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Review

Monitoring blood glucose control in diabetes mellitus: a systematic review

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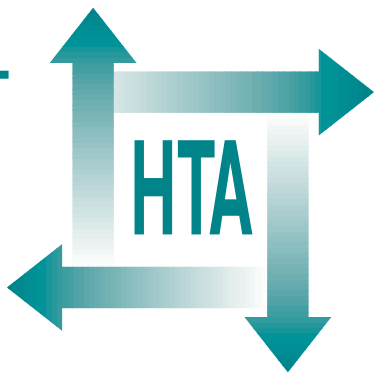
Health Technology Assessment
NHS R&D HTA Programme



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Monitoring blood glucose control in diabetes mellitus: a systematic review

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The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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List of abbreviations

ADA	American Diabetes Association
B	blood*
BDA	British Diabetic Association
BHS	British Hypertension Society
CI	confidence interval
CSII	continuous subcutaneous insulin infusion*
DCCT	Diabetes Control and Complications Trial
df	degree(s) of freedom
DM	diabetes mellitus
EGA	error-grid analysis*
FBG	fasting blood glucose
FPG	fasting plasma glucose
GDM	gestational diabetes mellitus
GHb	glycated haemoglobin
GP	general practitioner
HbA_1	haemoglobin A_1
HbA_{1c}	haemoglobin A_{1c}
HDL	high density lipoprotein*
HPLC	high performance liquid chromatography
IBSS	Index and Bibliography of Social Science
N	no monitoring*
NA	not applicable*
ND	no difference between groups*
NE	not estimated*
NG	not given*
RCT	randomised controlled trial
RPG	random plasma glucose
SD	standard deviation
SE	standard error
SEM	standard error of mean
SMBG	self-monitoring of blood glucose
U	urine*
UKPDS	United Kingdom Prospective Diabetes Study

*Used only in tables

Executive summary

Objectives

The aim of this review was to evaluate evidence for the clinical- and cost-effectiveness of different methods for monitoring blood glucose control in diabetes mellitus (DM). Self-monitoring by patients and near-patient or laboratory testing in healthcare settings were considered.

Methods

- The authors' personal collections, *Diabetes Care* and *Diabetic Medicine* (1990–99), the electronic databases MEDLINE, EMBASE, and the Index and Bibliography of Social Sciences were searched.
- Citations from papers retrieved were screened.
- Letters were sent to the British Diabetic Association and leading manufacturers.
- Retrieved papers were evaluated for quality by two independent reviewers.
- Data were abstracted and synthesised using meta-analysis where possible.

Results

Evaluation of blood glucose monitoring devices

There is no standard protocol for evaluating blood glucose monitoring devices. Published evaluations have often only evaluated a limited number of aspects of meter performance and have not always used appropriate methods to analyse the reliability of measurements.

Self-monitoring in type 2 DM

Eighteen papers were retrieved, including eight randomised controlled trials (RCTs) and ten non-randomised studies. The eight RCTs included comparisons of blood testing, urine testing and no testing in subjects with type 2 DM. Interventions were not standardised, patient training and adherence were not addressed systematically and no trial required subjects to modify their drug therapy in accordance with self-monitoring results. On a scale ranging from 0 to 28 the mean quality rating was 15.0 (standard deviation (SD) 1.69). Three studies had sufficient power to detect differences in glycated haemoglobin (GHb) of 0.5–1.0% but none had sufficient power to detect differences ≤ 0.5%.

After excluding two RCTs, six studies were included in meta-analyses. A random-effects meta-analysis, using data from four studies, showed that the mean difference in GHb between groups of patients performing blood or urine self-monitoring and those not was –0.25% (95% confidence interval (CI), –0.61 to 0.10). Meta-analysis of data from three studies showed that the difference in GHb for those performing self-monitoring of blood glucose compared with those performing urine testing was –0.03% (95% CI, –0.52 to 0.47). Published information on patient outcomes and the avoidance of hypoglycaemia was extremely limited. Blood testing was noted to be more costly than urine testing.

Self-monitoring in type 1 DM

Twenty-four papers were retrieved, including eight controlled trials and 16 non-controlled studies. The RCTs included either children or adults and compared different testing frequencies, blood or urine testing, or blood testing and no testing. The mean quality rating was 14.4 (SD 1.6) and only one study had sufficient power to detect differences in GHb of ≤ 1.0%.

Among the controlled trials, only one suggested a benefit of blood testing for GHb. The remaining studies showed no difference between blood or urine testing or different frequencies of blood testing. Three studies found that the frequency of hypoglycaemia was low and not different between blood monitoring and control groups. One study reported that blood glucose monitoring revealed asymptomatic hypoglycaemia in 11 of 16 children. A meta-analysis of data from studies that compared blood monitoring with urine monitoring in children or adults with type 1 DM suggested a mean difference in GHb of approximately –0.567% (95% CI, –1.073 to –0.061). This result, of borderline significance, was sensitive to two assumptions made in interpreting and analysing the data. Blood testing was noted to be more costly than urine testing but was preferred by patients, possibly because it provided better information.

Self-monitoring in diabetes mellitus in pregnancy

Eleven papers were retrieved, including five RCTs. Six studies included women with type 1 DM, one study included women with either type 1 or type 2 DM, three studies included women with gestational DM (GDM), and one included women with either type 1 DM or GDM. The studies generally included small numbers of subjects and the mean quality rating was 11.4 (SD 3.3). The studies showed that pregnant women with type 1 DM may be managed at home by self-monitoring blood glucose rather than be admitted to hospital. This approach resulted in a reduced level of hospital utilisation. Maternal and fetal outcomes appeared to be as good with home self-monitoring as with hospital inpatient admission in late pregnancy, but the studies did not have sufficient power to give conclusive results. Firm evidence for the best approach to managing GDM is lacking and the best strategy may depend on the severity of glucose intolerance. One RCT suggested that postprandial testing was associated with better outcomes than preprandial testing in women with GDM requiring insulin treatment.

Laboratory and near-patient testing

Results from the Diabetes Control and Complications Trial (DCCT) in type 1 DM and the UK Prospective Diabetes Study in type 2 DM have demonstrated the clinical effectiveness of using GHb estimations to monitor blood glucose control. Data from the DCCT suggest that the overall package of intervention employed would have acceptable cost-effectiveness. No unconfounded studies have addressed the optimal testing frequency for GHb, but current guidelines suggest from four tests per year in subjects with type 1 DM to two tests per year in subjects with stable type 2 DM.

Standardisation of GHb assays between and within laboratories is an important objective being addressed by current work. Near-patient testing for GHb is being developed, but it is too early to judge its value.

Fructosamine estimations, which measure glycaemic control over shorter intervals than GHb, may be useful in diabetic pregnancy, but have not been shown to be better than GHb at this time. Fructosamine assays are less costly than GHb.

Conclusions

A standard protocol should be drawn up for conducting and reporting evaluations of blood glucose monitoring devices.

Blood glucose self-monitoring is well established in clinical practice but the optimal use of the technique has not been established. Present evidence suggests that it may not be essential for all patients.

Recommendations for research

- Randomised studies should be carried out to provide decisive evidence on the clinical- and cost-effectiveness of blood glucose self-monitoring in type 2 DM and GDM.
- Observational studies should be carried out in samples of subjects with type 1 DM to identify groups of patients in whom blood glucose self-monitoring is of benefit and groups in whom it is not.
- Studies should include not just assessment of GHb, but also the occurrence of hypoglycaemia, patients' satisfaction with care and health-related quality of life.

Chapter 1
Introduction

Diabetes mellitus

Diabetes mellitus (DM) is an important health problem in the UK. The overall prevalence of DM is estimated to be just over 2%, but in some groups, including the elderly and adults of Afro-Caribbean or Indian subcontinent descent, more than 10–20% may be affected by DM.[1] With an increase in the proportion of older adults in the coming decades, an increase in the number of people affected by DM can be anticipated.[2] DM contributes to morbidity, ranking among the most common causes of renal failure, blindness and limb amputation in adults, and it also makes an underestimated contribution to overall mortality.[1]

People with DM have a continuing need for preventive care and hospital treatment and the health-service costs of DM are substantial. Gerard and co-workers[3] estimated that the health service costs of DM exceeded £259 million in 1984. Leese[4] estimated that DM accounted for 5% of health-service costs. More recently Currie and co-workers[5] estimated that DM accounted for 8.7% of NHS acute hospital expenditures. The costs of DM to patients, their families and to society can also be considerable because of loss of earnings and production, and the need for support of individuals affected by DM.

Good blood glucose control is one of the main treatment objectives in DM. An analysis of data from the Diabetes Control and Complications Trial (DCCT) in type 1 DM showed that a 10% reduction in glycated haemoglobin (GHb) concentration was associated with a 43% reduction in the risk of progression of retinopathy.[6] The results of this study suggested that morbidity from DM, and the health-service resource use from diabetic complications, might be reduced through improved blood glucose control. Monitoring is an important part of the process of improving blood glucose control. There are different approaches to blood glucose monitoring, but their costs are significant. For example, Gallichan[7] estimated that the NHS costs of self-monitoring by DM patients amounted to approximately £42 million per year.

For highly prevalent, treatable conditions like DM, improving the effectiveness of clinical care offers the potential to improve health outcomes. But for common conditions the costs of different interventions, even those which are of low cost at the individual level, are likely to be significant. Investing in packages of care in decreasing order of cost-effectiveness has been recommended as an appropriate strategy for allocating resources between conditions.[8] The principle can also be used to define packages of care for a given condition, by combining interventions in decreasing order of cost-effectiveness.[9] The purpose of this review is to establish, for glucose monitoring in DM, what evidence of clinical- and cost-effectiveness can be obtained from the published literature.

Definition and classification of diabetes mellitus

The definition and classification of DM are currently the subject of debate.[10] The American Diabetes Association (ADA) has proposed a new classification, which is based on the fasting blood glucose (FBG) concentration. The proposed new classification recognises the distinct category of impaired fasting glucose.[11] At the time when the studies reviewed in this report were carried out, the definition and classification of DM proposed by the WHO in 1985 were widely accepted.[12]

DM represents a heterogeneous group of conditions and several specific groups of people with DM can be identified.[12] Type 2, or non-insulin-dependent, DM accounts for 85–90% of prevalent cases of DM.[1] In spite of its lower incidence and prevalence, type 1, or insulin-dependent, DM is important because it affects younger people and causes serious complications at much younger ages. The WHO recognised gestational DM (GDM) as a separate entity, but this review considers DM and pregnancy, including pregnancy in women with antecedent DM as well as GDM. Women with antecedent DM require intensified care from before the time of conception in order to reduce the risk of malformations, while both groups of women require intensified treatment during pregnancy in order to reduce the risks of fetal and infant morbidity and mortality. Thus we defined three main groups of patients: those with type 1 DM, those with type 2 DM, and those with DM and pregnancy.

Other groups also need to be distinguished, including children, adolescents, the elderly, ethnic minority groups and the socially disadvantaged. In order to avoid a fragmented approach to analysis, and to combine results across groups where possible, where feasible we aimed to consider age, ethnicity and social factors as possible effect modifiers. Other specific groups also have particular needs, which may deserve separate consideration; for example, those with impaired vision or those with hypoglycaemic unawareness.

Blood glucose control as a treatment objective

The primary metabolic abnormality in DM is a high blood glucose concentration resulting from deficient insulin production or action. Hyperglycaemia is associated with the development of complications of DM. Acute complications include symptoms of hyperglycaemia and hyperglycaemic emergencies. Chronic complications include microvascular complications affecting the eyes and kidney, neuropathy leading to the development of foot problems, and macrovascular disease which contributes to coronary heart disease, stroke and lower-limb ischaemia. Diabetic microvascular disease is characteristic of the condition, but DM is only one of several risk factors for macrovascular disease. Treatment of hyperglycaemia may cause hypoglycaemia, which needs to be recognised promptly in order to avoid complications of its own.

Improved blood glucose control reduces hyperglycaemic symptoms but, until recently, the relationship between hyperglycaemia and the development of chronic complications of DM has been unclear. At the time when many of the studies reviewed for this report were carried out, the consensus of experts was that good blood glucose control was advisable especially for younger patients,[13] but unequivocal evidence of benefit was lacking.

In 1993 the results of the DCCT showed that in persons with type 1 DM strict blood glucose control, achieved through more frequent injections or continuous insulin infusion, intensified monitoring and an enhanced level of personal care, resulted in a reduced rate of onset and progression of diabetic retinopathy, neuropathy and nephropathy.[14] A subsequent analysis of data from the DCCT showed that, across both study groups, and throughout the range of GHb, a 10% lower haemoglobin A_{1c} (HbA_{1c}) was associated with a 43% lower risk of retinopathy progression during the course of the trial.[6] The results of the trial gave unequivocal evidence that 'tight' blood glucose control, in the range 3.8–6.7 mmol/l before meals and < 10.0 mmol/l after meals, should be an important treatment objective in type 1 DM.

In type 2 DM macrovascular complications are generally more important, and concerns have been raised that intensive treatment may have a negative impact on cardiovascular morbidity and mortality. The feasibility study for the Veterans Affairs Co-operative Study on glycaemic control and complications in type 2 DM provided evidence suggestive of an increased number of cardiovascular events in the intensively treated group.[15] The results of the UK Prospective Diabetes Study (UKPDS) have now been published.[16] In this study the aim of treatment in the intensively treated group was a fasting plasma glucose (FPG) of < 6 mmol/l, while in the control group treatment aimed to avoid symptoms or a FPG of > 15 mmol/l. Over 10 years the difference in HbA_{1c} between groups was 0.9% and this was associated with a 25% reduction in risk of microvascular end-points. The absolute risk reduction was 2.8 microvascular events per 1000 patient-years; in other words, it is necessary to treat 357 patients for 1 year to prevent one microvascular event. Intensive blood glucose control did not reduce the risk of myocardial infarction or stroke, but control of blood pressure was important in this respect.[17] As in other trials of antihypertensive therapy myocardial infarction was more frequent than stroke, but the risk reduction was smaller for the former. Recent studies have suggested that cholesterol-lowering treatment may also reduce the risk of coronary heart disease in type 2 DM.[18]

Management strategies

Current approaches to managing the blood glucose concentration in DM emphasise the role of the patient as part of a diabetes care team, which may include, among others, the physician, general practitioner (GP), nurse specialist and dietitian. Most patients need to regulate their diet and exercise habits, and patients with type 2 DM may require treatment with oral hypoglycaemic drugs or insulin.[13] Patients with type 1 DM always require insulin treatment.[19] Educating patients in techniques of self-care is important in achieving treatment objectives.[13,19] The effectiveness of treatment can be monitored by measuring

blood glucose levels in the clinic, and the patient or his/her carers may carry out self-monitoring techniques at home and elsewhere. The quality of blood glucose control over the longer term can be measured using GHb, fructosamine and other glycated proteins as indicators. Traditional methods of urine testing for glucose still have a place in the management of some patients with DM,[20] especially if they are not treated with oral hypoglycaemic drugs or insulin.

The control of hyperglycaemia in DM can be regarded as a complex intervention made up of a number of separate treatments. Mulrow and Pugh[21] pointed out that for complex interventions "although treatments aimed at certain facets may be more efficacious than others, we cannot expect interventions aimed at single parts of a complicated treatment to be highly efficacious". Monitoring of blood glucose control represents a single facet of an overall package of intervention. Techniques for monitoring may have small effects on outcomes, and these effects might be modified by other components of the package of intervention, by the treatment setting and by patient characteristics. For example, patient education may be an important influence on the effectiveness of self-monitoring.

Classification of monitoring methods

We initially envisaged a three-way classification of monitoring methods. First, we considered different testing modalities, including urine testing for glucose and blood testing for glucose, GHb and other glycated proteins.[20] We also considered different combinations of monitoring methods. Secondly, we considered different monitoring settings, including hospital wards and clinics, general practices, and the patient's home, social and work environments. In healthcare settings we considered both laboratory-based testing and near-patient testing. Thirdly, we considered the different patient groups defined above.

Aim

To carry out a systematic review to evaluate the clinical- and cost-effectiveness of different methods of monitoring blood glucose control in DM.

Specific objectives

To systematically search for research data concerning the clinical- and cost-effectiveness of different methods of monitoring blood glucose control in DM and to analyse and synthesise it into a review, in order to:

- evaluate methods of self-monitoring by the patient
- evaluate both laboratory-based testing and near-patient testing in healthcare settings
- analyse a range of outcomes, including intermediate outcomes such as changes in blood glucose control and patient satisfaction, as well as measures of health status and health-related quality of life
- analyse costs, including treatment costs and patient costs
- consider the separate needs of patients with type 1 DM, type 2 DM and DM in pregnancy, and to consider age, ethnic group and social factors as possible effect modifiers
- synthesise conclusive results to provide protocols for monitoring and to make recommendations for future primary research where existing evidence was insufficient.

Chapter 2
Methods

Focus for the review

The focus for the review was defined at the end of chapter 1. The clinical effectiveness of relevant interventions was assessed using all available outcome measures, including metabolic, clinical and self-rated measures. We did not include technical evaluations of laboratory methods unless they included an assessment of the impact on clinical or patient outcomes. However, because the reliability of self-monitoring may be an important influence on these outcomes we have included a short review of the reliability and validity of self-monitoring methods.

Search strategy

The following sources were searched.

Personal collections
The investigators' personal collections of articles on monitoring in DM were examined. These searches initially gave a total of 70 papers.

Handsearches
We handsearched the journals *Diabetic Medicine* (1990–99) and *Diabetes Care* (1990–99). Handsearching yielded several additional papers that were not located by the electronic search.

Electronic searches
The following databases were searched: MEDLINE, EMBASE, the Index and Bibliography of Social Science (IBSS) and the database of the Diabetes Health Economic Study Group.

MEDLINE
A MEDLINE (OVID) search was conducted for the years 1976–99. The Cochrane Review strategy for locating randomised controlled trials (RCTs) was followed. The search strategy used is given in appendix 1.

BIDS: EMBASE, Science Citation Index and Social Science Citation Index
The strategy used in BIDS was similar to that used for MEDLINE, with some minor alterations made to allow for terminology not common to both databases. EMBASE was searched for the years 1980–98. The keywords used were:

- diabetes mellitus (insulin-dependent diabetes mellitus or juvenile diabetes mellitus or maturity onset diabetes mellitus or non-insulin-dependent diabetes mellitus or pregnancy diabetes mellitus)
- self-care
- blood glucose self-monitoring
- patient compliance
- glucose blood level
- urinalysis.

A search was also conducted using IBSS (1975–98). This yielded a total of 42 additional references. The keyword 'diabetes mellitus/diabetes' was traced in the title, abstract and keywords of the references. Only 14 articles were retrieved, none of which were relevant to the review. No new primary research publications were found on the Diabetes Economics Study Group database (http://www.pitt.edu/~tjs/costrefs.html).

Other searches
Letters were sent to the British Diabetic Association (BDA) and to the two major manufacturers of testing equipment (Bayer and Roche Diagnostics), but these enquiries did not yield any new material.

Citations
All reference citations in papers retrieved were also examined for further relevant papers.

Criteria for retrieval

The search identified a large number of potential papers for review, yielding 42 papers from MEDLINE 1976–84, 112 from MEDLINE 1985–89, 109 from MEDLINE 1990–94 and 186 from MEDLINE 1995–98, giving a total of 449 references. EMBASE yielded a total of 42 additional references not identified from MEDLINE.

The titles and abstracts were inspected to evaluate their relevance to the focus of the review. In the analysis of clinical effectiveness we only included

RCTs. However, we also appraised patient-based quasi-experimental and observational studies to see if they provided information that was relevant to the focus of the review.

The search was initially restricted to English-language papers. However, due to the limited numbers of articles available in English, non-English-language papers were included if they added relevant information to the review.

We did not include studies that evaluated methods of measurement (with the exception of brief reviews of meter reliability studies and laboratory testing methods). We aimed to evaluate the evidence to show whether use of these methods of measurement was effective in improving clinical and patient outcomes. However, the quality of meter performance is likely to have some impact on outcomes of monitoring, and it is worth noting that meters have improved considerably during the time since the reviewed studies were reported.

Methods for quality assessment

Relevant papers were retrieved and reviewed for quality by two of the authors. SC and MCG reviewed papers using a quality checklist for randomised and non-randomised studies.[22] Each study was assessed for reporting quality, external validity and internal validity. We made two modifications to the checklist. First, we included an additional item concerning the range of outcome measures used (*Box 1*). Secondly, we considered the statistical power of the study separately from the quality score. After removing the item on power, the checklist had 27 items, which were distributed between four subscales:

- Reporting (11 items): this examined whether sufficient information was available in the paper for the reader to assess the findings of the study.
- External validity (3 items): this assessed the extent to which the findings could be generalised to the population from which the study sample was taken.
- Internal validity:
  - Bias (7 items): this examined whether there were biases in the measurement of the intervention and the outcome.
  - Confounding (6 items): this addressed the bias in the selection of the study sample.

Each question except one had a rating scale of 1 for 'yes' or 0 for 'no' or 'unable to determine'; the remaining question used the scores of 0, 1 or 2.

BOX 1 Items used to rate studies for quality*

Reporting

Is the hypothesis of the study clearly described?

Are the main outcomes identified in the Introduction or Methods sections?

Did the study evaluate the full range of outcome measures available?**

Are the characteristics of the subjects in the study clearly described?

Are the interventions of interest clearly described?

Are the distributions of confounders in each group clearly described?

Are the main findings of the study clearly described?

Does the study provide estimates of random variation for the main outcomes?

Have all the possible adverse events arising from the intervention been reported?

Have the characteristics of patients lost to follow-up been described?

Have actual *p*-values rather than $p < 0.05$ been reported for the main outcomes?

External validity

Were the subjects asked to participate representative of the entire population?

Were the subjects who were prepared to participate representative of the entire population from which they were recruited?

Were the staff/facilities representative of the majority of patient treatment?

Internal validity – bias

Was an attempt made to blind study subjects to the intervention they received?

Was an attempt made to blind those measuring the main outcomes to the intervention?

If any of the results of the study were based on 'data dredging' was this made clear?

Do the analyses allow for different lengths of follow-up among patients?

Were the statistical tests used to assess the main outcomes appropriate?

Was compliance with the intervention reliable?

Were the main outcome measures used accurate?

Internal validity – confounding

Were the patients in different groups recruited from the same population?

Were the subjects in the different groups recruited over the same period of time?

Were study subjects randomised to intervention groups?

Was the process of randomisation concealed from both subjects and personnel?

Was there adequate adjustment for confounding in the main analyses?

Were losses of subjects to follow-up taken into account?

[Did the study have sufficient power to detect a clinically important effect?]

Reproduced by kind permission of the BMJ Publishing Group from Downs and Black,* Journal of Epidemiology and Community Health 1998;52**:377–84.[22]

***Item added for this review*

Thus the overall total quality score ranged from 0 to 28, based on 27 items. The items are summarised in *Box 1*.

Reliability of quality ratings

Papers were independently rated by two observers (SC and MCG). The raters then compared each score, discussed items for which different ratings had been obtained, and agreed on a final grading for each item of the scale. The reviewers' independent ratings were compared, and the inter-rater reliability was calculated as the mean difference in score (95% confidence interval (CI)) for each section of the checklist (*Table 1*). It can be seen that differences were of acceptable size, but individual papers sometimes generated a large measure of disagreement. This was particularly so for items on external validity, which proved difficult to evaluate. However, there was greater consensus for papers on type 1 DM than for those on type 2 DM, which were reviewed first.

Assessment of statistical power

We assessed the statistical power of each study to detect given differences in GHb concentration as this was used as an outcome measure in most studies. We adapted the suggestion of Downs and Black[22] and estimated the power to detect clinically relevant differences in GHb. Based on estimates of the variance of GHb from the study data, we estimated whether the study had sufficient power to detect a difference in GHb between groups of ≤ 0.25%, ≤ 0.5%, ≤ 1%, ≤ 2% or ≤ 3%. We assumed values for α and $1 - \beta$ of 0.05 and 0.80, respectively. These differences were allocated scores from 1 to 5 (*Table 2*).

TABLE 2 *Scores for* post hoc *power calculations*

Detectable difference in mean GHb between groups (%)	Score
≤ 0.25	5
≤ 0.50	4
≤ 1.00	3
≤ 2.00	2
≤ 3.00	1

Critical appraisal and data abstraction

We abstracted relevant details from each paper and used these to prepare a critical appraisal. Study designs were generally classified following the suggestions of Cook and Campbell.[23]

TABLE 1 *Reliability studies on quality ratings (figures are differences in score between reviewer 1 and reviewer 2)*

Variable	No. of papers	Mean difference in score (95% CI)	Range of differences	
			Min.	Max.
Type 2 DM				
Reporting	18	0.39 (–0.34 to 1.12)	–3	3
External	18	–1.33 (–1.90 to –0.76)	–3	1
Internal	18	1.72 (1.16 to 2.29)	0	4
Confounding	18	–0.06 (–0.49 to 0.38)	–2	1
Total	18	0.72 (0.04 to 1.40)	–5	7
Type 1 DM*				
Reporting	22	0.23 (–0.45 to 0.91)	–3	4
External	22	0.05 (–0.65 to 0.74)	–3	2
Internal	22	0.45 (–0.02 to 0.93)	–1	3
Confounding	22	–0.32 (–0.86 to 0.22)	–2	2
Total	22	0.41 (–0.83 to 1.65)	–4	7
DM in pregnancy				
Reporting	11	0.64 (–0.49 to 0.77)	–2	4
External	11	0.27 (–0.19 to 0.74)	–2	1
Internal	11	1.09 (0.32 to 1.86)	–1	3
Confounding	11	0.18 (–0.40 to 0.76)	–2	2
Total	11	2.18 (0.26 to 4.10)	–3	7

**Two papers for type 1 DM were reviewed by one reviewer only*

Statistical methods

Where possible, data were synthesised using meta-analysis techniques. Comparisons were made between the effect of any monitoring (blood or urine) versus none, and of blood monitoring versus urine monitoring, with regard to changes in GHb and weight. For three-armed trials, values for blood monitoring and urine monitoring were combined as needed. The trials differed in the numbers of measurements made before and after randomised treatment, and in the methods used to estimate differences in outcome between treatment groups. For each trial, we used the most reliable estimate of these treatment differences for which a standard error could be estimated.[24] In order of preference, these methods were: results of ANCOVA (analysis of covariance, correcting for baseline measurement), mean change score (mean of all post-randomisation measurements minus initial measurements), final change score (last post-randomisation measurement minus the pre-randomisation measurement) and final score. Results were combined using random-effect meta-analysis, including tests for heterogeneity.[25] Publication bias was evaluated by funnel plots and associated tests.[26]

Chapter 3

Reliability and validity of self-monitoring

Introduction

This chapter provides a review of the reliability and validity of self-monitoring of blood glucose (SMBG). The aims of this chapter are to:

- summarise the methodological literature and provide suggestions for the conduct of future evaluations of blood glucose metering devices
- provide a systematic review of factors influencing reliability and validity
- estimate, where possible, the size of measurement errors
- identify conditions under which measurement error may be minimised.

Reliability is a measure of the extent to which a method gives the same results when repeated under the same conditions.[27] In the present context, a method should give very low error when repeated measurements are made on the same sample. **Validity** is a measure of the extent to which a method gives results that correspond to the true result.[27] Often a comparison will be made with a reference method such as the glucose oxidase method performed on laboratory equipment. It is important to consider both statistical and clinical significance in assessing measurement error.

Literature searches

A range of searches was carried out using MEDLINE for the years 1966–99. The terms 'diabetes mellitus', 'blood glucose self-monitoring' and 'reproducibility of results' were combined, together with the text words 'reliability', 'validity', 'comparison' and 'error-grid analysis'. Additional references were obtained by scanning citations and by handsearching recent issues of *Diabetes Care* and *Diabetic Medicine*. We used qualitative judgements to select the most relevant and recent publications for this summary.

Statistical assessment

Studies comparing different methods have not always used appropriate statistical methods for analysis. Bland and Altman[28] listed five reasons why the correlation coefficient is not a helpful measure of agreement between two methods of measuring the same thing. They point out that it would be surprising if two methods of measuring the same thing did not give results that were strongly associated. The strength of association will be higher if the range of observations is extended. However, a high correlation coefficient does not mean that differences between two methods are small. Bland and Altman suggested that the size and dispersion of the differences between replicate measurements should be used to assess the agreement between methods of measurement. Thus the mean difference between replicates provides an estimate of the bias of one method in relation to the other. The standard deviation (SD) of the differences provides a measure of the extent of random error. If the data are normally distributed, then 95% of differences should lie between ± 2 SD from the mean difference. These limits are referred to as the 'limits of agreement'. Two methods of measurement are equivalent if the mean difference between them is zero and the limits of agreement are small enough to be unimportant.

The importance of random error must be judged both on statistical and on clinical grounds. On statistical grounds one would argue that the contribution of variation due to measurement error should be small in relation to biological variation between samples. Thus if i observations are made on j samples then

$$y_{ij} = \mu + B_j + e_{ij}$$

where y_{ij} is the ith observation on the jth sample and μ is the mean of the observations. The B_j are the random effects for the j samples, which are normally distributed with zero mean and variance σ_b^2. The e_{ij} are the random-error components (which include measurement error) and these are also normally distributed with zero mean and variance σ_e^2. Then the quantity

$$\rho = \sigma_b^2/(\sigma_b^2 + \sigma_e^2)$$

should be as large as possible. Chinn[29] suggested that the intraclass correlation coefficient ρ should

be higher than 0.8; in other words, σ_e^2 should be $< 0.25\sigma_b^2$.

The simple model illustrated above can be extended to allow for identification of a number of different sources of error, including analytical error due to the measuring equipment and analytical errors due to the operator.

In 1987 the ADA[30] recommended that blood glucose measurements made by patients should be within 15% of the reference measurement and that in future meters should have less than 10% variability. However, in 1993, the ADA Consensus Development Panel[31] reported that this target had still not been reached and that new technology was still not meeting these criteria. In 1996, the ADA recommended an even stricter target of less than 5% variability for future home blood glucose meters. A recent study[32] measured the relative accuracy of 17 blood glucose monitors (two visually read, eight colorimetric and seven amperometric). At a mean glucose concentration of 9 mmol/l, monitor readings differed from the reference results by –5.1% to +19.5%, and three meters failed to meet the ADA's total error guidelines for existing meters of less than 15%.

Clinical assessment

The relevance of measurement error can also be judged clinically. This is because the importance of measurement error will depend on whether it results in inappropriate clinical management. Errors in the hypoglycaemic or borderline hyperglycaemic ranges will be particularly important from a clinical point of view. Clarke and co-authors[33,34] proposed a graphical method for identifying clinically important errors, which they called 'error-grid analysis' (*Figure 1*). Values in areas A and B of the graph are considered to be clinically accurate or acceptable, respectively. Values in area C may lead to unnecessary corrections because the meter reading shows the blood glucose value to be too high or too low, while the reference method shows that the true value is acceptable. Values in area D may be associated with a dangerous failure to detect or treat hyper- or hypoglycaemia, while values in area E may lead to erroneous treatment.

The use of error-grid analysis is helpful in drawing attention to the differing clinical consequences of measurement errors in different parts of the blood glucose range. The method also demonstrates the need to estimate the size of errors in different parts of the range, rather than to rely on overall summary measures. However, the method suffers from the limitations that the lines on the grid are drawn arbitrarily and are not fully standardised. The method does not allow for error in the reference measurements. Nor does the error-grid approach lend itself to the estimation of the magnitude of error and bias; instead percentage errors for each compartment on the graph are reported. Thus it is not appropriate to use error-grid analysis without supporting statistical analysis.[35] A consensus is emerging that error-grid analysis should be used together with conventional statistical approaches to method comparison in the assessment of reliability.

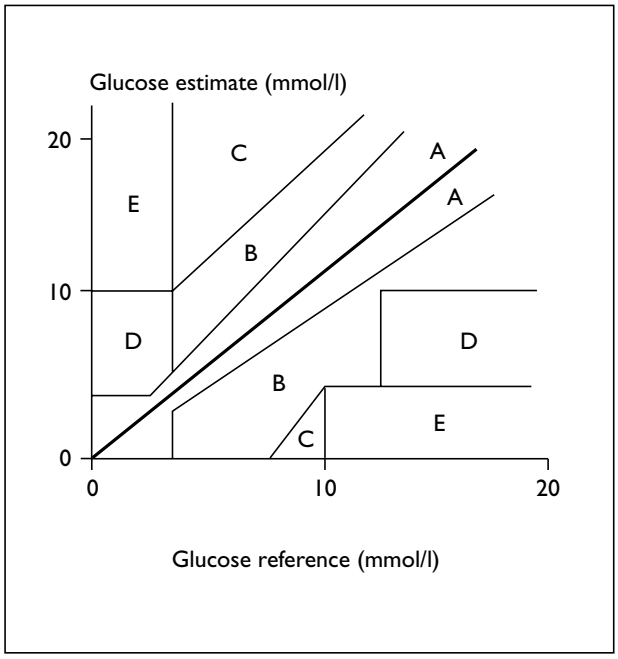

FIGURE 1 *Illustration of error-grid analysis (adapted from Gough and Botvinick[35])*

Evaluation of blood glucose monitoring devices

So far as we are aware, no standard protocol is available for the evaluation of blood glucose measuring devices. It is helpful to refer to the protocol developed by the British Hypertension Society (BHS) for the evaluation of blood pressure measuring devices[36] because of the attention which this report gives to several aspects of evaluation that have been neglected in the literature on diabetes. We use the term 'model' to identify a particular brand of equipment, and the term 'device' is used to refer to an individual meter.

Observer training

There is an obvious need for standardised training of observers in the correct use of the device. Meter-comparison studies often use laboratory staff to perform meter readings and are likely to produce smaller estimates of error than would be obtained by using a range of patient operators. This may compromise the generalisability or external validity of the findings.

Interdevice variability

The BHS report makes the point that evaluation of a single device may be misleading. A single device may give inaccurate results because it is faulty or incorrectly calibrated; conversely, a device giving accurate results may not be representative of the performance of the model. The BHS report suggested that at least three devices should be tested for interdevice variability and that the evaluation be discontinued if unacceptable and unexplained interdevice variability is identified. Evaluation of more devices will be needed to quantify the extent of interdevice variability with any precision. Few studies of blood glucose meters have examined interdevice variability. However, Chan and co-workers[37] evaluated six different models using four devices to represent each model. Their data showed significant interdevice variability for three of the six models studied.

In-use assessment

The BHS suggests that each device should be assessed by six subjects on a total of 8 days over a 4-week period. This is done so that the device may be subjected to 'fairly strenuous use' before further validation. A new device may have different characteristics from one that has been in use for a period of time.

User acceptability

The period of in-use assessment provides an opportunity to assess patients' views of the device, including ease of use, clarity of instructions, difficulties and suggestions for improvement. One of the few meter evaluations to report on user acceptability was that by Chan and co-workers,[37] who used the items shown in *Box 2*.

After-use interdevice variability

After a period of use, the three devices should again be tested for interdevice variability to see if they perform consistently. If all three devices are discordant at this point then further testing is not warranted.

BOX 2 Key items of meter performance information required

1. Mean (± 2 SD) difference from reference value at low, normal and high blood glucose values
2. Proportion of results in different areas of error-grid plot
3. Amount of interdevice variability
4. Effects of usage on meter performance
5. Acceptability to user, including: size and portability, ease of calibration, length of training time, ease of testing procedure, length of time to perform test, ease of maintenance, interpretation of error codes, cost and availability of meter and supplies

Formal device validation

Only when the preceding steps have been completed satisfactorily should the device be subjected to a formal validation study. This study should be carried out using a sufficiently large number of subjects, and it is advisable to obtain statistical advice on experimental design. The samples obtained should extend over a wide range of blood glucose values. Trajanoski and co-workers[38] noted that meters were likely to show substantial variation in performance in the hypoglycaemic range. Since overall summary statistics may conceal important variation in limited parts of the blood glucose range, they suggested that results should be reported separately for 'low', 'normal' and 'high' blood glucose values. An example of appropriate analysis is provided by the report of Brunner and co-workers,[39] who presented the results of error-grid analysis together with the mean (SD) difference between test and reference methods for three blood glucose ranges: the low glycaemic range (< 3.89 mmol/l), the near normoglycaemic range (3.89–9.99 mmol/l), and the high glycaemic range (> 9.99 mmol/l).

Table 3 provides an assessment of the extent to which these recommended evaluation procedures have been applied in a sample of meter evaluations published between 1983 and 1998. This was a convenience sample of papers known to the authors. This incomplete survey suggests that issues of observer training, interdevice variability, the effects of long-term use and patient acceptability have not usually been addressed. Most studies reported a formal assessment of meter reliability and validity but, at least in the earlier studies, inappropriate statistical methods were used for method comparison. More recent studies

TABLE 3 *Description of a sample of 12 published meter evaluations*

Report	Observer training	Inter-device vari-ability	In-use assess-ment	Patient accept-ability	After-use interdevice variability	Formal device validation	Report % different from reference	Report mean difference (SD) from reference	Present error-grid analysis	Report corre-lations
Frindik,1983[40]	No	No	No	No	No	Yes	No	Yes	Yes (modified)	Yes
Silverstein, 1983[41]	Yes	No	No	No	No	Yes	Yes	No	No	Yes
Aziz, 1983[42]	Yes	No	No	No	No	Yes	No	Yes	No	Yes
Gifford-Jorgensen, 1986[43]	No	No	No	No	No	Yes	No	No	No	Yes
Clarke, 1987[33]	No	No	No	No	No	Yes	No	No	Yes	Yes
North, 1987[44]	Yes	No	No	No	No	Yes	Yes	No	No	Yes
Tate, 1991[45]	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes
Devreese,1993[46]	Partial	No	Partial	No	No	Yes	No	No	Yes	Yes
Moses, 1997[47]	Partial	No	No	No	No	Yes	Yes	Yes	No	No
Chan, 1997[37]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Brunner,1998[39]	No	No	No	No	No	Yes	No	Yes	Yes	No
Poirier, 1998[48]	No	No	No	No	No	Yes	Yes	No	Yes	Yes

were more likely to present error-grid analyses in combination with appropriate statistical analyses to compare methods.

Table 4 provides illustrative results from one recent evaluation. Relevant findings include:

- less satisfactory meter performance in the low glycaemic range, as judged by clinical criteria
- satisfactory clinical assessment in the presence of statistically significant bias
- variation in the size and direction of bias in different parts of the glycaemic range.

It would be a large task to review all studies of blood glucose meter reliability and, given the speed at which such meters are produced, such a review would become dated extremely quickly.

Recording errors

The development of memory meters showed that diabetic patients often made incomplete or incorrect recordings of blood glucose values in their diary records. Williams and co-workers[49] studied 21 patients with type 1 DM and identified a number of sources of inaccurate readings, including rounding values to the nearest whole number, omission of outlying values and reporting of results when no test was recorded in the memory of the meter. Over- and under-reporting often occurred together and were associated with higher GHb values and poor testing technique. These findings were confirmed by Ziegler and co-workers[50] in 14 type 1 DM patients. In this sample, mean blood glucose values and the amplitude of blood glucose excursions were lower in logbook records

TABLE 4 *Illustrative result from an evaluation of several meters*[*]

Meter	Low glycaemic range		Normoglycaemic range		High glycaemic range	
	EGA (% A/B)	Difference (SE)	EGA (% A/B)	Difference (SE)	EGA (% A/B)	Difference (SE)
Reflolux S	100	–0.30 (0.09)	100	–0.33 (0.21)	100	0.32 (0.38)
One touch II	97	0.39 (0.03)	100	0.27 (0.05)	100	0.18 (0.17)
Precision QID	80	0.61 (0.08)	100	0.85 (0.10)	100	0.95 (0.25)

[*] *Figures are the per cent of readings in areas A or B of the error grid (EGA), and the mean difference (standard error (SE)) obtained using the reference method. Adapted from Brunner and co-workers*[39]

EGA, error-grid analysis

than in records from the meter memory. Addition of phantom values to the logbook, and omission of SMBG measurements from the logbook were common. The overall effect was to obscure the occurrence of hypo- or hyperglycaemia. Strowig and Raskin[51] found that informing patients of the memory capacity of the meter led to correct recording of blood glucose results.

Any strategy for intermittent monitoring is inevitably selective. Bolinder and co-workers[52] compared the results of SMBG with data obtained by continuous microdialysis measurement of glucose in subcutaneous adipose tissue. Their results showed that in some patients SMBG may be inaccurate because wide variations in glucose levels between SMBG measurements may go unrecognised. This was more likely to happen at night and could occur when subjects were testing as frequently as seven times per day. One-third of hypoglycaemic episodes were not identified by patients using the SMBG protocol. The study concluded that the true diurnal variability in glycaemia of subjects with type 1 DM is too great to be measured accurately even by frequent SMBG. They pointed out that advances in monitoring subcutaneous adipose tissue glucose using an automated device may eventually permit application in the routine care of persons with DM.

Other factors influencing reliability

Patient factors

Kabadi and co-workers[53] showed that more accurate blood glucose readings may be obtained by patients if they are given sufficient training. Bernbaum and co-workers[54] reported that older people (age 65–79 years) could produce results as reliable as those obtained by younger subjects.

Visual impairment presents obvious barriers to self-monitoring, and many affected patients do not use the technique. Two reports have suggested that, with extensive instruction, subjects may be able to use SMBG with satisfactory results.[55,56] This entailed using adapted devices with tactile and auditory feedback features.

Impairment of colour vision, which may result from diabetic retinopathy, can lead to misinterpretation of visually read strips. It has even been suggested that colour vision should be tested formally before self-monitoring with visually read strips is recommended.[57] This problem can be overcome by using a meter.

Technical factors

Severe haemolysis in blood samples may affect the readings from some meters, and this is thought to be caused by the effect of the coloured pigment on colorimetric reactions.[58] The use of small sample volumes can also lead to erroneously low readings with most models of meter.[46,59] Higher altitude (> 2000 m above sea level) may affect the readings from some types of meter, the usual effect being to cause underestimation of the blood glucose concentration.[60] A range of other technical influences may sometimes affect results. These include differences in haematocrit and use of renal dialysis.[61]

Recommendations

At present there is not always sufficient information available concerning the different contributions to analytical error in blood glucose meters. Published information is sufficient to show that portable meters may show significant differences from reference methods and that the magnitude of these differences may vary between different models of meter, between different devices of the same model[37] and according to the blood glucose level.[39] These differences may often be of little clinical relevance,[37,46] but may sometimes be important, particularly at low blood glucose values.[38,39] However, analytical error may often be small in comparison with observer errors.

The findings reported in this chapter also point to the need for formal training and updating of skills in the use of meters so that accurate results may be obtained. This is particularly important for subjects with special needs. The potential success of such an approach is illustrated by the success of the DCCT investigators in achieving a high level of compliance with a demanding self-monitoring protocol. By the end of this study, 85% of subjects in the intensively treated group were testing blood glucose at least three times daily.[62] However, these were highly selected and well-motivated patients.

A standard protocol for conducting and reporting evaluations of blood glucose monitoring devices should be developed. Further work should be done to develop standard packages to train subjects using self-monitoring devices and to provide them with the information needed to adjust their therapy in accordance with self-monitoring results.

Chapter 4

Effectiveness of self-monitoring in type 2 diabetes mellitus

Objectives

The results of the UKPDS provided the first clear evidence that intensive blood glucose control in type 2 DM is of clinical benefit and should be a treatment objective in this type of diabetes[16] (see chapter 1). The primary aim of this chapter is to review studies that aimed to determine whether blood or urine glucose self-monitoring was effective at contributing to improved blood glucose control in type 2 DM. As secondary objectives we reviewed the effect of self-monitoring on a range of other outcomes. This subject was reviewed recently by Faas and co-workers.[63]

Methods

The methods used to search for studies, evaluate their quality and synthesise the results are described in chapter 2. The search yielded eight RCTs and ten non-randomised studies. These were critically evaluated and the main findings are outlined and the results described.

Randomised controlled trials: study design, statistical power and quality ratings

The search identified eight RCTs, the main design characteristics of which are shown in *Tables 8* and *9* and summarised in *Box 3*. This small number of studies incorporated a wide range of designs, testing methods and outcomes.

Testing methods

Of the eight RCTs, three[64–66] compared the effectiveness of urine monitoring to blood monitoring, and four studies[67–70] compared blood monitoring to no monitoring. One three-armed trial[71] evaluated the difference between urine monitoring and blood monitoring, and between blood monitoring and no monitoring.

BOX 3 Summary of design features for RCTs

- Eight RCTs were identified
- No trial included enough subjects to detect a difference in GHb of ≤ 0.5%
- The studies included comparisons of blood testing, urine testing and no testing in patients with type 2 DM
- Interventions were not standardised, patient training and compliance were not addressed systematically and the mean (SD) quality rating was 15.0 (1.7)
- No study required patients to modify their drug therapy in accordance with their self-monitoring results

Study settings

Studies were set in France,[71] The Netherlands,[69] the UK,[64,66] Canada[70] and the USA.[65,67,68] Trials took place in veteran's hospitals, university hospitals and other specialist diabetes clinics.

Subject age

Two studies[65,68] included patients of specified ages: either > 35 and < 65 years, or > 40 and < 75 years old, respectively. All other trials included patients of any age, but the mean age of both control groups and experimental groups in all studies was between 50 and 65 years.

Drug treatment

Two studies[66,68] included only patients who were on oral hypoglycaemic drugs or insulin. The remaining trials included only patients who were not insulin users.

Other patient characteristics

Two studies[67,68] focused on patients who were obese. All other studies included patients with a range of body weights. Two studies[65,71] recruited patients who were poorly controlled (with a FPG of ≥ 8.8 mmol/l), while another study[66] involved only patients who had been recently diagnosed as having type 2 DM.

Randomisation

Three studies used simple randomisation of individual subjects to patient groups.[64,67,70] An additional study employed individual randomisation with stratification by clinic to allow for variation between three participating clinics.[71] One study changed patient allocation alternately each week and appeared not to be strictly randomised.[66] One study used individual randomisation, but intervention was by groups of patients.[68] In the study by Allen and co-workers,[65] patients were randomly allocated in groups of ten to each intervention. However, it was not clear whether individuals were also randomly allocated to groups. Rutten and co-workers[69] studied eight practices that were pair matched before randomisation to intervention and control groups. This study clearly used cluster randomisation.

Sample size and power

Sample sizes ranged from 208 participants in the largest trial[71] to only 27 participants in the smallest study.[64] One further study[66] included more than 100 patients, while the remaining trials had between 50 and 60 subjects each.

The results of power calculations are shown in *Table 5*. These show that none of the randomised studies had sufficient power to detect differences in GHb of < 0.5%, but three studies had sufficient power to detect a difference of 0.5–1.0%. Note that these estimates would overestimate power for the study, which employed cluster randomisation.[69] Note also that, because the variances in HbA_{1c} and HbA_1 differ, the clinical relevance of these differences would vary according to the species of GHb being measured. Results from the DCCT[14] and the UKPDS[16] show that small differences in GHb may be clinically relevant, but such small differences might not be detected with the sample sizes used in the studies reviewed here. The SD of GHb in diabetic subjects is much higher than in non-diabetic subjects, so that a small difference judged in relation to the SD for diabetic patients may still be a large difference in relation to the variation in GHb seen in non-diabetic subjects.

Drop-out rates

Two studies[65,67] had drop-out rates of less than 5%. Three more studies[64,68,70] lost around 10% of their participants, and two more[66,71] lost over 20%. Only one study[69] reported that no patients left during the trial period.

Main measures

All studies used GHb as the primary outcome, except for one[64] which used fructosamine. Three studies[67,70,71] specifically referred to using HbA_{1c}, one used HbA_1,[66] and the other three studies[65,66,68] did not specify the type of GHb assay. All studies except one[64] also considered body weight as an outcome. Two studies[66,69] measured FPG in addition to GHb. One study measured health-related quality of life using the Diabetes Quality of Life Inventory from the DCCT.[67]

Interventions

The duration of the trials differed considerably, with two trials lasting 52 weeks,[68,69] one for 44 weeks,[67] four for 24 weeks[66,71,72] and one for just 16 weeks.[70]

Study regimens also varied. Most programmes required tests either before meals or 2 hours after

TABLE 5 *Estimates of power calculations for RCTs in type 2 DM*

Study	Primary outcome	No. in smallest group	Estimated SD	Detectable difference in GHb (%)	Power score
Allen, 1990[65]	GHb	27	2.75	2.0–3.0	1
Estey, 1989[70]	HbA_{1c}	25	1.17	0.5–1.0	3
Fontbonne, 1989[71]	HbA_{1c}	54	2.00	1.0–2.0	2
Gallichan, 1994[64]	Fructosamine	12	NG	NE	0
Miles, 1997[66]*	GHb	56	1.80	0.5–1.0	3
Muchmore, 1994[67]	HbA_{1c}	11	1.89	1.0–2.0	2
Rutten, 1990[69]**	HbA_1	64	1.33	0.5–1.0	3
Wing, 1986[68]	GHb	21	2.23	1.0–2.0	2

**Crossover trial, not analysed as such*
***Cluster randomised study*
NG, not given; NE, not estimated

meals, but the frequency with which tests had to be carried out differed in each study. One trial[71] asked patients to test before and after meals twice every other day. Another[66] required patients to choose a different time to test their blood every day, either before meals or at bedtime. A third study[67] asked patients to test their blood six times daily before and after meals, and then reduced the requirements to just one set of tests, before and after meals, per day. In another study[68] the SMBG group had to complete five fasting and two before- and after-meal measurements per week, which reduced to just five fasting records per week for the rest of the trial. In the study by Rutten and co-workers[69] the protocol for blood monitoring involved no fixed regimen. Patients were told to monitor their blood when they did not feel well or if they had taken part in unusually strenuous activity. The remaining two studies[64,70] gave no details of the protocols for blood or urine monitoring.

Equipment used

One study[71] used Ketodiastix™ for measuring urine glucose and Detrostix™ strips with a Glucometer™ (Ames) for blood glucose. Another study[65] used Tes-tape™ (Lilly) for monitoring urine, and Chemstrips BG™ and Accuchek1™ reflectance meters for blood. One used[65] the Haemoglukotest™ or the Relolux1™ meter (Boehringer), another study[67] used One touch™ (Lifescan) reflectance meters, and a further trial[68] used Chemstrips BG. Two studies[64,70] did not provide details of the equipment used in their studies.

Use of therapy protocols

In two studies[69,71] patients were not given any instructions on how to alter their therapy according to SMBG readings, and all changes were made by their physician at each patient review. However, in other studies, although patients were not allowed to alter their own therapy, they were encouraged to alter their behavioural regimen or their diet in accordance with the SMBG readings.[65,67,68] The remaining three studies[64,66,70] did not give any details of any modifications made to therapy or life style either by patients or by diabetes clinic staff.

Reliability of monitoring

Research[73] has shown that patients can perform tests unreliably or can find home monitoring techniques complicated or confusing (see chapter 3). It was important that trials evaluated the reliability and validity of patient measurements. Half of the studies specifically evaluated the patients' accuracy on blood monitoring before entry into the trial. The remaining trials[64,66,70,71] did not explicitly mention evaluating patients' accuracy. However, some did provide follow-up sessions to initial training, in which patients' accuracy could have been evaluated.

Compliance or adherence to regimen

Compliance or adherence with home monitoring programmes has been shown to be inconsistent. Patients may either misunderstand what is required of them and not adhere to the protocol, or lose motivation to continue with testing during the programme. For these reasons, it is considered good practice to measure compliance with the intervention.

Studies measured compliance in a number of ways. One study inferred compliance from the fact that the monitoring records submitted by patients were complete on over 87% of visits for both blood and urine groups.[65] Another study calculated the number of reactive strips that should have been used during the course of the trial.[71] They found that the urine-monitoring group had used significantly less and showed poorer compliance than either the control or the blood-monitoring groups. Two studies examined patients' data sheets or the memory of the meters, to compare the number of tests conducted with those requested.[68,70] One study merely inferred compliance by noting the low number of trial drop-outs.[69] Only Wing and co-workers[68] used the 'marked item technique', an accepted measure of compliance, which employs a tracer on the blood monitoring strips. The study found that compliance was good, with patients detecting 87% of marked items during treatment.

Confounding of interventions

In a condition like type 2 DM, which is managed using a range of interventions, it is important to consider the extent to which advice on monitoring was confounded with other differences between intervention and control groups. Five studies represented unconfounded evaluations of monitoring strategies.[64–66,68,71] However, as noted above, these trials varied in the extent to which subjects were advised to modify their behaviour in the light of self-monitoring results. In partic-ular, the study by Wing and co-workers[68] required subjects to modify their diet and exercise habits according to self-monitoring results. In the study by Estey and co-workers,[70] subjects in the intervention group were contacted by phone and by home visits to promote adherence with self-monitoring. As a result they

used self-monitoring about twice as frequently as those in the control group. In the study by Muchmore and co-workers,[67] self-monitoring results in the intervention group were used to support a dietary intervention based on calorie counting. In the study by Rutten and co-workers,[69] general practices were allocated to conventional care or to a structured protocol for diabetes management. The protocol included use of regularly scheduled follow-up appointments, SMBG, a weight-control programme and stepped use of therapeutic drugs. This study was not included in meta-analyses because it used cluster randomisation and because use of self-monitoring was confounded with a range of other interventions.

Overall assessment of study quality

Table 6 shows the scores obtained on rating papers for quality. Most studies scored poorly on the external validity section. This addressed how representative the findings of the study were and whether they could be generalised to the general diabetic population. Few papers were able to clarify whether subjects were representative. Many trials relied on volunteers, and few papers compared the characteristics of trial patients with those of the general population of patients. It was also difficult to assess whether the treatments given in the trial were representative of the treatment that the majority of patients receive. No information was given about the care that patients would normally have received in the study facilities, and how this might differ from the care given within the trials.

Items on bias evaluated whether patients or staff were blind to the intervention assignment. None of the monitoring trials were able to conceal this, because of the nature of the self-monitoring intervention. Items on confounding in this section evaluated whether randomisation was adequate. There was often little detail in the papers on how patients were randomised to study groups. No studies took account of whether patient drop-out rates would affect the main results, even though a few had a substantial percentage of subjects leaving the trials.

Excluded studies: non-randomised designs

The search identified ten non-randomised studies. The main design features are shown in *Tables 10* and *11*. Studies included a wide range of testing protocols and techniques. The mean (SD) quality rating was 9.4 (2.0) (*Table 7*). Non-randomised studies tended to receive low scores, due to the inclusion of questions on interventions in the quality checklist, and because of the potential for bias and confounding. These studies were excluded from the evaluation of clinical effectiveness.

Results

Blood or urine monitoring compared with no monitoring

The results of the randomised studies are summarised in *Tables 12* and *13*. Five out of six randomised trials which compared blood or urine monitoring to no monitoring[64,67–71] found no difference in blood glucose control between subjects who monitored and those who did not. Note that the trials by Estey and co-workers[70]

TABLE 6 *Quality ratings for RCTs in type 2 DM*

Study	Reporting	External validity	Internal validity		Overall
			Bias	Confounding	
Allen, 1990[65]	9	0	3	3	15
Estey, 1989[70]	8	0	4	4	16
Fontbonne, 1989[71]	10	0	4	2	16
Gallichan, 1994[64]	4	3	3	3	13
Miles, 1997[66]	5	2	3	2	12
Muchmore, 1994[67]	8	0	5	2	15
Rutten, 1990[69]	8	2	4	3	17
Wing, 1986[68]	9	0	4	3	16
Mean (SD)					**15.0 (1.69)**

TABLE 7 *Quality ratings for excluded studies in type 2 DM*

Study	Reporting	External validity	Internal validity		Overall
			Bias	Confounding	
Cohen, 1983[74]	5	0	1	2	8
Gilden, 1990[75]	6	0	2	2	10
Klein, 1993[76]	6	1	3	2	12
Malik, 1989[77]	6	0	2	0	8
Martin, 1986[78]	3	1	3	1	8
Newman, 1990[79]	4	1	2	2	9
Oki, 1997[72]	7	1	3	1	12
Patrick, 1994[80]	6	0	3	1	10
Tajima, 1989[81]	7	0	3	1	11
Wieland, 1997[82]	5	0	1	0	6
Mean (SD)					**9.4 (1.96)**

and Fontbonne and co-workers[71] included a control intervention. For the former this was SMBG at home without reinforcement,[70] and for the latter GHb results were sent to the subjects every 2 months.[71] Only one study[69] found a small but significant decrease in HbA_{1c} in the experimental group, although none of the patients lost weight. In this trial, the effect of self-monitoring was confounded with a range of other differences in patient management between groups. Furthermore, as this was a cluster randomised study, it was not considered appropriate to include the data in meta-analyses. The study by Gallichan[64] could not be included in the meta-analysis because of the use of fructosamine, rather than GHb, as an outcome measure. A flow chart showing the selection of trials for inclusion in the meta-analysis is shown in *Figure 2*.

In a meta-analysis of four studies, the effect of blood or urine monitoring on GHb was estimated to be –0.25% (95% CI, –0.61 to 0.10) (*Table 14*). A negative sign indicates an effect in favour of monitoring. The effect of monitoring on body weight was estimated to be –0.28 kg (95% CI, –1.48 to 0.93) (*Table 15*). These results show no effect of self-monitoring on GHb or body weight. However, the results were imprecise, and self-monitoring might be associated with a decrease in GHb of up to 0.61% or a decrease in body weight of up to 1.48 kg (see *Figure 2*).

Blood monitoring compared with urine monitoring

None of the trials that compared blood monitoring with urine monitoring found a significant difference in blood glucose control between the two techniques.[64–66,71] Three of the studies found that neither blood nor urine testing had any effect on blood glucose control. One study[66] suggested that urine and blood monitoring were equally effective in improving diabetic control. This trial found a significant fall in HbA_{1c} in both groups of newly diagnosed patients who monitored blood or urine.

The results of meta-analyses for GHb (based on three studies) and body weight (based on two studies) are shown in *Tables 16* and *17*, respectively. The difference in GHb between groups who monitored blood and those who monitored urine was estimated to be –0.03% (95% CI, –0.52 to 0.47). The difference in body weight was estimated to be 0.36 kg (95% CI, –1.93 to 2.65). While these results were imprecise, they did not suggest a benefit from blood monitoring rather than urine monitoring (*Figure 3*).

Additional analyses

The results presented above rely solely on published data for estimates and standard errors (SEs) for GHb. In some cases this approach only permitted analysis of post-treatment differences in GHb, without including information for pre-treatment GHb values. For this reason analyses were repeated using estimates of the change in GHb between the start and the end of the studies.[24] The SE of the difference was estimated by assuming a correlation between pre- and post-treatment measurements of 0.7. The random-effects analysis gave an estimated difference in GHb between monitoring and no-monitoring groups of –0.138% (95% CI, –0.597 to 0.318).

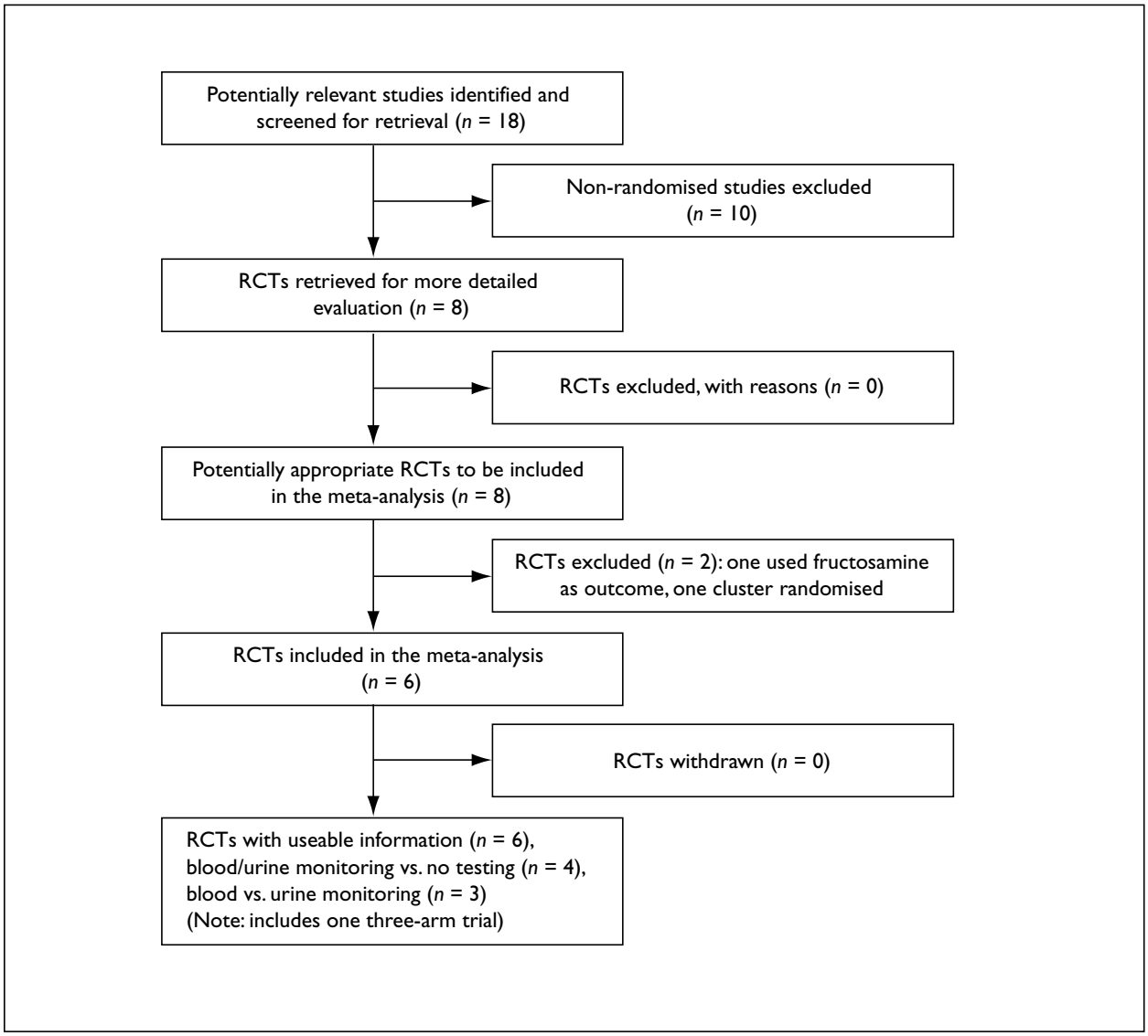

FIGURE 2 *The selection of studies for inclusion in the meta-analysis of the effect of self-monitoring on GHb in type 2 DM (adapted from QUORUM statement, Moher and co-workers[83])*

The estimated difference in GHb between blood and urine monitoring groups was –0.024% (95% CI, –0.505 to 0.458). These analyses incorporated additional assumptions and so they were not preferred for formal presentation. However, these additional analyses suggested that the results presented were not particularly sensitive to the approach used for meta-analysis.

Hypoglycaemia

It has been suggested that SMBG may help patients to avoid hypoglycaemia. The results of studies were specifically reviewed with respect to the effect of blood glucose monitoring on the occurrence of hypoglycaemia. None of the eight randomised trials presented data with respect to the occurrence of hypoglycaemia. Among the non-randomised studies, Newman and co-workers[79] reported evaluating symptoms of hypoglycaemia, but did not describe any results. Cohen and Zimmet[74] described using self-monitoring results to detect the occurrence of asymptomatic hypoglycaemia and using these findings to reduce patients' drug dose.

Patient outcomes

Four studies measured aspects of health-related quality of life[66–68,75] with no evidence of an effect of monitoring on the outcomes assessed (see *Table 12*). In the study by Miles and co-workers,[66] 70% of subjects preferred urine testing to blood testing, while 15% preferred blood testing. Similarly, in the study by Gallichan,[64] 71% of subjects preferred urine testing to blood testing. Many subjects expressed a dislike of finger-pricking.

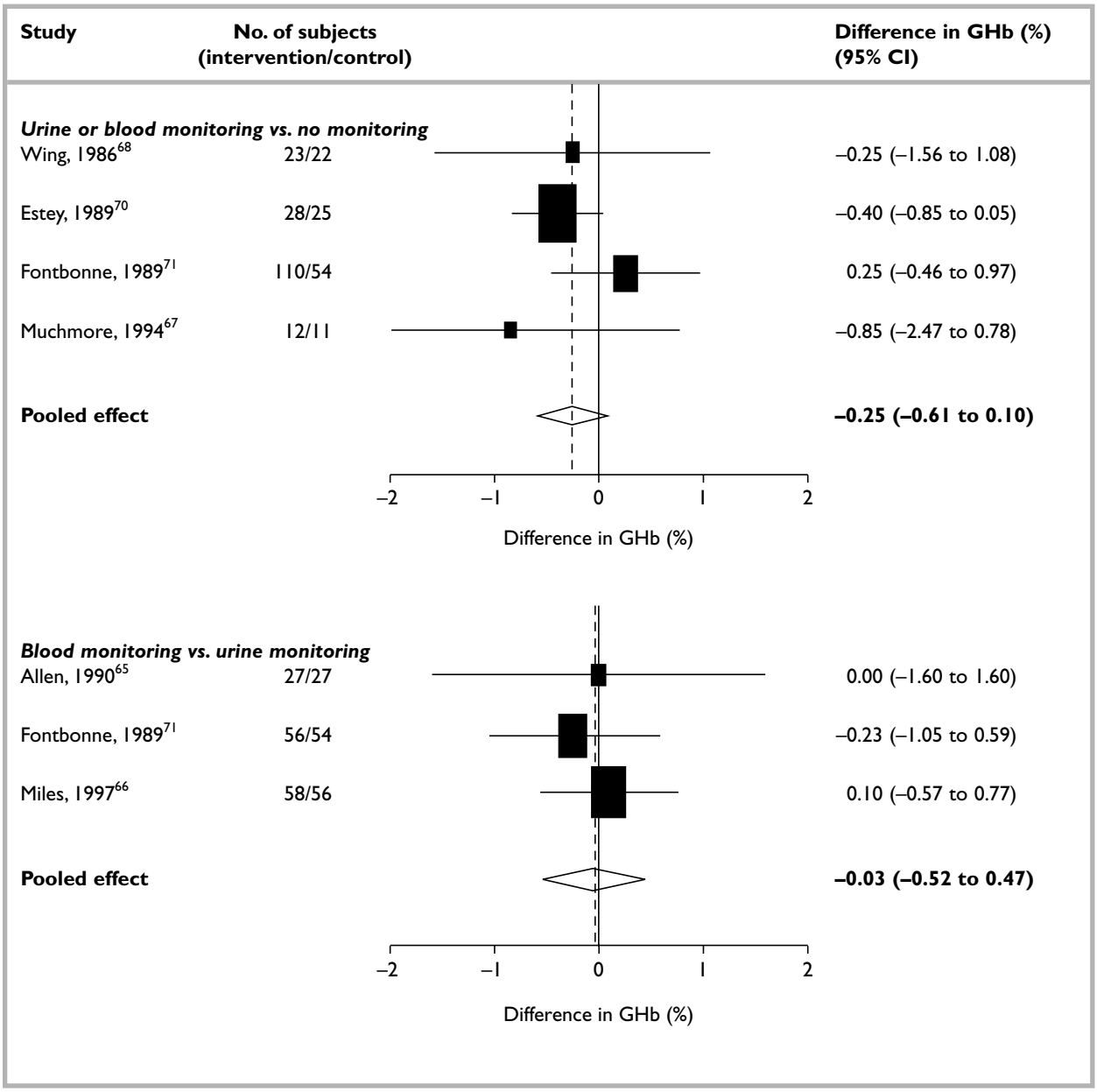

FIGURE 3 *Results of the meta-analysis of the effect of self-monitoring on GHb in type 2 DM*

Costs

Blood glucose monitoring was noted to be more costly than either urine glucose monitoring[65] or no monitoring.[79] In the USA, Oki and co-workers[72] found that patients indicated that the cost of supplies was a common reason for not performing SMBG.

Discussion

Main findings

The main findings of this chapter are summarised in *Box 4*. The meta-analysis of RCTs showed that self-monitoring of blood or urine was not effective at improving blood glucose control in type 2 DM. Neither was there any evidence for an effect on body weight, and there was only anecdotal evidence concerning the detection of hypoglycaemia. Blood monitoring was more costly than urine monitoring. Urine monitoring was often preferred because it avoided the need for finger-pricking. There are a number of reasons why this negative conclusion should be treated with caution. First, the studies included in the review suffered from low statistical power. The results of the meta-analysis showed that self-monitoring of blood or urine might be associated with a reduction in GHb of up to 0.6%. The results of the UKPDS[16] showed that a difference in GHb of 0.9% over

BOX 4 Main conclusions of the review of self-monitoring in type 2 DM

- There is no evidence to show that self-monitoring of blood or urine glucose improves blood glucose control measured using GHb or FPG
- There is no evidence that blood glucose monitoring is more effective than urine glucose monitoring in improving blood glucose control
- The studies reviewed had low statistical power and were poorly conducted and reported. Small but clinically relevant effects might not have been detectable
- Patients' perceptions of monitoring were neither completely nor rigorously studied and further work is needed in this area
- Urine testing is less costly than blood testing
- Urine testing is preferred by some patients

10 years was associated with a 25% reduction in risk of microvascular end-points. Small differences in GHb could therefore be clinically important. Secondly, quality ratings were low, making the possibility of error and bias substantial. Thirdly, few studies encouraged subjects to modify their therapy in response to self-monitoring results. Fourthly, the studies reviewed included a limited range of outcomes, and issues of quality of life and patient satisfaction were not fully evaluated. Self-monitoring may have psychological benefits to patients which were not evaluated in the studies reviewed. Fifthly, it is possible that self-monitoring may be effective in some groups of patients or under certain conditions of use. A failure to standardise interventions, monitor adherence and provide protocols for utilisation of self-monitoring data might have contributed to the negative findings of the studies reviewed.

Comparison with other reviews

Two recent reviews have evaluated the effectiveness of self-monitoring in type 2 DM. The systematic review by Faas and co-workers[63] published in 1997 included 11 of the studies which we identified for the present review. These included six randomised trials and five non-randomised studies. The review did not include the recently published trial by Miles and co-workers[66] or the study by Muchmore and co-workers.[67] The review did not use meta-analysis to synthesise the results. Nevertheless, the authors' conclusions are similar to ours, and these were that "the efficacy of SMBG in NIDDM patients is still questionable and should be tested in a rigorous high-quality randomised controlled trial". A narrative review by Halimi[84] was published in 1998 and this review supported the same conclusions; namely, a lack of effect of self-monitoring on blood glucose control or body weight in type 2 DM. This review noted the appreciable costs of self-monitoring and observed that there was a need to justify this with evidence of clinical effectiveness.

Comparison with current treatment recommendations

Management guidelines for type 2 DM from the European NIDDM Policy Group[13] suggest that self-monitoring of glucose is "essential to improve the safety and quality of treatment" in type 2 DM. The report observes that urine testing will not allow assessment of hypoglycaemia and suggests that SMBG is "mandatory" for patients treated with insulin and "desirable" for patients treated with oral hypoglycaemic drugs. A position statement from the ADA[85] supported this view, stating that SMBG is "recommended for all insulin treated patients with diabetes [and] may be desirable in patients treated with sulphonylureas and in all patients not achieving glycaemic goals". The paper suggests that 'the role of SMBG in stable diet-treated patients with type 2 diabetes is not known".

The advice from both groups appears to be influenced by the experience of the DCCT in which SMBG appeared to make an important contribution to achieving treatment objectives.[62] However, the evidence reviewed in this chapter does not provide support for current treatment recommendations. Data from the UKPDS will not help to clarify the situation because patients' use of self-monitoring in this study was confounded by the level of blood glucose control (R Turner, personal communication). In other words, patients with worse control were encouraged to perform more frequent tests. The consistency of the findings of our review with those of other reviewers is at odds with the lack of consistency with current treatment recommendations.

Recommendations

The findings of this review support the suggestion made by others[80] that self-monitoring in type 2 DM may often be unnecessary. We endorse the suggestion[63] that a further RCT should be carried out to evaluate the effectiveness of self-monitoring in type 2 DM. Such a trial should be designed so as to address some of the methodological issues

raised by our review and others.[63] Thus patient training, adherence with recommendations, and use of protocols for modification of therapy should be addressed. It is essential that such a trial should be designed so as to have sufficient statistical power after stratifying for important risk groups, including patient age and type of treatment. A range of outcomes should be evaluated, including not only GHb, but also symptom severity, satisfaction with care, changes in therapy and clinical outcomes, including hypoglycaemia.

We also suggest an alternative approach. RCTs could easily be carried out to explore the effect of discontinuing monitoring in well-defined groups of patients with type 2 DM. The rationale would be to identify groups of patients in whom it is safe to stop monitoring, thereby freeing resources for alternative use. This is a logical strategy in view of the evidence that self-monitoring is costly but not effective in type 2 DM. Since patients' behaviour may be permanently altered by the experience of using monitoring, trials of discontinuing monitoring would answer a different question than trials initiated in patients without previous experience of monitoring. Furthermore, subjects who are compliant with monitoring represent a selected group of patients.

We therefore recommend that RCTs be carried out both to provide a rigorous assessment of the effectiveness of self-monitoring in newly presenting patients with type 2 DM, and to provide a rigorous assessment of the consequences of discontinuing self-monitoring in patients with stable type 2 DM.

TABLE 8 *RCTs of self-monitoring in type 2 DM: design and subject selection*

Study	Setting	Design	No. of patients	Inclusion criteria
Allen, 1990[65]	USA, veterans' medical centre	Randomisation in groups of 10	61	FPG ≥ 8.8 and < 22 mmol/l No history of ketoacidosis Not using insulin No prior knowledge of monitoring
Estey, 1989[70]	Canada, medical centre	Simple randomisation of individuals	60	Referred for diabetes education Not on insulin Completed 3-day programme Prepared to monitor blood Access to telephone for follow-up
Fontbonne, 1989[71]	France, diabetes clinics	Individual randomisation, stratified by clinic	208	Poor control: ≥ 8.8 mmol/l FPG or post-prandial ≥ 11 mmmol/l three times in year Diabetes for > 3 years Clinic attender
Gallichan, 1994[64]	UK, diabetes centre	Simple randomisation of individuals	27	On oral hypoglycaemic agents
Miles, 1997[66]	UK, diabetes centre	Allocation alternated weekly, crossover trial	150	Newly diagnosed DM
Muchmore, 1994[67]	USA, medical centre	Simple randomisation of individuals	29	Obese, elevated HbA_{1c} No recent use of SMBG No calorie-control diet programme in last 3 months
Rutten, 1990[69]	The Netherlands, general practices	Cluster randomisation by practice, pair matched	149 in 8 practices	Age 40–75 years Not treated with insulin Not receiving treatment for other diseases
Wing, 1986[65]	USA, university medical school	Individual randomisation to patient groups	50	Age 35–65 years 120% or more ideal body weight Use of oral hypoglycaemic drugs or insulin Development of diabetes > 30 years

TABLE 9 *RCTs of self-monitoring in type 2 DM: interventions*

Study	Intervention	Groups in study	Duration	Main measures	Drop-outs
Allen, 1990[65]	SMBG and urine testing as part of a standard treatment programme	SMBG Urine monitoring	6 months	FPG Weight GHb	7
Estey, 1989[70]	Study group received the standard 3-day education + telephone follow-up at home to reinforce use of SMBG	Control group having had education session (including SMBG) Study group having education session (including SMBG) + SMBG reinforcement by telephone	4 months	HbA_{1c} Weight Frequency of SMBG	7
Fontbonne, 1989[71]	Programmes of urine monitoring or SMBG compared with feedback of GHb results	Urine monitoring SMBG GHb result sent to patient at home every 2 months	6 months	HbA_{1c} Body weight	44
Gallichan, 1994[64]	Randomisation to a programme of blood or urine testing	SMBG Urine monitoring	24 weeks	Fructosamine	10
Miles, 1997[66]	SMBG + education, or urine monitoring + education	SMBG + education Urine monitoring + education	6 months	GHb Body mass index Quality of life score	36
Muchmore, 1994[67]	Randomisation to a calorie-controlled diet or a calorie-controlled diet + SMBG programme	Calorie-controlled diet Calorie-controlled diet and SMBG	44 weeks	HbA_{1c} Body weight Quality of life score (DCCT)	6
Rutten, 1990[69]	Patients of study practices used SMBG as part of a protocol for diabetes management	Patients of study practices given a protocol to follow on SMBG Patients in non-study practice were given conventional GP care with no SMBG protocol	12 months	FPG Weight HbA_1	10
Wing, 1986[68]	Weight-control programme, including self-monitoring	Programme with monitoring Standard programme with no monitoring	12 months	Weight GHb Serum lipid Medication changes	5

TABLE 10 *Excluded studies in type 2 DM: design and subject selection*

Study	Setting	Design	No. of subjects	Inclusion criteria
Cohen, 1983[74]	Australia, hospital diabetes clinic	Single group, before and after	66	Consecutive referrals for blood monitoring instruction at a specialist clinic
Gilden, 1990[75]	USA, hospital	Cross-sectional	20	Age > 60 years Patients routinely performing blood or urine testing Patients with ability to understand and perform tests
Klein, 1993[76]	USA, veterans' medical centre	Cross-sectional	229	All patients registered as receiving diabetic supplies from clinic
Malik, 1989[77]	USA, veterans' medical centre	Cross-sectional; then single group, before and after	16	No previous experience of adjusting diet on basis of testing Patients with no serious medical problems Urine or blood < 180 mg/dl at least twice a week
Martin, 1986[78]	UK, general hospital	Single group, before and after	22	Age > 65 years Patients receiving sulphonylurea therapy
Newman, 1990[79]	USA, veterans' hospital	Non-equivalent group, after only	38	All patients using insulin All patients attending clinics All patients had two or more GHb records
Oki, 1997[72]	USA, veterans' medical centre	Cross-sectional	98	All patients coming to clinic for first time, who had had their GHb measured within 1 week of the study start date
Patrick, 1994[80]	UK, diabetes clinic	Cross-sectional	200	Type 2 DM patients attending review clinics of the 2 consultant authors Patients not being treated with insulin
Tajima, 1989[81]	Japan, flight crew medical department	Single group, before and after	7	Pilots with type 2 DM who were currently grounded due to hyperglycaemia All treated by diet alone
Wieland, 1997[82]	USA, veterans' medical centre	Cross-sectional	216	Male On Glibenclamide for at least 3 years

TABLE 11 *Excluded studies in type 2 DM: interventions and main findings*

Study	Intervention	Groups in study	Duration	Main measures	Drop-outs	Main findings
Cohen, 1983[74]	Introduction of blood monitoring regimen	Single group before and after blood monitoring intervention (*n* = 66)	6 months	Weight control Blood glucose Insulin dose	None	SMBG seems to faciliate weight loss, reduce insulin need and improve glucose control
Gilden, 1990[75]	None	SMBG (*n* = 10) Urine monitors (*n* = 10)	NA	Quality of life HbA_1	NA	No difference between SMBG and urine monitoring
Klein, 1993[76]	None	SMBG (*n* = 181) Urine monitors (*n* = 47)	NA	HbA_{1c} Serum glucose Complications	NA	No difference between SMBG and urine monitoring
Malik, 1989[77]	Educational seminar on diabetes management	Single group before and after blood or urine monitoring intervention (*n* = 16)	12 weeks	HbA_1 Weight gain	NA	Small changes in HbA_1 when monitoring was used to adjust insulin dose and calorific intake
Martin, 1986[78]	Introduction of blood monitoring regimen	Single group before and after blood monitoring intervention (*n* = 22)	16 weeks	HbA_1	10/22	Improved HbA_1 after SMBG
Newman, 1990[79]	None	SMBG (*n* = 21) No SMBG (*n* = 17)	NA	GHb Cost per year	NA	SMBG alone did not alter GHb levels signficantly
Oki, 1997[72]	None	SMBG (*n* = 61) No SMBG (*n* = 37)	NA	GHb	NA	No difference between SMBG and no SMBG
Patrick, 1994[80]	None	SMBG and urine monitoring (*n* = 103) Non-monitoring (*n* = 97)	NA	HbA_{1c} Diabetic complications	NA	No difference between monitoring and no monitoring
Tajima, 1989[81]	Introduction of blood monitoring regimen	Single group before and after blood monitoring	6 months	FPG HbA_{1c} Body mass index HDL	None	Only small significant change in FPG; other measures improved, but not significantly
Wieland, 1997[82]	None	No SMBG (*n* = 69) SMBG, once daily monitoring (*n* = 83) SMBG, twice daily monitoring (*n* = 64)	NA	HbA_{1c} Glibenclamide dose	NA	No difference between SMBG and on SMBG

HDL, high density lipoproptein; NA, not applicable

TABLE 12 *RCTs of SMBG in type 2 DM: results*

Study	Comparison	GHb	FPG	Weight	Other outcomes
Allen, 1990[65]	B vs. U	ND	ND	ND	Cost: B 12 times more in first year, 8 times more in later years
Estey, 1989[70]	Phone calls and home visit, leading to more SMBG	ND	–	ND	–
Fontbonne, 1989[71]	B vs. U vs. N	ND	–	ND	–
Gallichan, 1994[64]	B vs. U	–	–	–	Fructosamine: ND
Miles, 1997[66]	B vs. U	ND	–	ND	Well-being questionnaire: ND
Muchmore, 1994[67]	B + calorie control vs. control	ND	–	ND	Quality of life inventory: ND
Rutten, 1990[69]	GP protocol with SMBG vs. conventional GP care	Decrease in intervention group, increase in control group	–	ND	–
Wing, 1986[68]	Weight control + B vs. weight control only	ND	ND	ND	Cholesterol, triglycerides, blood pressure, diet and exercise habits, changes in medication or mood: ND

B, blood glucose monitoring; U, urine glucose monitoring; N, no monitoring; ND, no difference between groups

TABLE 13 *RCTs of SMBG on GHb in type 2 DM: results (mean (SD or SE))*

Study	Blood testing			Urine testing			No testing		
	Before	After	Δ	Before	After	Δ	Before	After	Δ
Blood vs. urine									
Allen, 1990[65]	12.4 (3.3)	10.4 (2.9)	–2.0 (3.4)	11.7 (3.0)	9.7 (2.6)	–2.0 (2.4)	–	–	–
Fontbonne, 1989[71]	8.2 (SE 0.3)	–	–0.36 (SE 0.29)	8.6 (SE 0.30)	–	–0.13 (SE 0.30)	8.2 (SE 0.3)	–	–0.50 (SE 0.21)
Miles, 1997[66]	10.3 (2.6)	8.8 (1.9)	–1.5	10.3 (2.3)	8.7 (1.7)	–1.6	–	–	–
Blood vs. no testing									
Estey, 1989[70]	6.3 (1.1)	5.6 (0.7)	–0.7 (0.9)	–	–	–	6.1 (1.4)	5.8 (1.5)	–0.3 (0.7)
Muchmore, 1994[67]	10.29 (SE 0.33)	8.75 (SE 0.48)	–	–	–	–	10.45 (SE 0.44)	9.60 (SE 0.63)	–
Wing, 1986[68]	10.19 (2.51)	10.19 (2.29)	–	–	–	–	10.86 (2.00)	10.44 (2.16)	–
GP protocol with SMBG vs. conventional care									
Rutten, 1990[69]	9.7 (2.1)	9.2 (1.49)	–	–	–	–	8.9 (1.9)	9.4 (1.14)	–

TABLE 14 *Results of meta-analysis for GHb in type 2 DM: blood or urine monitoring compared with no monitoring*

Study	Comparison	No. of subjects		Difference in GHb (%) (95% CI)	z	p
		Urine/blood monitoring	No monitoring			
Estey, 1989[70]	Blood vs. none	28	25	–0.40 (–0.84 to 0.04)	–1.755	0.079
Fontbonne, 1989[71]	Blood vs. urine vs. none	110	54	0.25 (–0.46 to 0.97)	0.693	0.488
Muchmore, 1994[67]	Blood vs. none	12	11	–0.85 (–2.47 to 0.78)	1.027	0.304
Wing, 1986[68]	Blood vs. none	23	22	–0.25 (–1.58 to 1.08)	–0.368	0.712
Combined	Blood/urine vs. none	173	112			
Fixed effects				–0.253 (–0.605 to 0.100)	–0.927	0.354
Random effects				–0.253 (–0.605 to 0.100)	–0.406	0.684
Test for heterogeneity					Q = 2.863 (df 3)	0.413
Tests for publication bias:						
Kendall's score					0.34	
Egger's test				Slope: –0.707 (0.449) Bias: 1.553 (1.724)	t = –1.576 t = 0.901	0.256 0.463

TABLE 15 *Results of meta-analysis for weight in type 2 DM: blood or urine monitoring compared with no monitoring*

Study	Comparison	No. of subjects		Difference in weight (kg) (95% CI)	z	p
		Urine/blood monitoring	No monitoring			
Estey, 1989[70]	Blood vs. none	28	25	–1.10 (–2.95 to 0.75)	–0.330	0.742
Fontbonne, 1989[71]	Blood vs. urine vs. none	110	54	–0.22 (–1.36 to 0.93)	–0.375	0.708
Muchmore, 1994[67]	Blood vs. none	12	11	–0.10 (–12.28 to 12.08)	0.016	0.987
Wing, 1986[68]	Blood vs. none	23	22	4.10 (–1.07 to 9.27)	1.571	0.116
Combined	Blood/urine vs. none	173	112			
Fixed effects				–0.306 (–1.260 to 0.648)	–0.063	0.950
Random effects				–0.278 (–1.484 to 0.928)	–0.063	0.950
Test for heterogeneity					Q = 2.661 (df 3)	0.447
Tests for publication bias:						
Kendall's score					–0.34	
Egger's test				Slope: 0.100 (1.000) Bias: –0.667 (1.529)	t = –0.100 t = –0.436	0.929 0.705

TABLE 16 *Results of meta-analysis for GHb in type 2 DM: blood monitoring compared with urine monitoring*

Study	No. of subjects		Difference in GHb (%) (95% CI)	*z*	*p*
	Blood monitoring	Urine monitoring			
Allen, 1990[65]	27	27	0.00 (–1.60 to 1.60)	0.000	1.000
Fontbonne, 1989[71]	56	54	–0.23 (–1.05 to 0.60)	–0.546	0.584
Miles, 1997[66]	58	56	0.10 (–0.57 to 0.77)	0.294	0.769
Combined	141	137			
Fixed effects			–0.028 (–0.521 to 0.466)	–0.109	0.913
Random effects			–0.028 (–0.521 to 0.466)	–0.109	0.913
Test for heterogeneity				*Q* = 0.373 (df 2)	0.830
Tests for publication bias:					
Kendall's score				0.00	
Egger's test			Slope: 0.375 (0.669)	*t* = 0.560	0.675
			Bias: –0.999 (1.755)	*t* = –0.569	0.670

TABLE 17 *Results of meta-analysis for weight in type 2 DM: blood monitoring compared with urine monitoring*

Study	No. of subjects		Difference in weight (kg) (95% CI)	*z*	*p*
	Blood monitoring	Urine monitoring			
Allen, 1990[65]	27	27	2.00 (–0.98 to 4.98)	1.317	0.188
Fontbonne, 1989[71]	56	54	–0.47 (–1.58 to 0.64)	–0.829	0.407
Combined	141	137			
Fixed effects			–0.167 (–1.209 to 0.874)	–0.315	0.753
Random effects			0.363 (–1.926 to 2.653)	0.311	0.756
Test for heterogeneity				Q = 2.323 (df 1)	0.128
Tests for publication bias:					
Kendall's score				0.00	
Egger's test			Slope: –1.944 (–)	–	–
			Bias: 2.597 (–)	–	–

Chapter 5

Effectiveness of self-monitoring in type 1 diabetes mellitus

Background

The DCCT[14] has had a lasting impact on the management of patients with type 1 DM. The results of the study provided convincing evidence that intensive control of blood glucose could reduce the onset and progression of microvascular complications in type 1 DM. The conduct of this trial is particularly relevant to understanding the clinical effectiveness of self-monitoring.

Recruitment to the DCCT took place between 1983 and 1989. Subjects in the conventional treatment group were managed according to locally developed protocols and SMBG was encouraged from 1986 onwards.[62] Control subjects were instructed to test at least once daily and more intensively when ill or taking more than usual exercise. In the intensively treated group, subjects were instructed to perform four blood tests each day, including three tests before meals and one at bedtime. A test at 3 a.m. was required once weekly. When blood glucose levels were high, additional tests were required after meals.[62] Data collected during the study showed that, by 1992, 53% of conventionally treated subjects were performing blood glucose monitoring at least once daily, and in the intensive-treatment group 86% of patients were performing blood tests three times daily and 67% were performing a weekly test at 3 a.m. Differences in self-monitoring between groups were confounded with differences in every aspect of diabetic care, including insulin treatment, diet, education and supervision by health professionals. Thus the independent contribution of self-monitoring to the outcome of the study cannot be estimated, and this was not the objective of the trial. The DCCT was important in the context of this review because it established evidence for the effectiveness a package of care that included self-monitoring. This approach to management is now widely accepted as a desirable strategy for the management of subjects with type 1 DM.

In this chapter we review studies that specifically examined the clinical effectiveness of self-monitoring at improving blood glucose control in type 1 DM.

Objective

To evaluate evidence for the clinical- and cost-effectiveness of self-monitoring in type 1 DM.

Methods

The methods are summarised in chapter 2. Briefly, searches were carried out as before, but substituting the terms 'insulin-dependent diabetes mellitus' for 'non-insulin-dependent diabetes mellitus'. Studies identified were evaluated for quality and for inclusion in a meta-analysis where possible.

In this chapter a distinction is made between 'controlled' studies and 'non-controlled studies' because randomisation did not appear to have been performed effectively in some of the trials identified for review. The searches identified 24 papers, including eight controlled trials and 16 non-controlled studies. The latter were appraised but excluded from the evaluation of the clinical effectiveness of monitoring.

Controlled trials: study design and statistical power

Details of the eight controlled studies are given in *Tables 21* to *23* and in the following paragraphs. The design features of the trials are summarised in *Box 5*.

Randomisation

One study used simple randomisation of individuals to groups[86] and a further three studies used randomised crossover designs.[87–89] The crossover trial reported by Daneman and co-workers[90] did not provide details of the method of allocation. Carney and co-workers[91] used a form of allocation by group. Children were allocated sequentially to one of five physicians, and three of five physicians prescribed

BOX 5 Design features for controlled studies in type 1 DM

- Eight controlled trials were identified
- There were four crossover trials, one study with group allocation, one controlled trial with sequential allocation of subjects, one study using simple randomisation and one study with a factorial design
- Six studies compared urine testing with blood testing, one compared blood testing with no testing and one evaluated different blood testing frequencies
- Estimates of statistical power showed that only one study had sufficient power to detect differences in GHb of < 1.0%
- The mean (SD) quality rating was 14.4 (1.6)
- In seven of the eight studies, patients were encouraged to change their therapy in response to monitoring results

a change in monitoring method (see *Table 21*). Starostina and co-workers[92] described the design of their study as a RCT, but patients were allocated systematically, the first 61 to urine testing and the next 60 to blood testing. The study by Terent and co-workers[93] was factorial in design, with subjects randomised to receive education or not and then randomised to be trained in SMBG or not.

Testing methods

Five studies[86,89,91–93] compared SMBG and self-monitoring of urine glucose. Daneman and co-workers[90] compared urine testing with urine testing plus SMBG. The remaining trials only evaluated SMBG: one[87] compared the effectiveness of three different frequencies of self-monitoring, and another[86] compared an education programme plus SMBG with an education programme alone.

Study settings

One study was set in Russia,[92] one in Sweden,[93] two in the USA[90,91] and four were conducted in the UK.[86–89] The trials took place either in children's hospitals, diabetes clinics or diabetes research centres. Only two studies were not set in an academic institution. Only one study recruited all the diabetic subjects from a geographically defined area.[93]

Subject age

Four studies included children aged less than 18 years. The remaining three studies included young adults (mean age 28–34 years) (see *Table 21*).

Insulin treatment

Six studies included patients on twice daily insulin injections. Daneman and co-workers[90] included patients using a mixture of twice and once daily dosages.

Other patient characteristics

Starostina and co-workers[92] recruited subjects who were waiting for inpatient treatment for diabetes-related complications. Gordon and co-workers[87] studied adult patients attending a diabetes clinic who were already self-monitoring and had had diabetes for more than 12 months. Worth and co-workers[89] studied adults with type 1 DM who were not pregnant and were free from renal disease or retinopathy. Terent and co-workers[93] studied patients who had had diabetes for less than 20 years. The remaining four studies included children who were attending paediatric or diabetes clinics.

TABLE 18 *Estimates of power for controlled trials in type 1 DM*

Study	Primary outcome	No. in smallest group	Estimated SD	Detectable difference in GHb (%)	Power score
Carney, 1983[91]*	HbA_{1c}	34	1.70	1.0–2.0	2
Daneman, 1985[90]**	GHb	7	1.48	1.0–2.0	2
Gordon, 1991[87]	GHb	14***	2.05	1.0–2.0	2
Mann, 1991[86]	HbA_{1c}	19	2.16	1.0–2.0	2
Miller, 1983[88]	HbA_{1c}	19***	5.55	> 3.0	0
Starostina, 1994[92]	HbA_1	52	1.46	0.5–1.0	3
Terent, 1985[93]	HbA_1	18	2.50	2.0–3.0	1
Worth, 1982[89]**	GHb	38	1.95	1.0–2.0	2

* *Group randomised study*
** *Crossover trial, not analysed as such*
*** *Based on total in two groups in crossover trial*

Sample size and power

Sample sizes were small, ranging from 181 patients in the largest study[92] to only 16 in the smallest study.[90] The study by Carney and co-workers[91] included 68 patients, but the remaining trials contained less than 40 patients each.

Post hoc calculations were made, where possible, to evaluate the power of the eight trials (*Table 18*). For the factorial trial, data were combined for self-monitoring groups because the education intervention appeared to have no independent effect. Only one of the trials had sufficient power to detect differences in GHb of < 1% but > 0.5%. Five studies had sufficient power to detect differences of < 2% but > 1%. Note that power will be overestimated for the group randomised study.[91] For the study by Miller and co-workers[88] it is possible that data were incorrectly reported to be SEs rather than SDs.

Drop-out rates

The studies by Starostina and co-workers[92] and Mann and co-workers[86] both had drop-out rates of < 10%, those by Carney and co-workers,[91] Gordon and co-workers[87] and Miller and co-workers[88] had drop-out rates of up to 20%, while Daneman and co-workers[90] did not specify whether any subjects were lost to follow-up. Worth and co-workers[89] excluded eight patients before the start of the trial and a further ten failed to complete the crossover period for a variety of reasons.

Main measures

All studies used GHb as an outcome measure. Three studies used HbA_{1c}, two used HbA_1 and the remaining studies did not specify the type of GHb assay used (see *Table 22*). A range of other metabolic outcomes was used in some studies, including C-peptide, serum cholesterol and creatinine. The studies also considered a range of psychological or social outcomes, including patient preferences, patient attitudes and patient knowledge, assessed using a range of different measures.

Interventions

The duration of trials varied greatly. Starostina and co-workers[92] conducted their study over 2 years. The other trials were of shorter duration. Worth's[89] study lasted 6 months, the study by Miller and co-workers[88] lasted 5 months, and the studies by Mann and co-workers[86] and Terent and co-workers[93] lasted 18 months. The other studies had durations of 26 weeks,[90] 3 months[90] and 24 weeks[91] (see *Table 22*). In general, at least 3 months is required for changes in GHb to evolve.

Regimens differed considerably in terms of their testing requirements and the type of monitoring (see *Tables 22* and *23*). Five studies compared blood monitoring to urine monitoring, one evaluated the efficacy of relative frequencies of blood monitoring and one evaluated the effects of adding SMBG to an educational programme.

Starostina and co-workers[92] and Daneman and co-workers[90] instructed patients to perform blood tests three times daily, every day. Miller and co-workers[88] and Carney and co-workers[91] requested tests at least twice daily, with measurements before meals or at bedtime. Mann and co-workers[86] required patients to monitor only twice weekly (before meals and at bedtime). Worth and co-workers[89] asked patients to monitor 2 days a week, but both before and after meals, and before bedtime. Gordon and co-workers[87] compared the use of three blood monitoring protocols, requiring patients to provide four-point profiles either twice weekly or once weekly, or to provide two-point profiles every day. All tests were scheduled before meals or at bedtime. Terent and co-workers[93] asked subjects to monitor on 2 days per fortnight, with tests before breakfast, 2 hours after meals and at bedtime.

Use of therapy protocols

The advice patients were given on making changes to their therapy in response to monitoring results could influence the outcome of the evaluation. In the studies by Starostina and co-workers[92], Worth and co-workers[89] and Mann and co-workers,[86] patients were given algorithms to modify their insulin doses. In the studies by Daneman and co-workers,[90] Carney and co-workers[91] and Gordon and co-workers,[87] patients were encouraged to adjust their insulin doses but were not given specific algorithms. Carney and co-workers[91] recommended that patients change their diet or exercise habits as a result of monitoring results. Miller and co-workers[88] did not ask patients to alter their therapy at all, insulin doses being reviewed by their physician at clinic visits. In the study by Terent and co-workers,[93] subjects were encouraged to change their insulin dose in order to achieve FBG values of < 7 mmol/l or postprandial values of < 10 mmol/l.

Reliability of monitoring

In the study by Gordon and co-workers,[87] patients were required to achieve an accuracy of within 10% of laboratory results before they could be

included in the study. In the study by Daneman and co-workers,[90] children were taught how to read strips accurately, and parents were advised to make checks on readings. Carney and co-workers[91] explained that the diabetic educators in their study provided feedback to patients regarding the accuracy of their blood glucose level determinations. The teaching programmes appeared, from the information given, to be fairly comprehensive, and it is likely therefore that such accuracy checks were made. However, none of the other studies gave specific information on reliability of testing.

Adherence to the regimen

Three controlled trials measured patient adherence to the study protocols using a range of different methods. Daneman and co-workers[90] reported that compliance varied greatly in both experimental groups. Three children were categorised as non-compliant, and the data were re-analysed to exclude these patients' scores, although this made no difference to the overall conclusion. Gordon and co-workers[87] reported that their laboratory results confirmed patient monitoring data and they inferred a satisfactory level of compliance from this. Mann and co-workers[86] assessed compliance in terms of completeness of patients' logbooks. They found that there were records of 74% of the urine tests and 94% of blood tests required by the protocol. Terent and co-workers[93] also reported a satisfactory level of compliance, but did not provide details. The remaining four studies did not mention assessment of compliance.

Overall assessment of study quality

The final quality ratings for the eight controlled trials are shown in *Table 19*.

Reporting

The majority of papers scored poorly in the reporting section. The most comprehensive papers only scored 8 out of a possible 11 marks. Although papers covered a greater range of patient perspectives than for type 2 DM, only the study by Starostina and co-workers[92] used them as a formal way of assessing outcome. Papers provided few details of the conduct of the study, often with no mention of the characteristics or confounders in the control or the experimental groups. Many studies also lost marks for poor quality of statistical reporting.

External validity

Most papers did not demonstrate, or did not give enough information to determine, whether the patients in the study groups, the interventions used or the staff involved were typical of general diabetes management. A few studies reported that they were trying to simulate the generality of practice, and these scored slightly higher. Studies that were conducted in specialist centres and which gave no information on patients or facilities were assumed to be unrepresentative and were marked down.

Internal validity

A common problem in this section was the use of *post hoc* analyses, associating measures that were not planned. Many papers also used inappropriate statistical tests. As with the quality rating on type 2 DM papers, studies did not usually score well on questions relating to concealment of randomisation or intervention assignment.

Most papers lost marks on this section, due to the number of patients lost to follow-up. In the majority

TABLE 19 *Quality ratings for controlled studies in type 1 DM*

Study	Reporting	External validity	Internal validity		Overall
			Bias	Selection bias	
Carney, 1983[91]	7	0	4	3	14
Daneman, 1985[90]	6	1	4	2	13
Gordon, 1991[87]	6	2	4	3	15
Mann, 1991[86]	7	1	4	2	14
Miller, 1983[88]	6	1	3	3	13
Starostina, 1994[92]	8	0	4	2	14
Terent, 1985[93]	7	3	5	3	18
Worth, 1982[89]	8	0	3	3	14
Mean (SD)					**14.4 (1.6)**

of the controlled trials drop-out rates were significant, and yet no study made an attempt to allow for this in the findings. Few studies attempted to adjust for confounding in the main analysis. As with type 2 DM papers, there was often little detail on the randomisation procedure, and if procedures were described they were often inadequate.

Excluded studies: non-controlled designs

Sixteen non-controlled studies were identified. These included ten case series, three cross-sectional surveys, two cohort studies and one non-equivalent group design. Details of the studies are given in *Tables 20* and *24* to *26*. Most studies were not designed to allow estimation of the effect self-monitoring, and statistical power could not be assessed. The mean (SD) quality rating was 9.9 (2.5) (*Table 20*). Non-controlled studies were excluded from the evaluation of effectiveness.

Results

The results for controlled trials are summarised in *Tables 27* and *28* and in *Box 6*.

BOX 6 Results for controlled studies in type 1 DM

- The results of the DCCT demonstrated the efficacy of a package of care which included frequent SMBG
- The studies reviewed here considered the independent effects of different approaches to self-monitoring
- Combining studies was difficult because of the different approaches to design, subject selection and comparison of testing modalities
- Only one study showed a benefit from using SMBG as compared to urine glucose self-monitoring
- Four studies that compared blood and urine testing in children or adults were combined in a meta-analysis. The estimated effect of blood monitoring on GHb was approximately –0.567% (95% CI, –1.073 to –0.061). This result was somewhat sensitive to the assumptions made
- Most studies showed that patients preferred blood monitoring to urine testing
- One study showed that blood testing was more costly than urine testing

TABLE 20 *Quality ratings for non-controlled studies in type 1 DM*

Study	Reporting	External validity	Internal validity		Overall
			Bias	Selection bias	
Belmonte, 1988[94]	8	0	3	0	11
Dorchy, 1997[95]	8	0	4	2	14
Geffner, 1983[96]	4	0	1	2	7
Gill, 1986[97]	5	0	2	1	8
Hemansson, 1986[98]	7	1	2	1	11
Kelly, 1981[99]	4	1	3	2	10
Lam, 1986[100]	7	0	1	0	8
Lombrail, 1986[101]	5	0	2	2	9
Peveler, 1993[102]	6	0	1	0	7
Sonksen, 1978[103]	7	0	3	1	11
Strowig, 1998[51]	7	0	4	0	11
Walford, 1978[104]	4	1	1	0	6
Wing, 1985[105]	5	3	2	3	13
Wysocki, 1992[106]	5	0	2	0	7
Ziegler, 1989[107]	6	0	3	3	12
Ziegler, 1993[108]	7	0	3	3	13
Mean (SD)					**9.9 (2.5)**

Metabolic control

Only one of the eight controlled studies demonstrated an effect of SMBG on blood glucose control. This was the study by Carney and co-workers,[91] who found that in children trained in blood testing the mean (standard error of the mean (SEM)) HbA_{1c} decreased from 11.88% (0.28%) to 11.0% (0.26%), while in children using urine testing the HbA_{1c} decreased from 12.04% (0.31%) to 11.88% (0.32%). An analysis of covariance showed this to be statistically significant. However, as noted above, the study employed a form of group allocation that was not accounted for at the time of analysis. The remaining studies did not demonstrate positive effects of monitoring on blood glucose control (see *Tables 27* and *28*).

Meta-analysis

We attempted a meta-analysis of the controlled trials in type 1 DM, but combining results was difficult because of the differences in study designs, subject selection and forms of intervention. The studies by Worth and co-workers[89] and Gordon and co-workers[87] evaluated differences in the frequency of blood monitoring and differences between the use of meters and strips in adults. These two studies were not comparable with any other studies.

The studies by Carney and co-workers,[91] Mann and co-workers,[86] Miller and co-workers[88] and Terent and co-workers[92] each compared blood and urine testing. The first three studies included children, while the last included adults. Results from these studies were combined in a meta-analysis. The study by Daneman and co-workers[90] was excluded because it compared urine monitoring with blood and urine monitoring together. The study by Starostina and co-workers[92] was excluded because it was not satisfactorily randomised. A flow chart showing the selection of studies for inclusion in the meta-analysis is shown in *Figure 4*.

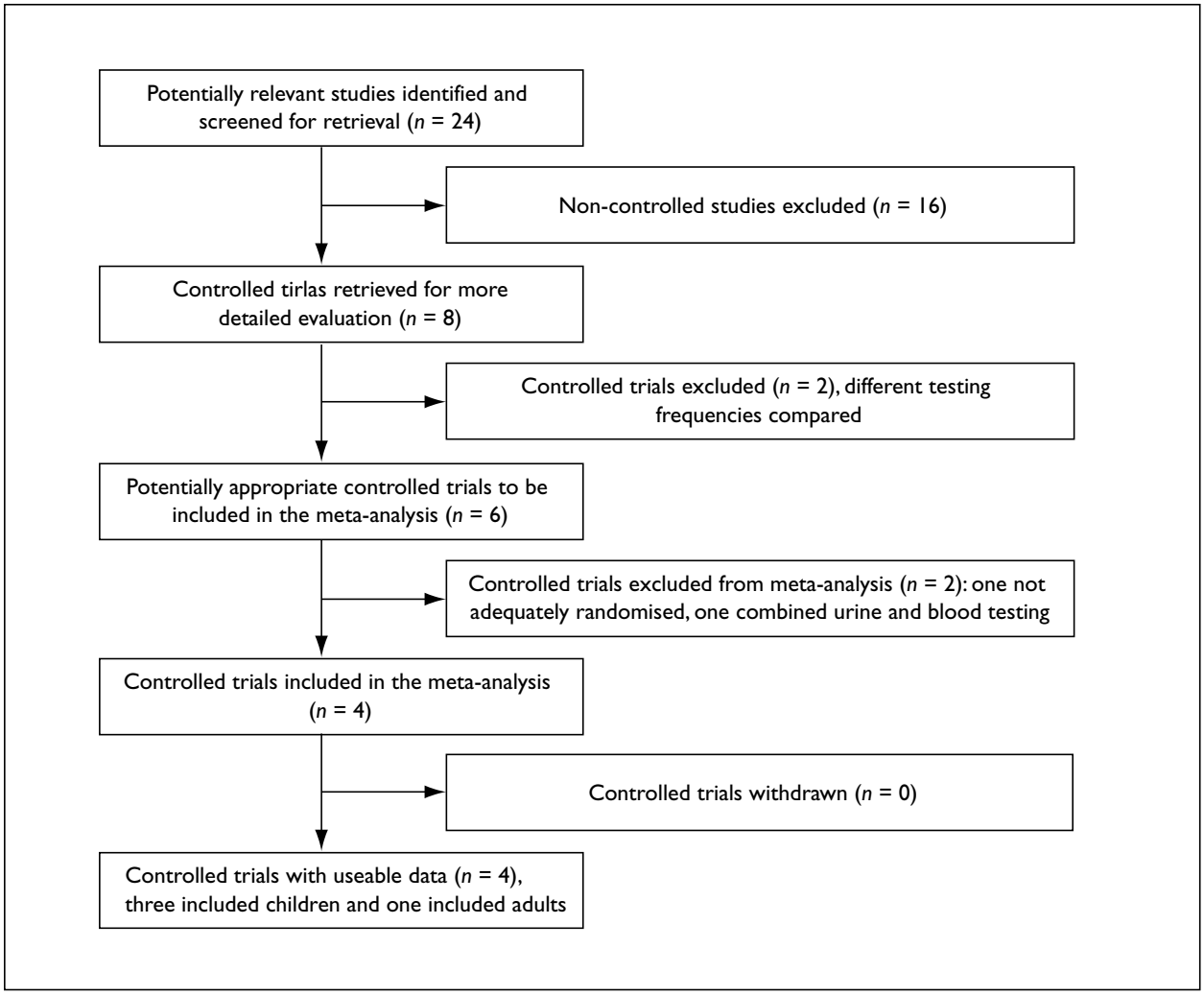

FIGURE 4 *The selection of studies for inclusion in the meta-analysis of the effecct of self-monitoring on GHb in type 1 DM (adapted from QUORUM statement, Moher and co-workers[83])*

The meta-analysis of the four studies was not straightforward.[86,88,91,93] Miller and co-workers[88] gave differences and SDs for differences in HbA_{1c} between urine and blood, but the other three studies did not. In the studies by Mann and co-workers,[86] Carney and co-workers[91] and Terent and co-workers[93] the change in HbA_{1c} between the start and the end of study was calculated for each treatment group. The SD of this change was estimated as

$$SD_{change} = \sqrt{(SD_{start})^2 + (SD_{end})^2 - 2r\, SD_{start}\, SD_{end}}$$

where r, the correlation between the initial and final measurements, was assumed variously as 0.5 and 0.7. However, the results were not very sensitive to the variation in the assumed level of correlation. Estimates of the treatment effect and SEs were produced by standard methods.[24] Note that, because we used the published data and not the individual patient data, the results of the analyses for individual studies are more conservative than those included in the original study reports.

Miller and co-workers[88] (who used a randomised crossover design) gave estimates with SEs for the change in HbA_{1c} between the first treatment and second treatment; that is, on changing from blood to urine testing (0.0, SE 1.6) or from urine to blood testing (0.8, SE 2.0). The treatment effect is equal to half the difference between these estimates.

There was a small difference between the effects of blood and urine testing. This was of borderline statistical significance, being significant with an assumed correlation of 0.7 but not with an assumed correlation of 0.5. The magnitude of the difference could still be clinically important (*Table 29* and *Figure 5*). The combined estimated treatment effect on GHb from blood monitoring compared with urine monitoring was –0.567% (95% CI, –1.073 to –0.061) in favour of blood testing (assuming a correlation of 0.7) or –0.584% (95% CI, –1.190 to 0.023) (assuming a correlation of 0.5). The lack of heterogeneity means that the fixed- and random-effects models give the same results, and suggests that monitoring has either a constant or no effect.

There were two problems with the data reported by Miller and co-workers.[88] First, the values given for changes in GHb were not consistent with the mean GHb values reported for each group (see *Table 28*). Secondly, the reported SEs in the paper were implausibly large and appeared likely to be SDs. If the calculations were repeated making this assumption, then the pooled estimates were –0.547 (95% CI, –1.139 to 0.044) (assuming a correlation of 0.7) or –0.545 (95% CI, –1.163 to 0.073) (assuming a correlation of 0.05).

Hypoglycaemia

Three studies found that the frequency of occurrence of hypoglycaemia was low and not different

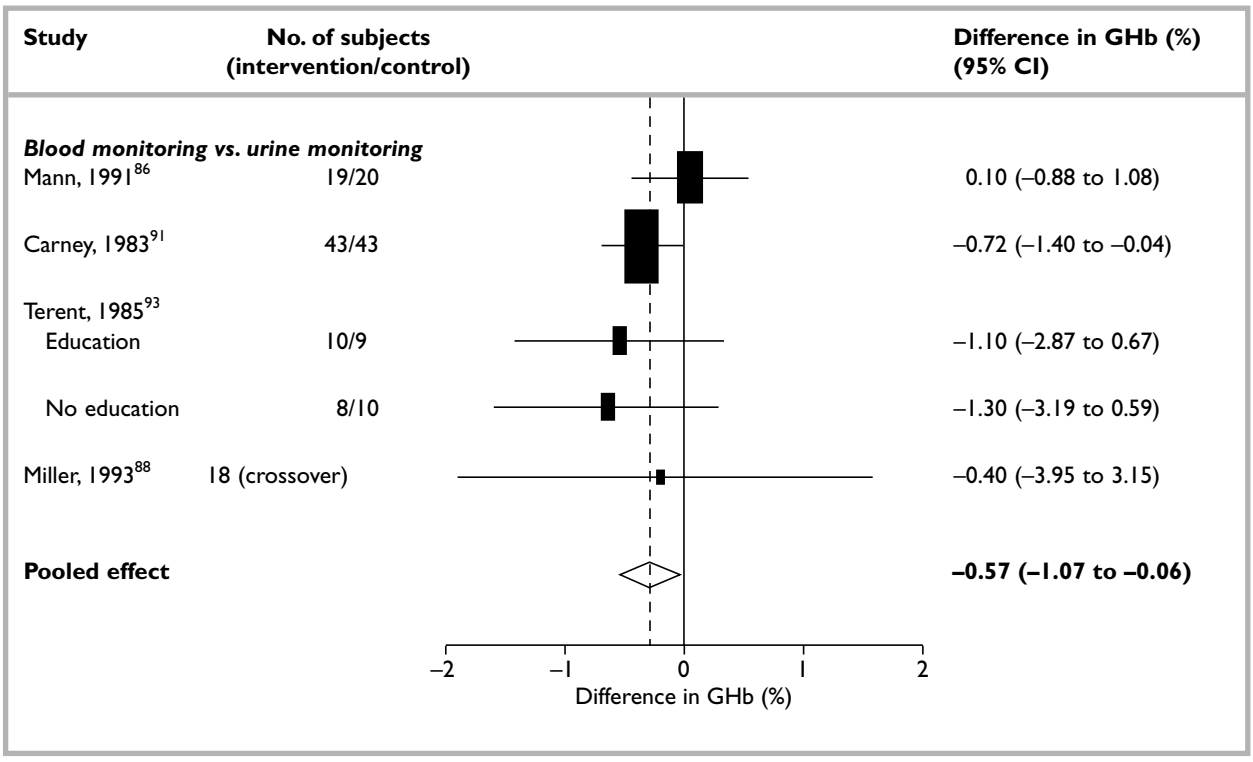

FIGURE 5 *Results of the meta-analysis of the effect of self-monitoring on GHb in type 1 DM*

in SMBG and control groups.[88,89,92] Daneman and co-workers[90] reported that blood monitoring confirmed symptomatic hypoglycaemia in up to 2% of measurements and revealed asymptomatic hypoglycaemia at some time in 11 of the 16 children in their study.

Patient outcomes

Six of the controlled trials considered the effect of introducing monitoring on patient outcomes. A range of patient attitude questionnaires and knowledge checklists were used for this purpose, but no study used an accepted, psychometrically valid instrument. Such instruments were often not available at the time the studies were conducted. We were not able to combine the findings of the different studies.

Worth and co-workers[89] gave a comprehensive questionnaire, which included questions on patient attitudes, to patients after the monitoring trial. They found that over half of patients surveyed thought that blood testing was superior to urine testing for assessing metabolic control, while 40% felt that a combination of blood and urine testing was better. No patient thought that urine testing alone was superior. No clear preference was expressed for using either visual strips or strips with meters. Miller and co-workers[88] also gave a questionnaire to children after completion of the trial. They found that 84% of patients preferred blood monitoring alone and 10% preferred a combination of both blood and urine monitoring, but no patient preferred just urine monitoring. Problems encountered by patients in the study by Miller and co-workers[88] included not being able to obtain blood samples, sore fingers and difficulty with the visual interpretation of strip results. In this study, 37% of patients wanted to continue with blood monitoring alone, 47% wanted to continue with a combination of blood monitoring and urine monitoring, and 10% wanted to continue with urine testing only. The remaining patients expressed no plans to continue testing.

Gordon and co-workers[87] evaluated the effectiveness of different frequencies of monitoring on metabolic control. After the trial was complete, patients were asked about which monitoring regimen they preferred. Of the 18 patients expressing an opinion, nine preferred testing four times daily twice weekly, six preferred four times daily once weekly and only three patients preferred monitoring twice daily for 7 days a week. Mann and co-workers[86] gave children a brief questionnaire on completion of the trial and reported that 77% of children wished to continue with more regular home visits, and all felt better informed about the practical aspects of diabetes since starting blood monitoring. Daneman and co-workers[90] also found that more families preferred blood to urine testing and intended to continue this after the trial. Only Starostina and co-workers[92] evaluated the effects of monitoring on diabetes-related knowledge. The evaluation was done both before and after intervention, and it was found that test scores were increased after the intervention to a comparable degree in the urine and blood monitoring groups, but not in the control group. However, subjects were given an overall educational package, of which monitoring was a part.

The findings from these studies suggest that the majority of patients in these trials, both children and adults, seemed to prefer blood monitoring, or a combination of blood and urine monitoring to just monitoring alone. Reasons for preferring blood monitoring included gaining a better understanding of diabetes and feeling in more control of their illness.

However, the conclusions that can be drawn from these studies are limited. In order to qualify as an outcome measure, preference questionnaires or interviews should be carried out before monitoring and after monitoring, allowing the two scores to be compared. Only the study by Starostina and co-workers[92] attempted to do this. Simply asking patients' for their views or testing knowledge after the intervention gives no indication of how much of an effect self-monitoring has had on each particular area. Feedback from patients after the study as to how they found the intervention is obviously useful, and can be used qualitatively to inform practice, but it would appear to have limited use as an outcome measure.

Cost-effectiveness of self-monitoring

Only one study considered the costs of different forms of intervention. Starostina and co-workers[92] analysed the costs of introducing either urine or blood monitoring techniques and attempted to determine whether the incremental benefits outweighed the incremental costs within 2 years. In addition to the direct costs of hospital care and medical supplies, lost productivity due to absence from work was included in the analysis. The potential benefits of monitoring, such as fewer hospital admissions and days off work, were calculated. It was found that the benefits outweighed the overall costs of the urine-monitoring supplies. When the same analysis was performed for blood monitoring, it was found that the benefits only accounted for half the cost of blood-monitoring supplies. However, a degree of caution should be exercised when generalising these findings to different national settings.

Discussion

The studies reviewed do not provide decisive evidence for the clinical effectiveness of SMBG in type 1 DM. The results of the meta-analysis show that the effect of SMBG compared to urine monitoring was small. However, because of the low statistical power of the studies, neither an appreciable beneficial effect nor a small adverse effect could be excluded with certainty.

Starostina and co-workers[92] evaluated introducing both SMBG and urine monitoring to two groups of patients, and compared these with a control group. They found that both SMBG and urine monitoring had a similar effect in terms of decreased levels of GHb compared to the control group. However, the effect of monitoring was completely confounded with a more complex educational intervention.

The only study that found a positive result was that by Carney and co-workers.[91] This study found that HbA_{1c} levels in children who were taught SMBG decreased significantly more from baseline than did those in a matched control group who monitored urine over the same time period. This was the case even though patients were not given any instruction or advice on how to use their readings in modifying diet, exercise or insulin. This was one of the few studies that did not encourage patients to utilise self-monitoring results. The analysis did not account for group randomisation, and a correct analysis would have attenuated further the level of statistical significance achieved.

Subjects in the study by Carney and co-workers[91] only monitored blood twice daily. In the study by Starostina and co-workers[92] tests were performed 3 or 4 times daily. Schriffin and co-workers[109] suggested that four tests daily or more may be necessary for optimal regulation. However, the study by Gordon and co-workers,[87] which evaluated the frequency of monitoring, found no difference between patients who monitored 4 times weekly to those who monitored 14 times weekly. There is, therefore, little consensus on an optimum frequency of SMBG.

Several of the trials concluded that self-monitoring has an effect by getting patients to focus intensively on the management of their diabetes. It was suggested that it was the increased attention by patients and staff that caused the metabolic improvement, rather than the actual effect of monitoring. Worth and co-workers[89] found that there was a significant improvement in GHb during a 6-month optimisation period, when patients received education and were taught to monitor urine, but that patients did not improve during the following 9 months when they monitored blood, regardless of the particular monitoring technique or testing frequency used. This study concluded that the main benefit of SMBG lies in its use as an educational modality, with increased motivation and more regular contact with staff. The study by Mann and co-workers[86] also compared patients who used urine testing after an education programme with those who were taught SMBG in addition. Patients using SMBG were given algorithms and asked to change management on the results of their testing. However, there was no difference in HbA_{1c} between the two groups.

Methodological issues

The studies reviewed suffered from several limitations. Few studies included a satisfactory evaluation of compliance with regimens, and only a few evaluated the reliability of patient tests. There was no consensus between studies regarding the frequency and timing of tests. With the exception of GHb, there was also little agreement about the most helpful outcomes to measure, and very little attempt was made to evaluate psychological issues associated with monitoring. No studies were done specifically with adolescents, who are known to experience difficulties with diabetic control. Finally, as the quality ratings show, many of the papers were very poorly reported and few studies gave sufficient statistical detail to perform useful analyses.

Recommendations

The studies reviewed in this chapter did not provide evidence to support the clinical effectiveness of self-monitoring in type 1 DM. However, because the studies were generally neither well conducted, nor well reported, and because they had low statistical power, the review must be considered to give inconclusive results.

As noted at the beginning of this chapter, the results of the DCCT provided evidence for the effectiveness of a package of care that includes self-monitoring.[14] Current clinical practice recommendations from the ADA encourage the use of self-monitoring. A review by Goldstein and co-workers[20] suggested that "major efforts should be undertaken to substantially increase use of self-monitoring of blood glucose by individuals with all types of diabetes".

This raises the question of whether evidence is needed to support recommending self-

monitoring for all patients. This question might best be addressed by carrying out prospective studies of groups of patients with type 1 DM in order to characterise those who do not use monitoring or do not use it effectively. These groups might then be the subject of future intervention studies, which could evaluate whether self-monitoring is of benefit or not.

A recent study by Evans and co-workers[110] provides an illustration of this point. The authors studied 807 patients with type 1 DM and 790 with type 2 DM using insulin. Only 20% of type 1 DM patients and 17% of type 2 DM patients redeemed enough prescriptions for testing materials to perform daily tests. In patients with type 1 DM there was an association between uptake of testing materials and lower GHb, but this relationship was not observed in type 2 DM patients. The study showed that regular testing is uncommon, even in patients with type 1 DM. Patients who monitored regularly were better controlled, but this may have reflected a greater level of adherence to other aspects of diabetes self-management. The study clearly raises the question of whether it is essential to recommend regular self-monitoring for all patients.

TABLE 21 *Controlled trials of self-monitoring in type 1 DM: design and subject selection*

Study	Setting	Design	No. of patients	Study sample	Inclusion criteria
Carney, 1983[91]	USA, diabetes clinic for children	Cluster allocation: children allocated to one of five physicians sequentially. Three out of five physicians prescribed change from urine to blood testing	86	Children	Diabetes for ≥ 12 months Controls matched for age and duration of diabetes
Daneman, 1985[90]	USA, children's hospital	Crossover trial, method of allocation not stated	16	Children	Recruitment at random from clinic
Gordon, 1991[87]	UK, general hospital	Randomised crossover trial	25	Adults	Age 18–50 years Diabetes for ≥ 12 months Two insulin injections daily Already using SMBG for ≥ 6 months
Mann, 1991[86]	UK, diabetes clinic	Randomisation of individuals to groups, stratifying for age, duration of diabetes, insulin dose, sex and carbohydrate intake	39 from a clinic of 158	Children	Diabetes for ≥ 15 months Two insulin injections daily
Miller, 1983[88]	UK, hospital paediatric clinic	Randomised crossover trial	19	Children	Age 8–13 years Live near to the clinic 4 patients refused, 2 were excluded (1 frequent hypoglycaemia, 1 early diabetes)
Starostina, 1994[92]	Russia, research centre for endocrinology	Allocation of consecutive attenders to groups: first 61 to urine, next 60 to blood testing, and next 60 to control group	181	Adult inpatients awaiting treatment	181 consecutive admissions to a diabetic inpatient facility All patients included except those with chronic conditions unrelated to diabetes
Terent, 1985[93]	Sweden, municipality	Factorial design with randomisation to receive education or not, followed by randomisation to receive SMBG or not	37	All patients with type 1 DM in the municipality	Age > 17 years Diabetes for ≤ 20 years Exclusions: renal transplant, pregnancy, in prison, alcohol problems
Worth, 1982[89]	UK, hospital diabetes clinic	Randomised crossover trial	38	Adults	All patients except those who were pregnant, taking oral contraceptives, had renal disease, or retinopathy

TABLE 22 *Controlled trials of self-monitoring in type 1 DM: interventions*

Study	Intervention	Groups in study	Duration	Main measures	Drop-outs
Carney, 1983[91]	Urine monitoring vs. SMBG	SMBG Urine testing	9 months	HbA_{1c}	0
Daneman, 1985[90]	Urine monitoring + SMBG vs. urine monitoring	Urine monitoring + SMBG, then urine monitoring only Urine monitoring only, then urine monitoring + SMBG	26 weeks	GHb	0
Gordon, 1991[87]	Three different frequencies of SMBG	SMBG 4-point profile, twice weekly SMBG 4-point profile, once weekly SMBG 2-point profile, daily	36 weeks	GHb Fructosamine Blood glucose	4
Mann, 1991[86]	Education + SMBG	Education (n = 20) Education + SMBG (n = 19)	72 weeks	HbA_{1c} Hospital admissions	1
Miller, 1983[88]	SMBG vs. urine monitoring	Urine monitoring then SMBG SMBG then urine monitoring	40 weeks	HbA_{1c} Blood glucose profiles 24-hour urine glucose	1
Starostina, 1994[92]	Urine monitoring vs. SMBG vs. no monitoring	SMBG Urine monitoring No monitoring (control)	104 weeks	HbA_1 Weight Cost	15
Terent, 1985[93]	Education, or SMBG, or education + SMBG vs. conventional care	SMBG Education Education + SMBG Conventional care	78 weeks	HbA_1	Not stated
Worth, 1982[89]	Urine monitoring vs. SMBG (visual) or SMBG (meter)	Six groups with different sequences of testing methods	60 weeks	GHb Blood glucose profile Urine glucose	0

TABLE 23 *Controlled trials of self-monitoring in type 1 DM: details of interventions*

Study	Programme	Equipment	Blood regimen	Urine regimen	Control	Modification of therapy
Carney, 1983[91]	Three of the five study doctors recommended changing to SMBG. The other two doctors kept patients on urine testing. All relevant patients had through training procedure on SMBG	Blood: Chemstrips BG (visual) or Dextrostix and Dextrometer Urine: Clinitest™ (Ames)	At least twice daily: in the morning before breakfast and before the evening evening meal. A third test before bedtime was recommended	At least twice daily: in the morning before breakfast and before the evening meal. A third test before bedtime, was recommended	–	Patients were given information regarding the desirable range of values and were informed, without specific instructions, to modify diet or exercise should values exceed this level
Daneman, 1985[90]	A programme of urine and blood monitoring. No details given on education/ training given	Urine: Clinitest (Ames) Blood: Chemstrips BG	Three times daily: before breakfast, before supper and before an evening snack	Three times daily: before breakfast, and first-voided specimens before supper and an evening snack	–	Families were encouraged to change the insulin dose once or twice weekly, in order to attain metabolic targets
Gordon, 1991[87]	Patients were randomised to one of 3 groups. At 12 and 24 weeks, groups crossed over. Patients were reviewed at 6-week intervals and GHb measured	BM-44 (Boehringer Mannheim), Visidex™ (Ames)	4-point profile twice weekly, 4-point profile once weekly, 2-point profile daily 4-point profile was after main meals and at 10 p.m.	None	–	Patients were encouraged to review their treatment between visits and to make changes to the insulin dose. No algorithms were used
Mann, 1991[86]	Education programme on all aspects of diabetes management. Period of talking and working out personal targets, followed by additional training on how to monitor	Blood: BM Glycemie 20-800™ (Boehringer Mannheim), Glucochek™ meter Urine: Clinitest (Ames)	Education and twice daily monitoring (before meals and at bedtime), twice weekly. Patients were told to perform extra monitoring in case of illness	Education programme and twice daily monitoring on first-voided specimens	–	Patients were given a series of algorithms and were asked to modify their insulin doses accordingly
Miller, 1983[88]	Child and parents were given an introduction to SMBG and then randomly allocated to an initial period of 5 months blood or urine testing	Dextrostix	Patients advised to vary the timing of the tests every day, but always before meals. No instructions on frequency	Patients advised to test urine twice daily	None	Insulin dose and diet were changed by physicians at monthly clinic visits, using the blood profile for the previous month
Starostina, 1994[92]	The protocol followed a 5-day teaching programme (Geneva–Dusseldorf, DTTP), which included education by physicians on how to perform monitoring	Urine: DiaburTest 5000™ (Boehringer Mannheim GMBH) Haemoglukotest 20-800 (Boehringer Mannheim GmBH)	Three times daily: before main meals and bedtime	3 or 4 times daily, in second-voided specimens. Patients told to aim for no glycosuria before meals	Treated as usual without structured education programme, monitoring or instructions to modify insulin. Given only dietary advice	Patients in experimental groups were given rules for adjustment of insulin doses. Patients given individual targets to use, depending on renal threshold

continued

TABLE 23 contd *Controlled trials of self-monitoring in type 1 DM: details of interventions*

Study	Programme	Equipment	Blood regimen	Urine regimen	Control	Modification of therapy
Terent, 1985[93]	Shown how to monitor and to record results in a book	BM 1-44 Glycemie™ sticks (Boehringer Mannheim)	Tests on two days per fortnight: before breakfast, 2 hours after meals and at bedtime	Not described	3-monthly hospital clinic follow-up	Patients were encouraged to change their insulin dose to reduce preprandial values to < 7 mmol/l and postprandial values to < 10 mmol/l
Worth, 1982[89]	In a 6-month optimisation period patients managed their diabetes solely with regular urine tests. They were then allocated to one of six groups to determine the sequence of monitoring	Urine: Diastix™ (Ames) BM Glycemie 20-800 Glukochek meters	At least 2 days each week: before meals, one hour after each main meal and before bedtime. Also at times of poor control. 7-point profile required on the day before clinic reviews	Four times daily: before meals and at bedtime. 24-hour urine collection on the day before clinic reviews	None	Patients were given algorithms to adjust insulin dose, when levels suggested such a change

TABLE 24 *Excluded studies in type 1 DM: subject selection*

Study	Setting	No. of subjects	Study sample	Inclusion criteria
Belmonte, 1988[94]	Canada, diabetes clinic, children's hospital	219	Children (< 16 years)	Age < 16 years No others given
Dorchy, 1997[95]	Belgium, diabetes clinic, children's hospital	60	Children	Using a memory meter Autonomous blood monitoring
Geffner, 1983[96]	USA, paediatric diabetes clinic	53	Children (< 21 years)	None. Consecutive patients
Gill, 1986[97]	South Africa, university hospital	64	Young adults (17–27 years)	Age < 30 years
Hermansson, 1986[98]	Sweden, department of paediatrics, university hospital	32	Children (< 21 years)	None given
Kelly, 1981[99]	Ireland, regional hospital	20	Adults	Three glucose values > 10 mmol/l in the last year Regular attenders
Lam, 1986[100]	Hong Kong, SMBG clinic, university hospital	38	Type 1 and type 2 DM subjects with poor control	None given
Lombrail, 1986[101]	France, hospital diabetic clinic	282	Insulin treated subjects	All insulin treated patients seen over a 4-month period
Peveler, 1993[102]	UK, young adult clinic	113	Young adults (17–27 years)	Diabetes for ≥ 1 year Pregnant women and students were excluded
Sonsken, 1978[103]	UK, hospital department of medicine	64	Adults	Patients taught at SMBG at clinic since October 1975 to 1978
Strowig, 1998[51]	USA, university hospital	22	Adults (intensively treated)	None stated
Walford, 1978[104]	UK, general hospital	69	Adults with good and poor control or pregnancy	None stated
Wing, 1985[105]	USA, children's hospital	282	Children	None stated
Wysocki, 1992[106]	USA, children's hospital	47	Children (< 18 years)	Age 9–18 years Type 1 DM for ≥ 1 year No more than one hospitalisation No other chronic diseases
Ziegler, 1989[107]	France, university hospital	14	Adults	Type 1 DM Continuous insulin infusion
Ziegler, 1993[108]	France, university hospital	80	Adults	Conventional insulin therapy SMBG for at least 6 months Previous 5-day hospital education period

TABLE 25 *Excluded studies in type 1 DM: design and methods*

Study	Design	Intervention	Groups in study	Duration	Main measures	Drop-outs
Belmonte, 1988[94]	Single group, before and after	Introduction of SMBG	SMBG	36 months	HbA_1 FPG Serum cholesterol	96
Dorchy, 1997[95]	Single group, before and after	Introduction of memory meter	SMBG with memory meter	Variable	HbA_{1c}	–
Geffner, 1983[96]	Single group, before and after	Introduction of SMBG	SMBG	18 months	GHb Plasma glucose	0
Gill, 1986[97]	Non-equivalent group design	Introduction of SMBG and urine monitoring	SMBG Urine monitoring	4 months	HbA_1	0
Hermansson, 1986[98]	Single group, before and after	Introduction of SMBG	SMBG	36 months	HbA_1 Attitude to monitoring	0
Kelly, 1981[99]	Single group, before and after	Introduction of SMBG	SMBG	2 months	HbA_1 C-Peptide	4
Lam, 1986[100]	Non-concurrent cohort study	None	27 insulin treated patients (type 1 and 2 DM) with poor control Eleven young patients using SMBG already due to complications and poor control	15 months	HbA_1	–
Lombrail, 1986[101]	Cross-sectional	None	Blood monitoring Urine monitoring Blood and urine monitoring No self-monitoring	NA	HbA_1	–
Peveler, 1993[102]	Cross-sectional	None	Type 1 DM patients	NA	HbA_{1c} Hypoglycaemia Nocturnal polyuria Knowledge	0
Sonsken, 1978[103]	Single group, before and after	None	Pregnant patients Type 1 DM: assessment only Type 1 DM: assessment and action to improve control	–	Blood glucose readings	–
Strowig, 1998[51]	Single group, before and after	Introduction of SMBG meter with a memory function	Type 1 DM patients	24 months	GHb	0
Walford, 1978[104]	Single group, before and after	Introduction of SMBG	SMBG	241 days	Blood glucose readings	2
Wing, 1985[105]	Cross-sectional	None	Children with type 1 DM	–	HbA_1	–
Wysocki, 1992[106]	Concurrent cohort	None	SMBG	4 months	HbA_1 Fructosamine	0
Ziegler, 1989[107]	Case series	Introduction of SMBG meter with a memory function	Type 1 DM adults on continuous insulin infusion	3 weeks	Blood glucose HbA_{1c}	0
Ziegler, 1993[108]	Case series	None	Type 1 DM patients using a reflectance meter	–	HbA_{1c} Adherence Knowledge of guidelines	–

NA, not applicable

TABLE 26 *Excluded studies in type 1 DM: details of interventions and main findings*

Trial	Programme	Equipment	Blood regimen	Urine regimen	Control	Main findings
Belmonte, 1988[94]	After a 4-month initiation period, patients performed SMBG every day before meals. They also tested urine for acetone. Intensive teaching was given	Chemstrip BG Chemstrip UG 5000K	2 or 3 times daily before meals, using strips	Urine acetone on the first morning urine and for urinary glucose on a second-voided specimen at bedtime	None	The 3-year study showed a worsening of control in year 1, an improvement in year 2, but no significant change over the 3-year period
Dorchy, 1997[95]	HbA_{1c} was measured every 1 or 2 months, for three visits. Subjects were then told of the meter's recording capability. HbA_{1c} was measured on the three subsequent visits	Medisense Pen™ Sensorlink™ system	None given	NA	NA	'Cheating' reduced dramatically after the introduction of the memory meter, which also resulted in an improvement in HbA_{1c} in poorly controlled patients
Geffner, 1983[96]	Patients were taught to monitor at clinic, and converted to intensified insulin therapy. They monitored for several weeks, but then reduced monitoring frequency as dose adjustment became less of a problem	Chemstrip BG Dextrostix	SMBG twice daily (before morning and evening insulin injections) for several weeks, and then on alternate days. Also, 2 or 3 times weekly tests after a meal	NA	NA	SMBG resulted in a significant reduction in GHb over 18 months in the majority of patients
Gill, 1986[97]	Patients were taught to monitor by their GP, with accuracy checks made at each visit. SMBG patients were seen monthly and HbA_1 levels were measured every 3–4 months. Patients were already using urine testing before the trial	BM Glycaemie 20-800 Autoclix™	SMBG 3 times weekly: 5 a.m. (before breakfast) on Thursdays, 11 a.m. (before lunch) on Sundays and 5 p.m. (before dinner) on Tuesdays	Urine: morning and evening every day	NA	HbA_1 fell significantly in the SMBG group but not in the urine monitoring group
Hermansson, 1986[98]	Patients were taught to monitor blood in addition to ongoing urine testing. There was a 3-month analysis at the beginning of the SMBG programme, and then patients were followed-up after 3 years	BM 1-44 Glycemie Clinitest	Seven samples daily: before and 1–2 hours after every meal, and at bedtime Either 3 consecutive days 2 or 3 times weekly, or one full week 3 times in 3 months	Urine: 2–4 times daily	None	Most patients were positive to the introduction of tests, but SMBG did not change metabolic control. The correlation between HbA_1 and home glycosuria was as good as SMBG, and pain seemed to restrict blood monitoring
Kelly, 1981[99]	Each patient was instructed individually on SMBG. Results were recorded in a logbook and each patient was encouraged to measure glucose when necessary. After a practice session of 10 days, patients attended the clinic every 1–2 weeks	Dextrostix	4 times daily: FPG, mid-morning, mid-afternoon and late evening on 2 days a week (one working day, one resting day)	NA	NA	HbA_1 was significantly different from baseline at 2 and 4 months, but as patients became more independent of the clinic, the improvement was not sustained. 60% of monitors had glucose values of less than 10 mmol/l

NA, not applicable

continued

TABLE 26 contd *Excluded studies in type 1 DM: details of interventions and main findings*

Trial	Programme	Equipment	Blood regimen	Urine regimen	Control	Main findings
Lam, 1986[100]	One group had been referred to the clinic for training at the start of the trial, for poor control (group 1). Group 2 patients had already been trained in self-monitoring and had been practising since diagnosis. All patients were given dietary advice	BM Glycemie 20-800 Hemoglukotest	SMBG protocol: 2 hours after dinner, at bedtime and at 3 a.m. when hypoglycaemia was suspected. Day profiles were performed 3 days per week at the beginning of SMBG. Once stable, patients recorded at least one day profile a week	Urine testing was performed before breakfast and at bedtime, at least on alternate days, aiming at negative glycosuria	NA	HbA_1 decreased after 6 and 12 months in group 1. In group 2 there was a significant decrease in insulin dependence during the first 6 months of study and at 12 months, but no significant change in HbA_1 or insulin dose was noted after 12 months
Lombrail, 1986[101]	A survey of regular diabetes clinic attenders was carried out to explore patients' use of monitoring and the relationship with GHb	Not stated	At least 14 tests per week, to be performed 1.5–2 hours after meals, and if hypoglycaemia was suspected	Not stated	NA	SMBG was used by 64.5% of 282 subjects, 79% of whom also used urine testing. HbA_1 did not differ according to use of blood testing, urine testing or no testing
Peveler, 1993[102]	Observational study	None specified	Patients were advised to monitor 4 times daily, twice weekly	NA	NA	Neither frequency of blood testing or thresholds for action were significantly associated with GHb. Non-attenders did not have significantly higher GHb than attenders. Knowledge was not correlated with GHb levels
Sonksen, 1978[103]	Observational study	Dextrostix Eyetone	Monitoring tended to be before meals, and varied from patient to patient. Advocated before lunch, before evening meal and at bedtime	NA	NA	Blood glucose readings made at home improved with time in virtually all patients. There was a significant difference in blood glucose levels during the first and last 7 days of monitoring in groups 1 and 3, who used levels for altering insulin doses
Strowig, 1998[51]	Patients were taught to use the meter by a nurse practitioner who monitored their progress through regular clinic visits. Patients were also given the opportunity to consult a dietitian or mental health professional at any time	Glucometer One touch II	Patients were encouraged to check blood glucose a minimum of 4 times daily and to achieve GHb levels as close to normal as was safely possible	NA	NA	Using computer-generated analyses derived from the memory can lead to improved intensive diabetes treatment, and can significantly lower GHb
Walford, 1978[104]	Patients were taught to measure blood glucose using a reflectance meter. Where possible simultaneous urine tests were carried out. Accuracy of patient monitoring was evaluated	Reflomat Reflotest	SMBG monitored on waking up, before meals, 1 and 2 hours after meals and at bedtime	Urine monitored simultaneously with blood	NA	32 of 67 patients had profiles in which no more than one blood glucose value exceeded 10 mmol/l. Monitoring proved useful for stabilising poorly controlled patients

NA, not applicable

continued

TABLE 26 contd *Excluded studies in type 1 DM: details of interventions and main findings*

Trial	Programme	Equipment	Blood regimen	Urine regimen	Control	Main findings
Wing, 1985[105]	Patients who agreed to participate were given a questionnaire asking about their monitoring habits. Patients' responses were compared with HbA_1 levels monitored at the same clinic visit	Chemstrip BG	NA	NA	NA	HbA_{1c} levels of patients who monitored their blood most frequently did not differ from those who monitored blood less frequently or who used urine monitoring
Wysocki, 1992[106]	All participants had been trained in SMBG as routine care. Families had also been trained in using data to respond to hypoglycaemia. Patients recorded actions for 1 day, and then 28 days later. Actions were categorised as proactive or reactive	None mentioned	No general regimen recommended. Individual patient profiles	NA	NA	Most families used SMBG data, but few were proactive. Families who reported more actions were better informed, but the child's actual control was not significantly better using HbA_1
Ziegler, 1989[107]	Patients who were treated with CSII had their usual reflectance meters replaced by memory meters for 21 days. They were not told about the change of meters and continued to keep records of their SMBG in logbooks. This allowed comparison	GlucometerT + memory meter	SMBG 3 times daily	NA	NA	The number of results in the meter record was negatively correlated with HbA_{1c}, while over-reporting was positively correlated with HbA_{1c}
Ziegler, 1993[108]	The clinic recommended at least 60 readings per month. Patients' memory meters were examined, and those achieving this were deemed 'compliant'. Patients were also tested on their knowledge and ability to use algorithms for changing treatment on the basis of blood glucose results	Dextrostix Glucometer	SMBG 4 times daily: once before each meal and at bedtime. Glucose to be kept between target levels	NA	NA	Patients who adhered to the monitoring regimen had significantly lower HbA_{1c} than non-compliers. Knowledge of treatment algorithms had no effect, but patients who were able to put these into practice also had lower HbA_{1c} than those who could not use them

NA, not applicable

TABLE 27 *Controlled trials of SMBG in type 1 DM: results*

Study	Design	Comparison	GHb	Blood glucose	Weight	Other outcomes
Carney, 1983[91]	Controlled trial	B vs. U	Lower GHb with monitoring	–	–	–
Daneman, 1985[90]	RCT crossover	B + U vs. U	ND	ND	–	–
Gordon, 1991[87]	RCT crossover	B, different frequencies	ND	ND	–	Fructosamine: ND
Mann, 1991[86]	RCT	B vs. U	ND	–	–	Creatinine, cholesterol or triglycerides: ND Possible decrease in hospital admissions
Miller, 1983[88]	RCT crossover	B vs. U	ND	ND	–	24-hour urine glucose: ND
Starostina, 1994[92]	Controlled trial	B + education vs. U + education vs. no monitoring/ education	Blood and urine testing: ND	–	Blood and urine testing: ND	Blood testing more expensive than urine testing
Terent, 1985[93]	Factorial trial	B vs. U + education vs. none	No effect of SMBG on HbA_1 at 18 months	–	–	–
Worth, 1982[89]	RCT crossover	B (meter or visual) vs. U	ND	ND	ND	Urinary glucose serum cholesterol, plasma urea, creatinine, dietary carbo-hydrate, insulin dose, frequency of hypo-glycaemia: ND Patients preferred blood to urine testing

B, blood glucose monitoring; U, urine glucose monitoring; ND, no difference between groups

TABLE 28 *Controlled trials of SMBG on GHb in type 1 DM: results (mean (SD or SE))*

Study	Blood testing		Urine testing	
	Before	After	Before	After
Carney, 1983[91]	11.88 (SE 0.28)	11.0 (SE 0.26)	12.04 (SE 0.31)	11.88 (SE 0.32)
Daneman, 1985[90]*				
Group 1	10.5 (SE 0.6)	10.9 (SE 0.6)	–	10.7 (SE 0.6)
Group 2	9.5 (SE 0.3)	10.1 (SE 0.4)	–	10.2 (SE 0.4)
Gordon, 1991[87]**	9.7 (1.8)	9.7 (2.0)	–	–
Mann, 1991[86]	14.1 (1.3)	14.3 (1.9)	12.7 (2.0)	12.8 (2.4)
Miller, 1983[88]*				
Group 1	11.0	10.5	–	10.5
Group 2	11.2	10.4	–	11.0
Starostina, 1994[92]	12.6 (SE 0.2)	9.2 (SE 0.2)	12.5 (SE 0.2)	9.2 (SE 0.2)
Terent, 1985[93]				
Education	12.3 (3.2)	10.2 (1.9)	11.2 (2.0)	10.2 (2.1)
No education	11.8 (1.4)	9.8 (3.0)	11.1 (2.3)	10.4 (2.1)
Worth, 1982[89]				
Visual	10.8 (1.8)	10.6 (2.1)	–	10.5 (2.0)
Meter	–	10.4 (1.9)	–	–

** Crossover trial*
*** 2 tests/day, 7 days/week*

TABLE 29 *Results of meta-analysis for GHb in children or adults with type 1 DM: blood monitoring compared with urine monitoring*

Study	Difference in GHb (%) (95% CI)	z	*p*
Assuming correlation of 0.7			
Carney, 1983[91]	–0.720 (–1.396 to –0.044)		
Mann, 1991[86]	0.100 (–0.878 to 1.078)		
Miller, 1983[88]	–0.400 (–3.950 to 3.150)		
Terent, 1985[93]			
No education	–1.300 (–3.189 to 0.589)		
Education	–1.100 (–2.869 to 0.669)		
Fixed effects	–0.567 (–1.073 to –0.061)	2.197	0.028
Random effects	–0.567 (–1.073 to –0.061)	2.197	0.028
Test for heterogeneity: Q = 2.919 (4 df) (p = 0.571)			
Moment-based estimate of between-studies variance: 0.000			
Assuming correlation of 0.5			
Carney, 1983[91]	–0.720 (–1.516 to 0.076)		
Mann, 1991[86]	0.100 (–1.135 to 1.335)		
Miller, 1983[88]	–0.400 (–3.950 to 3.150)		
Terent, 1985[93]			
No education	–1.300 (–3.287 to 1.087)		
Education	–1.100 (–3.717 to 1.517)		
Fixed effects	–0.584 (–1.190 to 0.023)	1.886	0.059
Random effects	–0.584 (–1.190 to 0.023)	1.886	0.059
Test for heterogeneity: Q = 1.900 (4 df) (p = 0.754)			
Moment-based estimate of between-studies variance: 0.000			

Chapter 6

Effectiveness of self-monitoring in gestational diabetes or diabetes in pregnancy

Background

Pregnancy is associated with the development of insulin resistance, especially in the third trimester, and may be complicated by the development of hyperglycaemia. The term 'gestational diabetes' (GDM) is used when diabetes is first diagnosed during pregnancy and glucose tolerance reverts to normal afterwards. The WHO recommended that the same criteria for the diagnosis of diabetes should be used in pregnant and non-pregnant women.[111] However, the WHO also recommended that impaired glucose tolerance in pregnancy (gestational impaired glucose tolerance) should be treated in the same way as diabetes.[112] In the USA, the criteria for the diagnosis of diabetes developed by O'Sullivan and Mahan were adopted by the National Diabetes Data Group. These differ from the WHO criteria and require a 100 g glucose load and a 3-hour glucose tolerance test.[11] One of the few studies comparing the two sets of criteria found that the WHO criteria had a higher sensitivity for predicting macrosomia (defined as birthweight > 4000 g).[113] Either type 1 or type 2 DM may be detected for the first time during pregnancy, and the glucose tolerance of women with GDM should be reassessed after the end of pregnancy.[112] In the UK, about 3% of pregnancies are complicated by diabetes, but in ethnic minority groups the proportion may be considerably higher.[112] GDM accounts for about 90% of cases of diabetes in pregnancy, with the remainder being accounted for by women with pre-existing type 1 or type 2 DM.

Diabetes in pregnancy carries a number of risks to the mother and baby. There is an increased incidence of macrosomia in infants of diabetic mothers. Because the fetus is large, delivery is more likely to be assisted and there is an increased risk of injury to the mother or baby.[112] There are also increased risks of metabolic abnormality (including hypoglycaemia, hypocalcaemia, hyperbilirubinaemia and polycythaemia) in the neonatal period. Women with antecedent diabetes also have an increased risk of having infants with congenital abnormalities.

For these reasons, it is generally recommended that good glucose control should be maintained for the duration of pregnancy in women with antecedent diabetes. It is recommended that management should aim for FBG values of 3.5–5.5 mmol/l and postprandial blood glucose values of 5.0–8.0 mmol/l.[114] The same goals have been advocated as for women with GDM, but there is continuing uncertainty concerning the implications of mild degrees of glucose intolerance for the mother or child.[112] In women with mild impairment of glucose tolerance not requiring insulin, management by means of diet and exercise is usually advocated.[115] However, a Cochrane Review in 1996 concluded that there was insufficient evidence available to evaluate the use of dietary therapy in pregnant women with abnormal glucose tolerance test results.[116]

Objective

To evaluate the clinical- and cost-effectiveness of self-monitoring of blood and urine glucose in women with GDM or diabetic pregnancy.

Methods

The methods used were described in chapter 2. The search yielded 11 papers for this section of the review.

Study design, statistical power and quality ratings

Details of the five RCTs included in the review are given in *Tables 31* to *33*. Six reports of case series are also discussed and details are given *Tables 34* to *36*. It was considered appropriate to discuss the case series studies because of the small number of studies identified for review with only one RCT including women with GDM.

Settings

All studies took place in either the diabetes or obstetrics and gynaecology departments of teaching hospitals.

Patient characteristics

The age range of the subjects studied was 16–45 years. Seven of the studies investigated women who had pre-existing type 1 DM. De Veciana and co-workers,[117] Goldberg and co-workers[118] and Wechter and co-workers[119] studied GDM. All the patients in the study by De Veciana and co-workers[117] had more severe GDM and were treated with insulin at the start of the trial. The patients in the studies by Wechter and co-workers[119] and Goldberg and co-workers[118] were treated with diet or insulin if required. The early study by Peacock and co-workers[120] included subjects with GDM and subjects with antecedent diabetes who were pregnant, and all but one were treated with insulin.

Studies varied with respect to gestational age at entry. Both the time of onset of GDM, and the gestational age at presentation to the clinic varied. In the studies by Stubbs and co-workers[121] and Hanson and co-workers[122] monitoring commenced at 32–36 weeks' gestation. Wechter and co-workers[119] and De Veciana and co-workers[117] introduced monitoring after identification of GDM at 24–28 weeks' gestation. Varner[123] recruited diabetic patients who were less than 20 weeks pregnant. Goldstein and co-workers[124] started monitoring with patients at different stages of pregnancy, but all were less than 30 weeks pregnant. In the two studies by Jovanovic and co-workers,[125,126] and the studies by Espersen and Klebe[127] and Goldberg and co-workers,[118] monitoring was started in the first trimester. Peacock and co-workers[120] did not give details of the gestational age at the start of monitoring.

Sample size and power

The largest study involved 153 women with GDM in the study group and a control group of 2153 non-diabetic pregnant subjects.[119] The next-largest studies contained 116[118] and 104 patients.[126] Three studies[117,122,127] involved between 60 and 100 patients. Less than 25 patients took part in the remaining four studies.[120,123–125] Studies included a range of different maternal and infant outcomes, and thus no comparable power calculations could be performed for each study.

Drop-outs

Because of the importance of maintaining good control in pregnancy, no women withdrew from the trials. Even those who were not adhering to their monitoring schedules were followed to the end of pregnancy and there were no patient losses as such.

Main measures

Metabolic control was assessed using blood glucose and GHb estimations (see *Tables 32* and *35*). A range of maternal and fetal outcomes was also evaluated. Most studies reported infant weight, either in terms of the occurrence of macrosomia or weight for gestational age. Some studies also examined complications during birth. Goldstein and co-workers[124] only examined the costs of hospital care versus home monitoring, and did not evaluate metabolic outcomes. Varner[123] also compared costs for a control group receiving normal care and a self-monitoring group.

Interventions

Regimens differed considerably with respect to testing requirements and the type of monitoring required. Goldstein and co-workers[124] required FBG and 4.00 p.m. blood glucose readings every day. Jovanovic and co-workers[125] required testing before every meal and 1 hour after food. Stubbs required patients to monitor seven times daily.[121] In the second study by Jovanovic and co-workers,[126] women were also required to monitor seven times daily, before and 1 hour after meals. Peacock and co-workers[120] required patients to monitor before and 1 hour after meals. Hanson and co-workers[122] asked patients to monitor four times daily, at 7 a.m., 9 a.m. 3 p.m. and 7 p.m. from 32 weeks' gestation until delivery. Goldberg and co-workers[118] required patients to monitor their FBG every day and, in addition, 1 hour after meals. Wechter and co-workers[119] started patients on a regimen of monitoring FBG and testing blood glucose 2 hours after meals, three to five times weekly. Once good control had been attained, this regimen was reduced to just once weekly testing. De Veciana and co-workers[117] compared two types of monitoring regimen: before- and after-meal monitoring. The preprandial monitoring regimen consisted of FBG and postprandial and bedtime readings. The postprandial regimen consisted of FBG and a measurement 1 hour after each meal.

Equipment used

Stubbs and co-workers[121] used Detrostrix (Ames), Jovanovic and co-workers[125] used Eyetone™ meters (Ames) and Wechter and co-workers[119] used the AccucheckII™ (see *Table 33*). Peacock and co-workers[120] and Hanson and co-workers[122] used Reflotest™ strips and Reflomat™ meters. Goldberg and co-workers[118] used Chemstrips BG. Patients in the study by Varner and co-workers[123] used Dextrometers™ (Ames). Four studies[117,124,126,127] did not specify the equipment used.

Use of therapy protocols

Patients in studies by Stubbs and co-workers,[121] De Veciana and co-workers,[117] Jovanovic and co-workers[125,126] and Goldberg and co-workers[18] all had their insulin dose and diet modified by medical staff, who reviewed the patients' self-monitoring results (see *Table 33*). In Varner's study,[123] self-monitoring subjects were permitted to modify their insulin dose, but only after consultation with a physician. The patients in the study by Wechter and co-workers[119] had their diet modified by staff according to their self-monitoring readings, and insulin therapy was introduced as a last resort. Four studies did not report whether therapy was changed as a result of self-monitoring. However, it did not appear that any study encouraged patients to make changes to their own therapy.

Reliability of patient monitoring

Five studies[117,119,121,122,125] did not evaluate patients' reliability at performing self-monitoring. Espersen and Klebe[127] compared self-monitoring results with results from a sample sent simultaneously to the laboratory. Goldstein and co-workers[124] reported satisfactory agreement between home-monitoring results and clinic results for fasting and 4 p.m. levels. Peacock and co-workers[120] continuously evaluated reliability throughout the trial by comparing self-monitoring results with simultaneous laboratory estimations of venous blood glucose. As a further check, some patients kept their test strips for later inspection. Jovanovic and co-workers[126] compared glucose determinations with simultaneous determinations from the laboratory using an autoanalyser, and patients only entered the study after satisfactory results were obtained. Goldberg and co-workers[118] also verified blood glucose measurements by comparing patients' strips with the reflectance meter readings obtained in the clinic. Similarly, Varner and co-workers[123] did not allow patients to enter the study until they were achieving reliable readings using their meters. Patient accuracy was tested in comparison with simultaneous samples sent to the laboratory.

Adherence to regimen

Goldberg and co-workers[118] reported that compliance with self-monitoring was greater than 90%, but did not give details of how this was measured. Peacock and co-workers[120] counted the average number of blood tests reported, but these were in the form of self-report diaries. De Veciana and co-workers[117] reported that compliance in both the experimental and the control group was similar, but no further details were given. Varner[123] inferred compliance from the fact that most patients wished to continue monitoring at the end of the study. Seven studies[119,121,122,124–127] did not report measuring patient adherence to the study protocol.

Quality ratings

The results of the quality ratings are given in *Table 30*.

Reporting

Common problems included inadequate descriptive information for subjects in the intervention or control groups, reporting of a limited range of outcomes, and inadequate reporting of statistical

TABLE 30 *Quality ratings for studies in DM in pregnancy*

Study	Reporting	External validity	Internal validity		Overall
			Bias	Selection bias	
RCTs					
Stubbs, 1980[121]	6	0	3	4	13
Goldstein, 1982[124]	3	0	0	4	7
Varner, 1983[123]	7	2	3	3	15
Hanson, 1984[122]	5	3	2	3	13
De Veciana, 1995[117]	9	0	3	4	16
Mean (SD)					**12.8 (3.5)**
Case series					
Peacock, 1979[120]	5	0	3	0	8
Jovanovic, 1980[125]	7	0	2	1	10
Jovanovic, 1981[126]	6	1	2	2	11
Espersen, 1985[127]	5	0	1	0	6
Goldberg, 1986[118]	7	1	4	1	13
Wechter, 1991[119]	6	1	4	2	13
Mean (SD)					**10.2 (2.8)**

methods and results. Hypotheses or aims were less clearly set out in these papers than in those selected for the reviews of type 1 and type 2 DM.

External validity

Nearly all studies were conducted in a clinic or department that was attached to a medical school or academic institution. One study was set in a series of hospitals in one district of Sweden. This was the only study that gained marks for external validity.

Internal validity

None of the studies were able to blind subjects due to the nature of the intervention. Almost all studies used some form of *post hoc* analysis, but this was partly the result of poorly formulated hypotheses, which did not stipulate how the study would be analysed. Compliance or adherence to the monitoring regimen was rarely adequately described in these papers.

Internal validity: selection bias

Many of the studies either did not have a control group, and were of single-group design, or had non-randomised control groups from the general population or historical controls. They therefore tended to score badly on this section, which considered the adequacy of randomisation and the recruitment of study and control groups. There was rarely any adjustment made for confounding factors such as baseline characteristics or gestational age at the start of monitoring.

BOX 7 Summary of findings from RCTs

- Patients with type 1 DM managed at home with SMBG can achieve as good blood glucose control as attained in patients admitted to hospital for intensive control
- Hospital utilisation is less in subjects managed at home with SMBG
- Maternal outcomes may be as good with SMBG at home, and this approach is preferred by patients
- Fetal outcomes may be as good with SMBG at home
- None of the studies had sufficient power to detect differences in frequency of less common maternal and fetal outcomes
- In GDM, monitoring of blood glucose values after meals, rather than before, may contribute to better metabolic control and better fetal outcomes in association with the use of stringent objectives for blood glucose control

Results

The main findings of the RCTs are shown in *Table 37* and the findings from case series are shown in *Table 38* (see also *Box 7*).

Case series studies

The initial aim of the non-randomised studies was to explore the feasibility of managing pregnant women with type 1 DM at home using SMBG, rather than by means of hospital admission. This approach was applied later in the management of GDM. Peacock and co-workers[120] reported data for 25 subjects (including four with GDM) who maintained satisfactory blood glucose profiles at home using SMBG. However, in this series eight infants were above the 90th centile for weight, five had hypoglycaemia in the perinatal period and three had congenital malformations. In the study by Jovanovic and co-workers[125] of 10 women with type 1 DM, metabolic control was again satisfactory according to blood glucose profiles and records of HbA_{1c}. In this series, birthweights were normal and there were no metabolic complications affecting the newborn infants. In their larger series of 52 subjects, Jovanovic and co-workers[126] again reported satisfactory blood glucose profiles and HbA_{1c} values, normal birthweights and only one case of neonatal hypoglycaemia. Espersen and co-workers,[127] Goldberg and co-workers[118] and Wechter and co-workers[119] confirmed satisfactory metabolic control in pregnant diabetic women using self-monitoring, and they suggested that birthweights and indicators of macrosomia were more favourable in subjects using self-monitoring than in those not (see *Table 38*). Hospital utilisation was lower in women using self-monitoring.[127]

RCTs

Five RCTs were identified. Stubbs and co-workers[121] compared the effect of monitoring using either a meter or strips on blood glucose control and plasma levels of intermediary metabolites in women with type 1 DM. Goldstein and co-workers[124] compared the frequency of hospital admission during pregnancy in women with type 1 DM who performed self-monitoring and those who did not. Hanson and co-workers[122] compared the outcomes for women with either type 1 or type 2 DM who were admitted to hospital between 32 and 36 weeks of pregnancy with those of women who used SMBG at home. Varner[123] compared the control, complications and costs of care for a group of women with type 1 DM performing self-monitoring and a group being monitored at an outpatient clinic.

De Veciana and co-workers[117] compared the effect of self-monitoring either before or after meals in women with insulin-treated GDM. These trials used different interventions and measured different outcomes and could not be combined in a meta-analysis. The results of these trials are summarised in the following paragraphs.

Metabolic control

The study by Stubbs and co-workers[121] compared metabolic control for seven pregnant women with type 1 DM who were allocated to home blood glucose testing using a meter, with the results for six women who were allocated to home monitoring using test strips only. A group of non-diabetic controls was also studied. The results of the study showed that mean concentrations of blood glucose, lactate, alanine and glycerol were similar throughout the day in all three groups. Furthermore, there were no differences in metabolic profiles of the diabetic women when they were in hospital compared with when they were at home.

The study by Hanson and co-workers[122] included a larger number of women, and confirmed that there were no differences in blood glucose or HbA_{1c} concentrations between women treated in hospital or at home. Similarly, Varner[123] found no difference in HbA_{1c} between control and self-monitoring groups.

De Veciana and co-workers[117] showed that metabolic control was better for women with insulin-treated GDM who were instructed to test their blood glucose concentrations after meals rather than before. At the end of the study the mean (SD) GHb was 8.1% (2.2%) in the before-meal monitoring group and 6.5% (1.4%) in the after-meal monitoring group; this difference was statistically significant. In subsequent correspondence it was suggested that this result reflected the fact that the postprandial blood glucose target of < 7.8 mmol/l was a more stringent target than the FBG value of 3.3–5.8 mmol/l. Thus Miles and Coppack[128] suggested that the favourable outcomes observed related to the stringency of the targets used in each group rather than to the timing of monitoring *per se*.

Maternal outcomes

The small study by Goldstein and co-workers[124] included 18 women who were randomised either to conventional management or to home SMBG with a meter. Two of the nine patients using SMBG required admission to hospital compared with five of the nine subjects in the control group. This difference was not statistically significant. The authors expressed the view that women in the SMBG group preferred monitoring and felt that its use reduced their anxiety.

In the study by Hanson and co-workers[122] there was no difference in the duration of gestation for women using self-monitoring at home compared with hospital admission, nor was there any difference in the frequency of a range of maternal complications. Hospital admission was required for 10 of 54 (19%) patients in the self-monitoring group. However, the median duration of hospital care before labour was 39 days (range 1–70 days) in the hospital group compared with 20 (range 0–51) days in the self-monitoring group. This difference was statistically significant.

Varner[123] found that women who used self-monitoring were less likely to require hospital admission for the control of their diabetes than were patients who did not monitor. There was an overall difference between groups of 193 hospital-days and a substantial estimated cost saving. Varner also reported that women using self-monitoring were more enthusiastic about the management of diabetes in their pregnancy. However, this aspect was not explored formally.

Fetal outcomes

The study by Stubbs and co-workers[121] lacked statistical power. There was one infant death in the group using self-monitoring with strips, and this was attributed to sudden infant death syndrome. Goldstein and co-workers[124] reported that all women delivered healthy term babies. In the study by Hanson and co-workers[122] there was one perinatal death in each group, and no difference in the frequency of congenital malformations, respiratory disorders, hypoglycaemia or hyperbilirubinaemia between groups. Varner[123] found no difference in birthweight or perinatal outcomes between self-monitoring and control groups.

The study be De Veciana and co-workers[117] found that there were fewer Caesarean sections performed for cephalopelvic disproportion in the group performing after-meal monitoring (4 of 33 compared with 12 of 33 patients, relative risk 0.33 (0.12–0.93), $p = 0.04$). There were also fewer babies who were large for gestational age or who weighed more than 4000 g, and fewer episodes of neonatal hypoglycaemia in this group.

Discussion

More studies considered the role of SMBG in pregnant women with insulin-dependent diabetes than in women with GDM. Studies by Goldberg and co-workers[118] and Jovanovic and co-workers[125,126] suggested that SMBG by pregnant women with type 1 DM is feasible, that it can help to normalise blood glucose levels and can lead to neonatal outcomes that are similar to those achieved in non-diabetic pregnancies. Four studies[120,122,123,127] suggested that patients can be managed on an outpatient basis or with reduced hospitalisation if self-monitoring is instigated, without a detrimental effect on care or outcomes. Varner[123] and Goldstein and co-workers[124] also suggested that self-monitoring offered significant savings by reducing the costs of hospital care.

The role of self-monitoring in GDM has been less well studied, especially in patients with mild GDM who do not require insulin. Wechter and co-workers[119] included in their study women with GDM who did not require insulin. They found that women using self-monitoring gave birth to infants who were not significantly different in weight to those born to non-diabetic women. Goldberg and co-workers[118] found that patients with GDM who were introduced to self-monitoring had a lower incidence of macrosomia than did patients in a retrospective control group who had not been given the opportunity to monitor. The results of the study by Goldberg and co-workers[118] also emphasised the importance of using self-monitoring to tailor patients' management. In their study, almost 50% of patients were placed on insulin therapy as a result of their self-obtained readings. However, the studies by Goldberg and co-workers[118] and Wechter and co-workers[119] differed according to their blood glucose target levels, and in the choice of glucose levels that were considered high enough to start insulin therapy. With regard to the most effective type of monitoring, De Veciana and co-workers[117] found that monitoring postprandially was more effective at reducing the incidence of birth complications and blood glucose in GDM than was preprandial monitoring.

Methodological issues

The studies in this part of the review were not of high quality. Due to perceived ethical problems of randomising pregnant women to a control group with no self-monitoring throughout pregnancy, few studies were able to use adequate control groups. Jovanovic and co-workers[126] reported that they originally intended to include a randomised comparison but, following a number of adverse events, it was decided to terminate the control arm of the study and comparison was made with non-diabetic controls instead. Studies tended either to have no control group, to use retrospective historical controls who did not monitor, or to use non-diabetic controls. Varner's study[123] was one of the few to provide a control group, by allowing some patients to monitor at home and some to receive standard care.

There was wide variation in the type of monitoring regimen advised by different studies and in the time at which monitoring was first initiated. Some studies started monitoring as early as 8 weeks' gestation, while others began at 32 weeks. Within studies, there was also a wide variation between gestational ages in the self-monitoring groups. This confounder was not always controlled for in subsequent analysis. It is not known whether the time at which self-monitoring commences is associated with pregnancy outcomes. It might be expected that earlier tightening of metabolic control will lead to an improved fetal prognosis. However, this aspect was not addressed by any of the studies reviewed.

Very few of the papers reported checking patients' reliability at self-monitoring or their adherence to study protocols. There was a general assumption that pregnant women are particularly compliant, because of their circumstances. However, Langer and Mazze[129] found marked discrepancies between self-reported and actual blood glucose data from pregnant women with diabetes. They found that in 80% of subjects there were significant differences between the readings in memory meters and the readings noted in logbooks. In the studies located, clinics often changed therapy on the basis of self-monitoring records. If these records were not accurate, the benefits of monitoring for both mother and baby would be reduced.

There was little attention paid to psychological or social outcomes resulting from self-monitoring. The study by Goldstein and co-workers[124] suggested that monitoring empowers mothers, and that this reduced overall stress associated with the pregnancy. However, few other studies have evaluated this area systematically. If self-monitoring causes anxiety or unnecessary strain on patients who may not be used to the procedure, this could be detrimental to mother and baby. No paper evaluated the psychological effects either of self-monitoring or of reducing inpatient care for diabetic mothers. However, two studies reported that self-monitoring was well accepted by pregnant women.

Recommendations

For women with GDM, the best approach to management in pregnancy is uncertain. In fact the definition of GDM itself remains the subject of uncertainty. The WHO study group[112] pointed out that studies are needed to relate pregnancy outcomes, as well as long-term maternal and fetal outcomes, to glucose tolerance during pregnancy. Such studies are now in progress[130] and they go well beyond evaluating the importance of different monitoring methods for diabetes in pregnancy.

TABLE 31 *RCTs of self-monitoring in DM in pregnancy: design and subject selection*

Study	Setting	Design	No. of patients	Sample	Inclusion criteria
Stubbs, 1980[121]	UK, hospital	RCT	13	Type 1 DM	None stated
Goldstein, 1982[124]	USA, department of obstetrics	RCT	18	Type 1 DM	None stated
Varner, 1983[123]	USA, department of obstetrics	RCT	30	Type 1 DM	Consecutive patients from February 1980 to September 1981 from a high-risk clinic
Hanson, 1984[122]	Sweden, department of obstetrics	RCT	97	Type 1 (*n* = 83) Type 2 DM (*n* = 14)	No GDM Insulin treated
De Veciana, 1995[117]	USA, department of obstetrics	RCT	66	Insulin-treated GDM	GDM requiring insulin before 30 weeks of gestation Pregnant with singleton fetus Excluded those with previous renal failure

TABLE 32 *RCTs of self-monitoring in DM in pregnancy: interventions*

Study	Design	Intervention	Groups in study	Duration of study	Main measures
Stubbs, 1980[121]	RCT	Self-monitoring with meter vs. without meter	SMBG without meter: 4 times daily (*n* = 6) SMBG with meter: 7 times daily (*n* = 7)	Monitoring started at 32–35 weeks of gestation	Blood glucose Profile of intermediary metabolites
Goldstein, 1982[124]	RCT	SMBG	Reflectance meter (*n* = 9) Conventional (*n* = 9)	Not documented	Hospital utilisation and costs
Varner, 1983[123]	RCT	SMBG	SMBG (*n* = 15) Conventional (*n* = 15)	Monitoring started at < 20 weeks of gestation	HbA_{1c} Perinatal morbidity Costs
Hanson, 1984[122]	RCT	SMBG at home or with hospital care	SMBG (*n* = 54) Hospital care (*n* = 46)	Monitoring started between 32 and 36 weeks of gestation in both groups	Blood glucose HBA_{1c} Maternal and fetal outcomes
De Veciana, 1995[117]	RCT	SMBG either before or after meals	SMBG before meals (*n* = 33) SMBG after meals (*n* = 33)	Monitoring started after screening at 24–28 weeks of gestation	GHb Maternal and fetal outcomes

TABLE 33 *RCTs of self-monitoring in DM in pregnancy: details of interventions*

Study	Equipment	Programme	Blood regimen	Control regimen	Modification of therapy
Stubbs, 1980[121]	Detrostix™ (Ames)	Both groups monitored blood for 2 weeks, and then were routinely admitted to hospital at 36 weeks, when blood was monitored with no change to routine	7 times daily, twice weekly: before and after meals	Use of meter vs. strips	Insulin dose and diet changes made for both meter and non-meter groups by consultation with a doctor
Goldstein, 1982[124]	Reflectometer	Patients were instructed on meter use at the first clinic visit. Patients were monitored on an outpatient basis. The control group had their fasting and 4 p.m. glucose tested weekly at the clinic	None given	Patients' blood was tested weekly or more frequently at the clinic	No details given
Varner, 1983[123]	Dextrometer (Ames)	Patients were trained in meter use during a hospital admission and satisfactory performance was documented by comparison with laboratory results	Fasting and three after-meal tests daily; results reported by phone to the physician at least weekly	Patients were seen every 2 weeks and a blood sugar series recorded weekly	Insulin dose was adjusted by patients only after consulting with the doctor
Hanson, 1984[122]	Reflomat	Blood glucose was determined 4 times daily from 32 weeks until delivery. HBA_{1c} was measured at the first examination and then at 32 and 36 weeks of pregnancy. All subjects were prescribed a diet. The regimen was interrupted if hospitalisation occurred	Blood glucose determined 4 times daily: 7 a.m., 9 a.m., 3 p.m. and 7 p.m., from 32 weeks until delivery	Comparison was made with patients admitted to hospital from 32 to 36 weeks of pregnancy	No details given
De Veciana, 1995[117]	Reflectance meter, not specified	Both groups were seen at clinics once weekly. During any hospitalisations the protocol of the allotted group was followed. Diet and insulin dose were changed in both groups according to a doctor's prescription. Both groups were on recommended diets	FPG before meals and at bedtime vs. FPG after meals	Comparison was made between before- and after-meal monitoring	Insulin doses and dietary changes were recommended as necessary

TABLE 34 *Case series studies in DM in pregnancy: design and subject selection*

Study	Setting	Design	No. of patients	Sample	Inclusion criteria
Peacock, 1979[120]	UK, medical centre	Case series	25	GDM (*n* = 4) Insulin-treated diabetes (*n* = 20) Non-insulin-treated diabetes (*n* = 1)	None stated
Jovanovic, 1980[125]	USA, obstetrics clinic	Case series	10	Type 1 DM (*n* = 10)	Educational level higher than secondary
Jovanovic, 1981[126]	USA, obstetrics clinic	Case series, non-diabetic controls	104	Type 1 DM (*n* = 52) Non-diabetic controls (*n* = 52)	None stated
Espersen, 1985[127]	Denmark, department of obstetrics	Case series, historical controls	123	Type 1 DM pregnant 1979–81 (*n* = 61) Type 1 DM pregnant 1978–79 (*n* = 62)	White group A excluded
Goldberg, 1986[118]	USA, department of obstetrics	Case series, historical controls	116	GDM	Control group enrolled in prenatal clinic 1979–83 Experimental group 1983–84
Wechter, 1991[119]	USA, department of obstetrics	Case series, non-diabetic controls	153	GDM	Criteria fulfilling GDM at hospital

TABLE 35 *Case series studies of DM in pregnancy: interventions*

Study	Intervention	Groups in study	Duration	Main measures
Peacock, 1979[120]	SMBG	–	No mention of gestational age on introduction of monitoring	Blood glucose Maternal and fetal outcomes
Jovanovic, 1980[125]	SMBG	–	Monitoring started with patients < 8 weeks pregnant	HBA_{1c} Blood glucose Maternal and fetal outcomes
Jovanovic, 1981[126]	SMBG	Non-diabetic women (*n* = 52) Diabetic women (*n* = 52)	Monitoring started with patients < 12 weeks pregnant	HbA_{1c} Blood glucose Maternal and fetal outcomes
Epsersen, 1985[127]	SMBG	SMBG (*n* = 61) Non-SMBG (*n* = 62)	Monitoring started at 8–15 weeks of pregnancy	Blood glucose Birthweight
Goldberg, 1986[118]	SMBG	SMBG (n = 58) Conventional treatment (*n* = 58)	From diagnosis of GDM	Insulin therapy Blood glucose Birthweight
Wechter, 1991[119]	SMBG	GDM (*n* = 153) Non-diabetic control group (*n* = 2153)	Monitoring started at around 24–28 weeks of pregnancy	HBA_1 Birthweight

TABLE 36 *Case series studies of DM in pregnancy: details of interventions*

Study	Equipment	Programme	Blood regimen	Control regimen	Modification of therapy
Peacock, 1979[120]	Reflotest strips Reflomat meter	Patients measured blood glucose using strips/meters. No routine admissions were made unless problems occurred	SMBG before and 1 and 2 hours after main meals, and at bedtime, and occasionally at 3 a.m.	None	Visits and telephone calls with nurses or doctors allowed for changes in treatment if control was unsatisfactory
Jovanovic, 1980[125]	Eyetone	Patients underwent an evaluation, therapy, and education to test their blood and modify their diet as a result. Control was achieved by diet, SMBG and insulin. Patients continued to monitor blood as outpatients	Blood glucose monitored as outpatient before breakfast and dinner, and 1 hour before meals every day	None	Patients told to report any problems to their doctor, who modified diet and insulin
Jovanovic, 1981[126]	Not specified	Initial hospitalisation for 5–7 days to achieve normal blood glucose levels. Calculation of diet made. Patient then discharged and they attended once weekly while home monitoring	7 times daily: before and 1 hour after each meal, and once before bedtime	Non-diabetic subjects	Insulin and diet changes made during hospitalisation. No mention of changes made at home
Epsersen, 1985[127]	Reflectometer Haemoglukotest strips	No further details	Blood glucose 5 times daily	Pregnant diabetic subjects from years where no monitoring was offered	No details given
Goldberg, 1986[118]	Chemstrips BG	Control patients enrolled in the clinic between 1979 and 1983 were not offered SMBG. Patients enrolling after this time were offered SMBG and formed the experimental group	Blood glucose daily: fasting and 1 hour after meals	Same prenatal care, but without SMBG	–
Wechter, 1991[119]	AccuchekII	After identification, all patients were seen by a dietitian and instructed in an 1800–2000 calorie diet, plus instructions to test blood 5 times weekly (FPG 2 hours after meals), then at a reduced frequency	Blood glucose five times weekly: FPG and 2 hours after meals. Then reduced to once weekly if blood glucose appropriate	Non-diabetic subjects	Diet changes were made in accordance with blood glucose readings. Insulin was introduced as a last resort

TABLE 37 *RCTs of DM in pregnancy: main findings*

Study	Metabolic factors	Maternal complications	Fetal complications
Stubbs, 1980[121]	Profiles of blood glucose and intermediary metabolites similar in non-diabetic controls, meter users and non-meter users	Not stated	One case of sudden infant death Birthweight range: 2.70–4.54 kg (meter) and 2.80–4.14 kg (non-meter)
Goldstein, 1982[124]	No details provided	2 of 9 SMBG patients were admitted to hospital compared with 5 of 9 controls (average 1.3 and 3.8 hospital days, respectively). Women preferred SMBG	All women delivered healthy babies
Varner, 1983[123]	No difference in HbA_{1c} between self-monitoring and weekly venepuncture groups	Fewer hospital admissions, fewer days in hospital and lower total patient costs with SMBG	Method of delivery, weeks of gestation, birthweight, perinatal morbidity: ND
Hanson, 1984[122]	No difference in blood glucose or HbA_{1c} between home and hospital groups	10 of 54 (19%) of self-monitoring group had to be admitted to hospital. Other complications: ND	Congenital and neonatal complications: ND
De Veciana, 1995[117]	Better glycaemic control with monitoring after, rather than before, meals	Fewer Caesarean sections for cephalopelvic disproportion in women using after-meal monitoring	Lower birthweights, less often large for gestational age, and less hypoglycaemia with after-meal monitoring

ND, no difference between groups

TABLE 38 *Case series of DM in pregnancy: main findings*

Study	Metabolic factors	Maternal complications	Fetal complications
Peacock, 1979[120]	Satisfactory blood glucose control according to blood glucose profiles	12 Caesarean sections, 13 vaginal deliveries	> 90th centile in 8 of 25 cases Apgar score < 4 in 6 of 25 cases Hypoglycaemia in 5 of 25 cases Congenital malformations in 3 of 25 cases
Jovanovic, 1980[125]	Satisfactory blood glucose profiles and HbA_{1c}	No change in renal function or in fundoscopic appearances	Mean birthweight normal for gestational age No evidence of hypoglycaemia, hyperbilirubinaemia, hypocalcaemia or respiratory distress No major congenital malformations
Jovanovic, 1981[126]	Satisfactory blood glucose profiles HbA_{1c} in non-diabetic range	Two episodes of maternal hypoglycaemia requiring medical treatment	Mean Apgar score at 5 minutes: 10 No babies with body weight > 75th percentile Hpoglycaemia in 1 case No hyperbilirubinaemia or hypocalcaemia
Espersen, 1985[127]	Lower blood glucose in subjects who self-monitored	Fewer hospital admissions in the self-monitoring group	> 90th centile for weight in 12 of 61 cases (monitoring) and in 19 of 61 cases (non-monitoring)
Goldberg, 1986[118]	More subjects in self-monitoring group received insulin therapy	No significant differences in mode of delivery	Lower mean birthweight and lower incidence of macrosomia in the self-monitoring group
Wechter, 1991[119]	Diet-treated patients had similar FBG to non-diabetic pregnant subjects, but insulin-treated subjects had higher blood glucose	GDM patients had shorter pregnancies than did non-diabetic subjects	Mean birthweight, indicators of macrosomia: ND

Chapter 7

Laboratory and near-patient testing

Background

This chapter is primarily concerned with the clinical effectiveness of using laboratory GHb, fructosamine and blood glucose measurements in the assessment of glycaemic control in subjects with diabetes. A recent review by Kilpatrick[61] discussed this issue in depth and also considered the problems associated with present laboratory methods. Goldstein and co-workers[20] reviewed the subject from a North American perspective.

Before the mid-1970s routine monitoring of diabetic patients consisted of urine or blood glucose determinations performed during regular clinic visits in order to provide healthcare workers and patients with information to help control the symptoms of hyperglycaemia. The development of GHb assays allowed providers and patients to monitor not only current metabolic status, but also the quality of long-term blood glucose control. This made it possible to set long-term targets for therapy, and to see whether they were achieved.[61]

The advances made in technology have led to the development of microprocessors, which has enabled the miniaturisation of equipment. It has been possible for a greater range of laboratory testing procedures to be moved to decentralised units. Near-patient testing methods are now available for monitoring blood glucose and GHb. The subject of near-patient testing has been discussed in two previous *Health Technology Assessment* monographs in relation to near-patient testing in primary care[131] and near-patient testing in diabetes clinics.[132]

Objective

To review evidence for the clinical- and cost-effectiveness of tests for monitoring glycaemic control in healthcare and laboratory settings.

Methods

The primary literature search was performed on MEDLINE (see appendix 1) and this search yielded a total of 282 references. A search on EMBASE produced a further ten papers. Further references were identified by screening citations. Papers retrieved for this section of the review were either narrative reviews or clinical or laboratory studies that compared the reliability or validity of two or more glycaemic tests.

A search for papers on near-patient testing was performed using MEDLINE (see appendix 1). This yielded a total of 377 references from 1996–99, 185 from 1991–95, and 33 from 1985–90. Papers were chosen for their relevance in constructing a review of near-patient testing.

Glycated haemoglobin

GHb is formed when haemoglobin molecules bind glucose, a process that occurs in diabetic and non-diabetic subjects. Higher ambient blood glucose concentrations are associated with more glycation of haemoglobin. The average lifespan of red blood cells is 90–120 days. Measuring the amount of GHb in the blood provides an indicator of the patient's average blood glucose level for the last 3–4 months. Patients with diabetes have higher concentrations of glucose in their blood and thus elevated GHb levels.

HbA_{1c}

GHb occurs in several variants and can be measured using several different methods.[61] Haemoglobin A (HbA) contributes 90% of the total. Use of cation-exchange chromatography showed that HbA could be separated into at least three components: HbA_{1a}, HbA_{1b} and HbA_{1c}. These components were found to be elevated in diabetic patients.[133] Subsequent studies have found a particularly strong relationship between HbA_{1c} and fasting blood sugar levels over the preceding weeks in both diabetic and non-diabetic subjects.[13] HbA_{1c} is the most frequently measured GHb in clinical practice, but some laboratories continue to use total GHb or HbA_1 assays.

Standardisation of GHb testing

GHb testing first became available in the late 1970s. Several different GHb assay methods can be used and these are either based on charge differences between glycated and non-glycated

haemoglobin (cation-exchange chromatography and electrophoresis) or on structural characteristics of glycated groups within haemoglobin (affinity chromatography and immunoassay). HbA_{1c} is detected by cation-exchange chromatographic and electrophoretic methods. Total GHb refers to all GHb species as measured by affinity chromatographic methods.[61]

The wide range of methods available for measuring GHb means that techniques that measure different species (HbA_1 and HbA_{1c}) produce results that are not comparable. Laboratories using the same methods to measure the same species can have widely different reference ranges and give varying results with patient samples. One study[135] found an overall coefficient of variation of 20% between laboratories in the UK. A study from Scandinavia[136] found significant, and clinically important, differences between the HbA_{1c} values presented by different laboratories on the same samples of blood. It is therefore difficult to generalise GHb measurements between laboratories. Given these problems, laboratories should at a minimum provide clinicians with information about the assay method used, the non-diabetic range and the assay performance. Because GHb is used to monitor patients over a long period of time, it is important to maintain assay precision within laboratories.[137]

A number of groups have proposed alternative solutions. European guidelines[19] developed before the DCCT report recommended classifying glycaemic control by the number of SDs the subject value was from the non-diabetic mean for the particular HbA_1 or HbA_{1c} assay. However, HbA_1 assays classify patients markedly differently than do HbA_{1c} assays. One study[138] found large differences between HbA_1 and HbA_{1c} in the classification of glycaemic control in diabetic patients, and found that using European guidelines. HbA_1 measurement classified fewer patients as poorly controlled and more as well controlled in comparison with HbA_{1c}. Patients may thus appear to be less at risk of long-term complications when HbA_1 is used rather than HbA_{1c}.

A second approach is to relate local HbA_{1c} estimations to the methods used in the DCCT. This is known as the method of 'designated comparison'.[20] A recent consensus statement from a number of professional groups involved in diabetes care in the UK recommended that only HbA_{1c} should be used to monitor blood glucose control, and that the assay used should be aligned with the method used in the DCCT.[139]

The International Federation of Clinical Chemistry has organised a working party to explore the feasibility of developing a scientifically based reference system. It is investigating the production of primary reference material for HbA_{1c}, rather than comparing or calibrating equipment to a particular instrument.[137] The expectation is that the full standardisation process will not be complete until after the end of 2010.[140]

Validity of GHb testing as an indicator of blood glucose control

GHb levels vary significantly within and between individuals. A study by Kilpatrick and Maylor[141] examined the biological variation in GHb in non-diabetic subjects. This study showed that HbA_{1c} values varied markedly between subjects, but were fairly constant in the same individual over time. Kilpatrick and Maylor concluded that, even if methods of measuring GHb improve, because of the interindividual differences, patients with the same blood glucose control may give GHb values that vary by at least 1–2%. This may have implications for setting targets for individual patients to attain satisfactory glycaemic control.

Other work has evaluated intra-individual variability in GHb in diabetic subjects,[142] using patients with either stable or variable control, and samples taken over short time intervals (28 days) or longer periods of time (85 days). This study showed that for patients with stable or variable control, there was substantial intra-individual variation for GHb and this increased as the sampling interval increased. These results suggest that GHb is affected by both clinical control and sampling interval, and this also has implications for setting clinical goals and interpreting differences in serial GHb measurements.

In evaluating the use of GHb, most authors advise a degree of caution in interpreting results and setting glycaemic targets. It is important to consider the relationships between the test results, average blood glucose levels and the kinetics of GHb, as well as factors within the individual patient. Due to the interindividual and intra-individual differences in GHb, levels of GHb must be interpreted with care. There may be biological differences in the rate of glycation and red blood cell lifespan among individuals, which may alter the relationship between average blood glucose levels and GHb. In addition, individual differences in, for example, renal thresholds, may affect the ease with which patients can achieve their GHb targets. The higher the renal threshold, the higher the steady-state blood glucose, and therefore GHb,

that can be obtained. As noted above, glycation may vary between patients with similar capillary blood glucose concentrations, and glycation appears to be lower in patients with a higher body mass index.[143]

A range of clinical conditions may influence GHb levels.[61] Any condition, such as a haemolytic anaemia, that affects the turnover of red blood cells or the overall age of those cells in circulation may lower GHb levels. Other conditions such as jaundice and hyperlipidaemia may give falsely elevated HbA_1 values with some methods.[144]

Clinical effectiveness of GHb testing

There is now good evidence to support the use of GHb measurements in the assessment of glycaemic control and thus the risk of developing long-term complications of diabetes. The DCCT[14] in type 1 DM and the UKPDS[16] were large-scale, long-term randomised studies that provided conclusive evidence concerning the relationship of blood glucose control in diabetes and the risk of complications. Each trial used HbA_{1c} measurements in the assessment of blood glucose control and provided evidence of the usefulness of these assays in contributing to improved long-term blood glucose control and reducing morbidity in subjects with diabetes (*Table 39*).

A recent Danish medical technology assessment[145] systematically reviewed the clinical usefulness of GHb in diabetes care. In subjects with type 1 DM, the authors reported that HbA_{1c} values allowed clinicians to identify patients with poor glycaemic control, a task that is often impossible by using clinical judgement alone. In patients with type 2 DM the authors also reported that HbA_{1c} provided information that was otherwise unobtainable in most clinical settings in primary healthcare. It was concluded that GHb should be regarded as the most clinically appropriate test of long-term glycaemia and should be used in the routine management of adult patients with type 1 and type 2 DM. The authors cautioned that GHb testing should always be performed with appropriate regard to its limitations.

Cost-effectiveness of GHb testing

The use of GHb assays can only be evaluated as part of a package of care for subjects with diabetes. In the DCCT the annual cost of intensive therapy was estimated to be approximately US$ 4000 to 6000.[146] GHb estimations would make a minor contribution to this cost. Analyses carried out using a Monte Carlo simulation model suggested that the incremental cost of intensive therapy per year of life gained was US$ 28,661. The authors noted that treatment would also reduce morbidity and improve quality of life, and suggested that intensive therapy for type 1 DM was well within the range of cost-effectiveness that is considered to represent good value.[147] Eastman and co-workers[148] used data obtained from the DCCT to model the possible effects of intensive therapy in type 2 DM. They concluded that the incremental cost per quality-adjusted life-year would be approximately US$ 16,000. The costs of GHb estimations would be a relatively minor contribution to this figure.

These estimates must be viewed with considerable caution for several reasons. First, the DCCT used surrogate markers, rather than clinical end-points, as outcome measures. Projections of the incidence of clinical complications from the incidence of surrogate end-points, such as the development of albuminuria, are associated with considerable imprecision. Secondly, estimates of costs are highly dependent on the healthcare system in which the

TABLE 39 *Main results of the DCCT and UKPDS studies*

	DCCT[14]	UKPDS[16]
No. of subjects		
Intervention	711	2729
Control	730	1138
Duration of follow-up (years)	6.5	10
Objective	Preprandial blood glucose 3.9–6.7 mmol/l Post-prandial blood glucose < 10.0 mmol/l	FPG < 6.0 mmol/l
Percentage risk reduction (95% CI) in intensively treated group		
Retinopathy requiring photocoagulation	51 (21 to 70)	29 (4 to 47)
Clinical neuropathy	60 (38 to 74)	8 (–20 to 30)*
Microalbuminuria	39 (21 to 52)	33 (14 to 47)*
Any diabetes-related end-point	–	12 (1 to 21)

**Outcomes at 12 years*

intervention is implemented. Thirdly, results from type 1 DM are not easily generalised to type 2 DM because of the greater degree of insulin resistance in and the progressive nature of the latter condition. Despite these limitations, these data provide some indirect evidence for the cost-effectiveness of using GHb estimations to monitor blood glucose control in both type 1 and type 2 DM.

Optimal GHb testing frequency

The optimal frequency for measuring GHb has not been established.[20,149] Given the relatively slow change in GHb accompanying changes in plasma glucose, one study[20] recommended that no more than four to six GHb assays should be done each year for patients with type 1 DM, and for type 2 diabetic patients tests should be repeated approximately every 6 months.

The ADA has recommended that GHb measurements should be performed in accordance with clinical judgement. Tests should always be performed at the initial patient assessment, and then for any individual patient the frequency of further testing should depend on the treatment regimen employed and the judgement of the clinician. The ADA suggests that "in the absence of well-controlled studies that suggest a definite testing protocol, expert opinion recommends GHb testing at least twice a year in patients who are meeting treatment goals and who have stable glycaemic control and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycaemic goals".[85]

In the DCCT, determinations of GHb were conducted monthly in the intensive-treatment group and quarterly in the standard-treatment group. Although the intensive-treatment group had lower GHb values, none of the patients had access to their GHb results, and use of GHb estimations was confounded with a range of other interventions. One study[150] evaluated GHb testing in a health maintenance organisation. Less than 20% of subjects received the recommended number of tests specified by the ADA, and patients with poor control tended to have fewer tests.

In GDM, GHb may not be sufficiently sensitive to the levels of glycaemia deemed optimal to fetal well-being, but it can be used to detect large departures from these targets. GHb testing every 6 weeks has been recommended for pregnant women with type 1 DM.[151] The recommendations made in this area are based largely on the experience of those in clinical practice, with little experimental evidence to suggest an optimal testing frequency.

Near-patient GHb testing

Obtaining GHb results during the consultation has potential benefits for both patients and clinicians. Clinicians who have immediate access to indicators of a patient's long-term control can make immediate, responsive changes to therapy or diet. Such changes could be made at the initial consultation, avoiding the need for a follow-up appointment. Usually such a second appointment is necessary after the GHb determination has been returned by the central laboratory. The most important factors for technology in these settings is accuracy of results and the turnaround time from specimen collection to result reporting. There are few near-patient testing devices available that provide GHb estimations.

Ames DCA 2000™ analyser

The Ames DCA 2000 is a benchtop analyser that measures HbA_{1c} by an agglutination inhibition immunoassay using a monoclonal antibody. It enables the clinician to obtain a HbA_{1c} result in 9 minutes with 1 µl of venous or capillary blood. McGlone and co-workers[152] compared the DCA 2000 with an established laboratory method (Dako™ HbA_{1c} system) and found that the DCA 2000 and laboratory estimations of HbA_{1c} were closely correlated. Carter and co-workers[153] found that the DCA 2000 gave valid and reliable HbA_{1c} results when operated in a community setting by non-medical personnel. Guerci and co-workers[154] also compared the performance of the DCA 2000 system for HbA_{1c} measurement with that of high performance liquid chromatography (HPLC) and found that the DCA 2000 was generally reliable but tended to underestimate HbA_{1c} slightly as compared to HPLC.

Primus CLC330™ analyser

The Primus CLC330 provides an HPLC method for quantification of HbA_{1c} concentration. Phillipov and co-workers[155] conducted a comparison study between the Primus HPLC and the DCA-2000. They reported that the Primus HPLC delivered rapid HbA_{1c} results with high precision and accuracy, and that the turnaround time was considerably shorter than with any other current method. The DCA 2000 instrument was found to be more operator-demanding. The Primus also has the advantage of being able to automatically process large numbers of specimens at once. The DCA 2000 is not able to process so many specimens, which means that clinics may need several DCA 2000 machines working at one time. In

addition, the DCA 2000 has a longer assay time than the Primus HPLC and has negligible scope for connection to a laboratory information system.

Only limited data are available on the clinical effectiveness of near-patient GHb testing. Grieve and co-workers[132] conducted a controlled study of patients attending a diabetes clinic. HbA_{1c} was monitored in two groups of patients: in one group monitoring was done using a Bayer DCA 2000 before the consultation, and in the other group samples were sent to the routine laboratory. The study found that patients with poor diabetes control were significantly more likely to have a change in their management if they had access to near-patient testing rather than conventional testing. The authors suggested that clinicians may not receive test information at an optimal time for decision-making under conventional testing. Grieve and co-workers[132] found that the use of near-patient testing GHb testing resulted in higher costs per clinic visit. However, the annual costs were similar for conventional and near-patient testing, because patients receiving the latter made fewer clinic visits. They suggested that the introduction of near-patient testing for GHb reduced the number of clinic visits needed.

Near-patient testing for GHb is at an early stage of development. It can be anticipated that technical developments will make this technique more accessible and less costly. Preliminary data suggest that near-patient GHb testing in hospital diabetes clinics has practical clinical use and may contribute efficiency savings if used appropriately. The use of near-patient GHb testing in primary care has not been adequately evaluated.[131]

Glycated serum proteins

Serum proteins (mostly albumin) also undergo a process of glycation. The turnover of human serum albumin is much shorter (half-life 25 days) than that of haemoglobin (half-life 120 days), and thus the degree of glycation of serum proteins provides a similar index of glycaemia as does haemoglobin but over a shorter period of time. Measurements of total glycated serum protein and glycated serum albumin correlate well with one another, and both have been suggested as alternative methods for monitoring glycaemic control.

Fructosamine

Several methods have been defined for monitoring either total glycated serum protein or glycated serum albumin. Currently, the fructosamine assay is the most widely used technique for measuring glycated serum protein.[156]

Due to the short half-life of glycated serum protein, fructosamine only correlates with the average blood glucose levels of the previous 2–3 weeks, and can therefore be used to detect shorter or more recent fluctuations in blood glucose than can GHb. Unlike the GHb assay, a standardised fructosamine test is available, making results from different laboratories comparable. In addition, fructosamine can be measured using instruments found in most clinical biochemistry laboratories, and so results may be obtained more rapidly and at lower cost.[61]

Validity of fructosamine testing as an indicator of glycaemic control

The use of fructosamine as an indicator of metabolic control is based largely on the ability to predict GHb levels. Early cross-sectional studies showed a good correlation between fructosamine and GHb. For example, one study[157] found a correlation of 0.76 between fructosamine and HbA_{1c} in a group of diabetic patients. Another study[158] reported a good correlation between FPG, fructosamine and GHb. However, further studies suggested that fructosamine was not a good predictor of GHb[159,160] or self-monitored blood glucose levels.[161] Although fructosamine levels generally correlate well with HbA_{1c} within a population, the value of HbA_{1c} in an individual cannot be inferred with any reliability from the level of fructosamine.[162]

Standardisation of fructosamine testing

Fructosamine has also been found to be unreliable in certain circumstances, because results can be influenced by a range of chronic conditions rather than by metabolic control.[163] Whereas the HbA_{1c} concentration depends largely on the ambient glucose concentration and haemoglobin levels of patients, the concentration of fructosamine depends mainly on the concentration of glucose and albumin. Evidence from *in vitro* studies suggests that the amount of fructosamine formed is more closely related to albumin concentration than to glucose concentration. Clinical evidence also suggests that changes in serum proteins can affect the level of fructosamine.[164] The occurrence of hypoalbuminaemia in children with protein-energy malnourishment has been reported to affect fructosamine levels.[165] It has been suggested that fructosamine levels may be unreliable in diabetic subjects with renal failure, due to the increased turnover of albumin in this condition.[166] In contrast, GHb correlated well with capillary

blood glucose measurements in both patients with normal renal function and those with renal failure.[166] A further study[159] found weak correlations between fructosamine, HbA_{1c} and blood glucose in type 2 DM elderly patients, and suggested that the presence of other chronic conditions, such as liver cirrhosis and nephrotic syndrome,[61] could also influence fructosamine levels.

Currently, the issue of correcting fructosamine for serum protein concentrations is unresolved. Some authors[167] have suggested that the albumin concentration should not be used to correct fructosamine values because the albumin concentration influences its own turnover, which in turn influences the amount of glycation. Others have argued that correcting fructosamine levels is justified.[168] Hill and co-workers[169] concluded that, while in a given population a relationship between serum fructosamine and protein may be apparent, the clinical utility of routine fructosamine corrections has not been clearly established. Further studies are needed to resolve these issues.

Clinical effectiveness of fructosamine testing

Some studies have found that fructosamine responds to changes in the level of blood glucose more quickly than does GHb.[170,171] Consequently, fructosamine levels can be more easily manipulated by patients who become compliant with their regimen only a week or so before their clinic visit, while GHb is much more resistant to short-term fluctuations.[172] This could have an impact on the reliability of glycaemic control as measured by the clinician at the clinic. In addition, it has been suggested that daily variations in protein concentrations limit the clinical usefulness of fructosamine, especially in patients on haemodialysis, where variations in total-protein and albumin concentration during dialysis are common.[173] The authors found that GHb measurements correlated well before and after dialysis, whereas the fructosamine level did not, until it was corrected for total protein or albumin.

It has been argued that short-term measures of glycaemia in chronic conditions are not clinically useful. However, the responsiveness of fructosamine and its ability to detect shorter or more recent fluctuations in blood glucose make it particularly useful in the management of pregnant diabetic patients.[174,175] It has been suggested[176] that HbA_{1c} is of limited value in the third trimester in pregnant diabetic women as it is not sufficiently sensitive to changing glycaemic control to monitor the control of diabetes during pregnancy or to predict perinatal outcome. A more recent study[177] compared the utility of fructosamine to GHb in verifying the self-monitoring by pregnant diabetic patients. The authors found that in well-controlled pregnant diabetic patients both fructosamine and HbA_{1c} accurately reflected blood glucose throughout pregnancy, but fructosamine estimated blood glucose levels more precisely.

However, another recent study[178] compared fructosamine and HbA_{1c}, in order to determine which was the best index of blood glucose control during pregnancy. This study found that HbA_{1c} correlated better with mean blood glucose levels than did fructosamine. However, the authors suggested that HbA_{1c} correlated better with FBG and preprandial mean blood glucose, while fructosamine correlated better with postprandial mean blood glucose. In addition, they showed that fructosamine decreased with gestational age while HbA_{1c} did not. In conclusion, they found that both assays were useful in evaluating the self-monitoring of pregnant diabetic subjects, but that HbA_{1c} was the best predictor of mean blood glucose during pregnancy.

The effects of age on both HbA_{1c} and fructosamine were investigated in a group of non-diabetic subjects.[179] HbA_{1c} increased with age, but serum fructosamine and fasting glucose did not. Kilpatrick and co-workers[179] suggested that this may help to explain some of the discrepancies that occur when comparing patients' HbA_{1c} with their fructosamine levels. They also suggested that this fact implies the need for age-adjusted reference ranges for maintaining accurate GHb readings in diabetic patients.[179]

Cockram and co-workers[180] evaluated the acceptability of using fructosamine as a less costly alternative to HbA_{1c} in a diabetes clinic. Patients had their blood glucose, fructosamine and HbA_{1c} tested at each visit. An analysis of the correlation between the two assays and blood glucose samples taken at the clinic showed that fructosamine correlated less well with blood glucose than did HbA_{1c}. This same study also evaluated clinicians' attitudes to the two assays. For each patient, either the fructosamine or the HbA_{1c} reading was given to the clinician at the beginning of the consultation. The other result was given at the end of the clinic visit. Clinicians were then asked to comment on whether they would have changed the patient's treatment as a result of the measurement given at the end of the consultation. Fewer clinicians reported that they would have altered management

on the results of the fructosamine readings. The authors concluded that fructosamine tests can be an alternative to HbA_{1c} tests in most cases, but care should be taken to monitor patients with persistently normal fructosamine levels.

Optimal fructosamine testing frequency

According to the ADA position statement on long-term glycaemic testing,[85] "measurement of glycated serum protein, regardless of the specific assay method, should not be considered equivalent to measurement of GHb, since it only indicates glycaemic control over a short period of time. Therefore, glycated serum protein assays would have to be performed on a monthly basis to gather the same information as measured in GHb three to four times a year".

In light of the fact that patients can improve their fructosamine values by increasing compliance a week or two before seeing their doctor, caution should be taken in the interpretation of glycated serum protein measurements unless they are performed frequently. As GHb values are much more difficult to manipulate and are not so responsive to sudden changes, tests can be performed much less often. There is currently an attempt to develop home-use meters that can measure fructosamine. With the development of such products, it becomes doubly important to assess the utility and frequency of fructosamine testing.

Fasting blood glucose

Validity of FPG testing as an indicator of metabolic control

The FPG concentration has been shown to be stable from day to day in type 2 DM patients who are treated with diet alone,[181] and for this reason may be used as a measure of glycaemic control in subjects with type 2 DM.[182,183] Plasma glucose is less labile in type 2 DM patients because the levels are stabilised by residual endogenous insulin secretion. In African-Americans with type 2 DM[184] both FPG and random plasma glucose (RPG) values were significant predictors of HbA_{1c}, and these measures permitted the identification of poorly controlled type 2 DM patients with reasonable certainty. While type 2 DM patients who are receiving treatment using oral hypoglycaemic agents or insulin are also thought to be less likely to have a stable FPG level, one study[182] that compared the stability of FPG and GHb measurements over time found evidence to suggest that FPG was substantially more reliable in type 2 DM patients treated by diet or insulin than in patients with type 1 DM.

One study[185] found the value of FPG in predicting glycaemic control was limited when using fructosamine to estimate long-term control. Avignon and co-workers[186] reported that the correlation between plasma glucose and HbA_{1c} was always better for non-fasting than for fasting values. They suggest that postprandial plasma glucose rather than FPG would better reflect the overall pathophysiological processes of type 2 DM. The processes that they cite are insulin resistance, inadequately suppressed hepatic glucose output and defective insulin responses to meals. In addition, under normal circumstances, an individual is only in the fasting state during the second part of the night, whereas they are in a postprandial or postabsorptive state for the remainder of the day.

Monitoring of FPG has not been found to be as useful for patients with type 1 DM.[183] Prendergast and co-workers[187] reported that, while there are significant correlations between HbA_1 and FPG and RBG measurements in both type 1 and type 2 DM, these measurements are only sufficiently accurate to provide clinical information for type 2 DM patients. They argue that the correlation is not sufficiently high in type 1 DM patients to recommend substitution of plasma glucose for HbA_1 determinations, despite the obvious cost advantages. In combination, these reports suggest that FPG or RPG levels are more reliable as glycaemic markers in type 2 DM patients who are managed with sulphonylureas or diet alone compared with patients treated with insulin.

Clinical effectiveness of FPG testing

Several observational studies have suggested that type 2 DM patients can achieve near-normal glucose control by using FPG tests every 3 months.[188,189] The FPG can provide the clinician with an inexpensive, widely available and reliable measure of glycaemic control for type 2 DM patients not requiring insulin. It allows patients' therapy to be altered according to readings at a single clinic visit, and therefore does not require follow-up appointments. It has been suggested that, in general, HbA_{1c} should be measured regularly, in combination with FPG, to ensure optimal management of diabetes.

However, the use of FPG measurements in type 1 DM patients and type 2 DM patients treated with insulin would seem to be inappropriate and unreliable. Sindrup and co-workers[190] have suggested that FPG, postprandial glucose

and SMBG only reflect glycaemic control to a minor degree. In another study[191] it was concluded that FBG and serum fructosamine measurements cannot replace HbA_{1c} measurement for monitoring diabetic control, but are additional extras for assessing control over short and long periods of time.

Optimal FPG testing frequency

There is little consensus about the optimal frequency with which FPG should be measured. Two studies have shown that monitoring FPG every 2–4 weeks in type 2 DM patients appears to improve patient motivation.[188,189] Others have suggested that type 2 DM patients on oral hypoglycaemic agents or insulin should have their FPG measured every 2 weeks and shortly after dose adjustment.[192] Some studies suggest that, once stability of glycaemic levels has been achieved, measurement of FPG once every 3 months is sufficient to maintain control.[188,189]

In patients with diabetes who become pregnant, self-monitoring is always advocated.[100] If this is not possible, it is advised that FPG should be measured regularly by the clinician in order to check on glycaemic control. In patients with GDM, a typical regimen may include fasting and postprandial plasma glucose measurements every 1–2 weeks from diagnosis until 30 weeks of gestation, and then once or twice weekly until birth.[193,194]

Cost-effectiveness of FPG testing

The most critical question remaining is whether the measurement of glycated serum protein or FPG can provide simple and less costly alternatives to measuring GHb. The direct cost of tests obviously differ internationally, but the relative differences in cost between the three assays is fairly universal. Fructosamine and FPG assays are always much less costly to perform than are GHb estimations. Whereas FPG and fructosamine levels can be analysed fairly quickly, specialist laboratory facilities are necessary for the analysis of GHb. A Canadian review[195] cited the following prices for each test: GHb, $11.50 per test; fructosamine, $4.70 per test; and venous blood glucose, $2.70 per test. It is worth pointing out that, although fructosamine is a cheaper test to perform, clinicians are encouraged to obtain samples much more frequently than for GHb testing, because the fructosamine level is a measure of recent control. This increases the cost of fructosamine testing. Many clinicians also follow professional recommendations to implement fructosamine tests to supplement rather than replace GHb tests, largely because of uncertainty regarding the clinical utility of fructosamine tests. The ADA[85] currently recommends that fructosamine tests should not be used in isolation, as they have not yet been shown to relate to complication risks. Unfortunately, few studies have produced reliable economic appraisals. We are not aware of any published research on the effectiveness of fructosamine or FPG tests in reducing long-term diabetes complications. A paper by Gilmer and co-workers[196] suggests that HbA_{1c} tests provide useful information to providers and patients regarding both health status and future medical-care charges. A cost analysis showed that the increase in treatment charges for related complications accelerated as the HbA_{1c} values increased, and suggested that there is a benefit of keeping HbA_{1c} levels below 8%.

Recommendations

Indirect evidence from the DDCT and UKPDS suggests that GHb monitoring in type 1 and type 2 DM patients will be clinically and cost-effective. There is no evidence of the clinical-effectiveness of different testing frequencies, but 6-monthly tests in stable patients with type 2 DM and 3-monthly tests in subjects with type 1 DM or unstable type 2 DM may be reasonable. When the use of GHb assays is limited on the grounds of cost, FBG estimations will be of value in subjects with type 2 DM who are not being treated with insulin. Fructosamine and FBG and postprandial blood glucose estimations may provide additional information in pregnant women with diabetes, but no definitive evidence for the clinical- or cost-effectiveness of the former is available. Further research is needed to evaluate the clinical- and cost-effectiveness of near-patient GHb testing in diabetes clinics and in primary care.

Chapter 8

Recommendations

The publication in the 1990s of two major trials that demonstrated the clinical effectiveness of intensive therapy in both type 1 and type 2 DM should give new impetus to efforts to improve blood glucose control in people with diabetes. GDM is also an increasingly recognised problem, particularly in black and ethnic minority groups. Many of the studies reviewed for this report were not recent. Furthermore, this review cannot give decisive results because of the small sample sizes used in the trials and the limited quality of the papers reviewed. Our report identifies several areas where research and development are needed. The recommendations arising from our review have been given at the end of each chapter and are collected together here for reference.

Self-monitoring

A standard protocol for conducting and reporting evaluations of blood glucose monitoring devices should be developed.

Further work should be done to develop standard packages of proven effectiveness, to train patients in the use of self-monitoring devices and to provide them with the information needed to adjust their therapy according to self-monitoring results. These packages should form part of the overall approach to patient education in diabetes.

Self-monitoring in type 2 DM

At the present time there is insufficient evidence to support the self-monitoring recommendations made by professional and patient organisations. The studies reviewed suggest that the independent effects of self-monitoring on blood glucose control are small, and the effects on patient outcomes have not been documented adequately. RCTs should be carried out to provide a rigorous assessment of:

- the effectiveness of self-monitoring in newly presenting patients with type 2 DM
- the consequences of discontinuing self-monitoring in patients with stable type 2 DM.

Such studies would require relatively large numbers of patients. For example, if the SD of HbA_{1c} in diabetes is 1.6% and the aim is to detect a difference between groups of 0.25%, then approximately 643 patients per group are required (significance 5%, power 80%). A study of this size would require several participating centres.

Self-monitoring in type 1 DM

The use of SMBG is well established in type 1 DM and has received support from the results of the DCCT. Unconfounded studies do not provide convincing evidence for an effect of self-monitoring on blood glucose control. The question of whether SMBG is necessary for all patients might best be addressed by carrying out prospective observational studies of groups of patients with type 1 DM in order to characterise those who do not use monitoring or do not use it effectively. These groups might be the subject of future intervention studies.

Self-monitoring in diabetes in pregnancy

For women with GDM the best approach to management in pregnancy is uncertain. The definition of GDM itself remains the subject of debate. The WHO Study Group[112] pointed out that studies are needed to relate pregnancy outcomes, as well as long-term maternal and fetal outcomes, to glucose tolerance during pregnancy. Such studies go well beyond evaluating the importance of different monitoring methods.

Laboratory testing

There is evidence from RCTs that GHb assays should be used to monitor blood glucose control in both type 1 and type 2 DM patients. Indirect evidence from the DDCT and UKPDS suggests that this will be cost-effective. A standard method for estimating GHb should be adopted when it becomes available, and current work is addressing this objective. Further research is needed to evaluate the clinical- and cost-effectiveness of near-patient GHb testing both in diabetes clinics and in primary care. Fructosamine and FBG and postprandial blood glucose estimations may provide additional information in pregnant women with diabetes, but definitive information concerning the clinical effectiveness of these measures has yet to be obtained.

Trajectory of knowledge base

The development of methods of monitoring has been the subject of considerable technical innovation, but the evaluation of the clinical- and cost-effectiveness of the application of these methods has not been the subject of many recent studies. This cannot be considered to be a rapidly developing field, as evidenced by the age of the studies included in this review. *Table 40* summarises the extent to which it has been possible to achieve the objectives of this review.

TABLE 40 *Evaluation of the objectives of this review*

Objective	Outcome
To evaluate self-monitoring	Chapters 3–6
To evaluate laboratory-based and near-patient testing	Chapter 7
To evaluate a range of outcomes:	
Blood glucose control	Chapters 4–6
Patient satisfaction	Limited poor-quality information
Complications of diabetes	Some information (chapter 7)
Health-related quality of life	Limited poor-quality information
To evaluate the needs of different groups:	
Type 1 DM, type 2 DM and GDM	Chapters 4–6
Children and the elderly	Chapters 4 and 5
Ethnic group and social factors	Not addressed due to insufficient information
To synthesise results:	
Provide an evidence-based protocol	Insufficient information
Recommendations for primary research	Chapters 3–8

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Appendix 1

MEDLINE search strategy

Type 1 and 2 DM, GDM and DM in pregnancy

The keywords used were:

- diabetes mellitus (insulin-dependent or diabetes mellitus, non-insulin-dependent or pregnancy in diabetes)
- self-care
- blood glucose self-monitoring
- patient compliance
- blood glucose or hypoglycaemic agents or hyperglycaemia or urinalysis.

The MEDLINE search strategy used was as follows:

1. randomised controlled trial.pt.
2. randomised controlled trials.sh.
3. random allocation.sh.
4. double blind method.sh.
5. single blind method.sh.
6. 1 or 2 or 3 or 4 or 5
7. animal.sh.
8. human.sh.
9. 7 not (7 and 8)
10. 6 not 9
11. clinical trial.pt.
12. clinical trials.sh.
13. (clin$ adj3 trial$).ti, ab.
14. ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti, ab.
15. placebos.sh.
16. placebo$.ti, ab.
17. random.ti, ab.
18. research design.sh.
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 19 not 9
21. 20 not 10
22. comparative study.sh.
23. evaluation studies.sh.
24. follow-up studies.sh.
25. prospective studies.sh.
26. (control$ or prospectiv$ or volunteer$).ti, ab.
27. 21 or 22 or 23 or 24 or 25
28. 26 not 9
29. 28 not (10 or 21)
30. Diabetes mellitus, insulin-dependent/ or diabetes mellitus, non-insulin-dependent/ or pregnancy in diabetes/
31. 30 and (10 or 21 or 29)
32. exp Self care/
33. Blood glucose self-monitoring/ or blood glucose self monitoring.ti, ab, sh.
34. 32 or 33
35. exp patient compliance/ or patient compliance.ti, ab, sh.
36. Blood glucose/ or hypoglycemic agents/ or hyperglycemia/ or hemoglobin a, glycosylated/ or metabolic control.ti, ab, sh.
37. 31 and 34
38. 34 or 35 or 36
39. 38 and (10 or 21 or 29)
40. exp urinalysis/ or urinalysis.ti, ab, sh.
41. 38 or 40
42. 41 and (10 or 21 or 29)

Laboratory testing

The MEDLINE search strategy used was as follows:

1. Hemoglobin a, glycosylated/ or "hemoglobin a glycosylated".mp.
2. Fructosamine/ or "fructosamine".mp.
3. "HBA1".mp.
4. "HBA1C".mp.
5. "GLYCATED HEMOGLOBIN".mp.
6. "GLYCATED HAEMOGLOBIN".mp.
7. "GHB".mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. an.fs.
10. st.fs.
11. mt.fs.
12. 9 or 10 or 11
13. 12 and 8
14. Mass screening/ or "screening".mp.
15. 13 not 14
16. limit 15 to human
17. ec.fs.
18. exp "Costs and cost analysis"/
19. 17 or 18
20. 19 and 16
21. exp "sensitivity and specificity"/
22. Reproducibility of results/
23. validity.mp. [mp = title, abstract, registry number word, mesh subject heading]

24. sensitive.mp. [mp = title, abstract, registry number word, mesh subject heading]
25. 21 or 22 or 23 or 24
26. 25 and 16
27. "FPG".mp.
28. "FASTING BLOOD GLUCOSE".mp.
29. "FPG OR FBG".mp.
30. 27 or 28 or 29
31. 26 and 30
32. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 30
33. 12 and 32
34. 33 not 14
35. limit 34 to human
36. 19 and 35
37. 25 and 35
38. 37 not 26

Near-patient testing

The MEDLINE search strategy used was as follows:

1. "NEAR PATIENT TESTING".mp.
2. Near patient.tw.
3. Point-of-care systems/ or "point of care".mp.
4. Set testing.tw.
5. 1 or 2 or 3 or 4
6. Point of care.tw.
7. 5 or 6
8. Primary healthcare/ or "primary care".mp.
9. "OFFICE LABORATORY".mp.
10. exp family practice/ or "family practice".mp.
11. 9 or 10 or 11
12. 7 or 12
13. not 12

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We look forward to hearing from you.

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