	-0.28 (-0.91; 0.43)	80
SMBG + FB* vs. SMUG†	-0.89 (-1.67; -0.04)	98	-1.01 (-1.91; -0.11)	98	-1.07 (-1.88; -0.17)	99
SMBG + FB* vs. SMBG†	-0.62 (-1.19; -0.03)	98	-0.82 (-1.55; -0.10)	98	-0.78 (-1.49; -0.13)	99

CrI = credible interval; SMUG = self-monitoring of urine glucose; SMBG = self-monitoring of blood glucose; NSM: No self-monitoring; FB = feedback; Pr = probability that first intervention (\*) results in greater HbA<sub>1c</sub> reductions than second intervention (†)

depends on baseline HbA<sub>1c</sub>; when starting at a high HbA<sub>1c</sub> patients are more likely to show a decrease as a result of self-monitoring. Hence, baseline HbA<sub>1c</sub> was taken into consideration in the analysis. With the regression model used (see Equation 1) not only differences in HbA<sub>1c</sub> at baseline between studies was adjusted for, but also differences in baseline HbA<sub>1c</sub> between interventions within studies.

The internal validity of many of the trials included (nine out of the 13 identified trials) was, with a quality score of less than or equal to 9 points, considered low. Considering the nature of the interventions – self-monitoring – the maximum score of 13 points cannot be easily reached. Nevertheless, a RCT without blinding of patients, but with an independent observer, can still reach a maximum internal validity score of 12 points. The question that arises is whether the treatment effects among studies were influenced by limited internal validity. In this light, Schulz *et al.*<sup>31</sup> demonstrated that inadequate trial methods, especially inadequate concealment of treatment allocation and lack of blinding, can result in bias of the treatment effect. Excluding studies with a low quality from analysis is often used approach. The rationale of this is to only use the best evidence to quantify the effect. However, it is quite arbitrary to define a study as low quality and exclude it from analysis. In addition, a drawback of such an approach is that a lot of available information is not taken into consideration. Alternatively, a meta-analysis can be performed where all studies are included, and afterward the impact of differences in methodological quality of the included studies discussed in a qualitative way. Sarol *et al.*<sup>16</sup> and Welschen *et al.*<sup>17</sup> used this approach, although Sarol *et al.*<sup>16</sup> also used an analysis which excluded the lowest quality studies. A compromise between the exclusion of low quality studies and inclusion of all studies is weighting of studies in the analysis according to the quality score. The impact of inferior studies on the overall effect estimates is reduced, while uncertainty is not increased due to less use of information. Since in the present meta-analysis none of the included studies had a quality score of 11 or more (which can be considered high), weighting has only a limited effect, and the question of whether studies with a better methodological quality would have displaced other results is only partly addressed. The result of downgrading the lower quality studies was that the effect of SMUG versus no self-monitoring decreased and the effect of SMBG versus SMUG increased.

The generalizability of results obtained from RCTs in a controlled setting to routine practice might be limited, given, for example, differences in patient characteristics and compliance. It can be argued that the ideal source of effectiveness data in the 'real world' is a prospective,

randomised, controlled trial with a naturalistic design, which imposes the minimum restriction on the normal decision-making processes. The study by Guerci *et al.*<sup>13</sup>, a randomised study in general practice in France, is a good example. In addition, final outcomes, such as cardiovascular endpoints, are preferred over intermediate outcomes (i.e. glycated haemoglobin) as primary measures to obtain information regarding effectiveness. These measures reflect the full benefit of SMBG on the health of patients. However, the feasibility of naturalistic prospective randomized studies, with a naturalistic design that includes final endpoints, is limited. As an alternative, a feasible study design for the effectiveness of SMBG in routine practice is a retrospective cohort study by which final endpoints can be taken into account. Although, by design, these observational studies have a lower internal validity than naturalistic randomized prospective studies, the main sources of bias, due to selection and confounding, can to a great extent be adjusted for using statistical methods. As a result studies with final endpoints will provide added value compared to randomised naturalistic studies with intermediate endpoints. The ROSSO study is a recent example<sup>32</sup>.

In conclusion, the randomized clinical trials performed to date, provided positive results on the effectiveness of SMBG in reducing HbA<sub>1c</sub> in type 2 DM. Regular medical feedback of the results is important. Furthermore, SMBG is likely to be more effective in reducing HbA<sub>1c</sub> than SMUG. However, a definite judgement on the effectiveness of SMBG is difficult to make, due to limited methodological quality and lack of final endpoints. It is recommended that additional studies are performed, with high methodology quality and including final endpoints. Apart from clinical endpoints, studies with patient reported outcomes, such as quality of life or satisfaction, are also of interest.

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