CHAPTER 8

GENERAL DISCUSSION

Uriël L. Malanda
The principal aim of this thesis was to investigate effects of self-monitoring of glucose in patients with non-insulin treated type 2 diabetes. We performed a systematic review to explore the evidence base of effects of self-monitoring on glycaemic control and quality of life. Subsequently, a randomised controlled trial was performed to assess effects on diabetes-specific distress, self-efficacy and illness perceptions. Finally, a prospective cohort study was performed, to explore associations between experiencing diabetes symptoms and changes in illness beliefs in patients self-monitoring using the DiGEM cohort. In the first section, we summarize the main findings. The second section discusses methodological considerations of the studies included. In the third section, possible explanations for our results are given. The fourth section describes recent developments in self-monitoring research. Finally, suggestions for future research and implications for clinical practice are provided.

**Part 1: Main Findings**

**Self-monitoring, conclusions from a systematic review**

Effects of self-monitoring of glucose in non-insulin treated type 2 diabetes patients have been studied extensively over the past 20 years resulting in a total of 12 randomised controlled trials and 14 systematic reviews, of which 6 trials and 10 reviews have been published after 2005. All these trials and reviews primarily focused on the impact of self-monitoring of blood glucose on glycaemic control, while information on disease specific quality of life and well-being has been collected sparsely. Consequently, a best-evidence synthesis had to be used to conclude that effects of self-monitoring of blood glucose (SMBG) and urine glucose (SMUG) on general health related quality of life and well-being were not significantly beneficial (Chapter 2). Regarding the impact of self-monitoring on glycaemic control it was concluded that medium-term SMBG (between 6 and 12 months follow-up) is beneficial in lowering HbA1c in newly diagnosed patients with non-insulin treated type 2 diabetes. However, when diabetes duration is over one year, the overall glycaemic effect of SMBG is small and more likely to be present at short-term. (Chapter 2).
**Self-monitoring, effects on glycaemic control**

In **Chapter 4** it was demonstrated that short-term (4 months) and long-term (12 months) self-monitoring of glucose levels in blood or urine in combination with a standard training, guidance and a flowchart describing what actions to take in case of high or low readings did not change glycaemic control differently than in patients not monitoring. In addition, no statistically significant between group difference in change in glucose lowering medication was observed.

**Self-monitoring, effects on diabetes related distress & self-efficacy**

Self-monitoring of glucose in blood or urine did not statistically significant reduce diabetes-specific distress over a short-term (4 months) and a long-term (12 months) follow-up in moderately controlled non-insulin treated type 2 diabetes patients, compared to patients not monitoring (**Chapter 5**). In addition, self-efficacy did not seem to change differently in patients monitoring or not monitoring, and evidence for an association with onset of depression was not confirmed (**Chapter 5**).

**Self-monitoring, cost-effectiveness**

Based on the results described in **Chapter 4** and **Chapter 5** we concluded that both SMBG and SMUG would not be cost-effective for diabetes-specific distress, self-efficacy and HbA1c. Consequently, we decided not to perform an economic evaluation study.

**Self-monitoring, what lies beneath?**

The hypothesis that self-monitoring of glucose induces changes in diabetes-specific distress, self-efficacy as well as glycaemic control was not proven. (**Chapters 4 & 5**). To explore the theory underlying the effects of self-monitoring changes in illness perceptions were studied.

According to the common sense model, feedback from self-monitoring allows adaptation of illness perceptions, which, supported by adaptations of perceived social support, mediate changes in distress and self-efficacy.
However, the results showed no differences between patients self-monitoring or not (Chapter 6).

Experiencing a-symptomatic hypoglycaemia was associated with a higher self-reported personal control over diabetes in well-controlled, non-insulin treated patients with type 2 diabetes using SMBG. Furthermore, no evidence of a long-term adverse impact on health status from the experience of mild, symptomatic hypoglycaemia, in well-controlled, non-insulin treated patients with type 2 diabetes using SMBG was found (Chapter 7).

**Part 2: Methodological considerations**

The interpretation of the findings of this thesis should be done carefully and should contemplate the strengths and limitations of the studies included. Therefore, in this section several methodological considerations and decisions of the thesis are addressed in detail.

**Systematic review (Chapter 2)**

In Chapter 2 we systematically assessed the literature on whether reported effects of self-monitoring of glucose were consistent under the conditions of a well-defined research question and an explicit search strategy. Additionally, the accompanying exploration of risk of bias of included studies provided valid information on the robustness of the found effects.

The main purpose for conducting a systematic review was firstly to map the results of all trials and systematic reviews, which explored the effects of self-monitoring of glucose published after the systematic review and meta-analysis of Welschen et al. \(^2;^3\). Secondly, to add results from newly performed trials to the existing literature to resolve conflicting evidence on the effects of self-monitoring of blood glucose for non-insulin treated patients with type 2 diabetes. And finally, to develop new hypotheses on the effects of self-monitoring based on newly gained information.

Our search strategy was conform the strict Cochrane Collaboration criteria for detailed, systematic and comprehensive reviews \(^4\) and included a search for ongoing trials and unpublished studies and was therefore less sensitive to publication bias compared to other reviews \(^5;^7\). The newly identified trials all incorporated improvements in design, validity or outcome measures, as
recommended by Welschen et al. \textsuperscript{2,3} and McAndrew et al. \textsuperscript{8}. This contributed to an increased methodological quality of included trials and resulted in an overall lower risk of bias in the presented evidence.

Estimating the pooled effect of self-monitoring in clinical homogeneous subgroups only is new in self-monitoring systematic reviews. By doing so, it allowed us to make suggestions on the real effects of SMBG in subgroups of patients with similar patient characteristics and similar diabetes duration. In addition, it improved precision of SMBG induced effects based on multiple studies with similar trial characteristics. The presence of statistical heterogeneity, indicating inconsistency in found evidence, was taken into account.

Our results revealed evidence regarding the short and long-term effects of self-monitoring on glycaemic control. However, effects of self-monitoring on quality of life, well-being and patient satisfaction were underexposed, collected with different measures, not diabetes-specific or not investigated as a primary outcome. Therefore, a best evidence synthesis was the best possibility in estimating effects of self-monitoring on quality of life and well-being outcomes. Further, best evidence results on (general) quality of life and well-being factors did not address suggested associations with feelings of depression and anxiety \textsuperscript{1,9-11}.

These conclusions from the systematic review made us decide to design a randomised clinical trial primarily focused on exploration of diabetes-specific quality of life and self-efficacy in patients with type 2 diabetes treated with diet or oral hypoglycaemic agents.

**IN CONTROL-trial (CHAPTERS 3, 4, 5 & 6)**

*External validity*

Primarily Caucasians, with an age between 45 and 75 and with moderate controlled diabetes enrolled our trial. The sample of patients consisted out of slightly more male patients, was educated at a secondary level and approximately half of them enjoyed their pension. Most were controlled with at least one oral hyperglycaemic agent, and half of them with a sulphonyl-urea. The results of the study can be generalised to Caucasian moderately controlled patients with type 2 diabetes not using insulin in Western-Europe \textsuperscript{12,13}. 
Contrary to expectations most patients eligible for inclusion had easy access to a glucose meter and frequently used it. Consequently, including patients into our study was more difficult than initially thought and resulted into including 60% of the minimally aimed recruitment target. Nevertheless, 60% of the recruitment target was sufficient to make conclusions on diabetes-specific emotional distress.

**Internal validity**

The design of the IN CONTROL-trial (CHAPTER 3) has been registered in an international trial register for the unique identification of randomised controlled trials of studies designed to assess the efficacy of health-care interventions worldwide (International Standard Randomised Controlled Trial Number (ISRCTN) Register). In addition, we have published the design in an open access journal, thereby providing the opportunity to describe the trial in detail and ensuring a rapid and efficient communication of our hypotheses, a priori stated outcomes and intentions to present research findings.

**Selection & attrition bias**

Lessons learned from trials with a high risk of bias included in our review, influenced the design and ensured a solid method of sequence generation (computerized randomisation) and a proper allocation concealment performed by a research manager who was not involved in patient care or data analyses.

Our study had a small loss to follow-up after 12 months (5.5%) and an overall high response to questionnaires after 2 months (82%), 4 months (78%) and after 12 months (74%). We did notice a higher rate of patients not returning questionnaires in one of three randomisation arms (SMUG), which raised the possibility of systematic differences between groups. However, analyses of baseline characteristics of patients returning and not returning questionnaires showed this was not the case. Furthermore, despite randomisation, at baseline there were differences in levels of distress and self-efficacy between the intervention and control groups. We have accounted for this by adjusting the primary outcome analyses presented in CHAPTER 4 for baseline values. The use of imputation techniques did not change the results. Thus, the presence of attrition bias in our data is not likely.
**Performance bias**

The incorporation of the IN CONTROL-trial into an already existing care structure and the use of detailed scripts outlining topics to be covered during visits prevented co-interventions and guaranteed a similar timing of outcome assessments in all groups. Integrating the trial into existing care had benefits. As described above, offering standardised care to all participants in the trial prevented co-interventions. Furthermore, the SMBG intervention as performed in our trial was already care-as-usual \(^{14}\). Consequently, the intervention protocol, the script outlining the topics to be covered in the follow-up visits, self-monitoring instructions as well as the flow-chart were already familiar to the caregivers (GP, diabetes nurse, research nurse) from the start.

**Self-monitoring frequency**

Consensus on the self-monitoring frequency minimally needed to receive sufficient feedback from the impact of medication, diet and lifestyle on glucose levels is not available \(^{15;16;17}\). The decision to request two six-point blood glucose profiles a week was made after careful considerations \(^{15;17;18}\) and served mainly to provide sufficient feedback. The rationale for this frequency was that collecting data of glucose levels on different time-points might contribute to a better understanding of day-to-day variation in glucose levels, and thus enable recognition of patterns. The requested timing of the SMUG measurements was based on the renal threshold for urine glucose excretion \(^{19}\). Compliance with the minimal requested self-monitoring frequency was moderate and marginally changed over time. The decision not to adhere to the recommended frequency may be related to a variety of reasons \(^{20}\). Patients who find their readings most of the time in line with their expectations and experience no symptoms may be reassured and possibly feel no need to test frequently. Others may want to intermittently check concordance between the real values and the expected values, as a way of reassuring that they are doing fine and that there is no need to test frequently. However, when readings are out of range without experiencing symptoms, this may prompt patients to test less frequently or stop self-monitoring to avoid the confrontation with threatening health information and unfavourable outcomes \(^{21}\).
In addition, patients may be motivated to monitor, but not able to carry this out, due to situational factors or they simply forget to do so. In contrast, others may be very keen on knowing all there is to know about their health state leading them to test their glucose levels very frequently, thereby running the risk of reinforcing their worries and concerns related to diabetes and its management.

Allowing patients in the intervention groups to adjust their monitoring frequency to ‘one they feel comfortable with’ was intended to prevent extra distress rising from an excess in self-monitoring. We were aware that this freedom could also be a carte blanche to stop monitoring. However, we believe that if patients decide to stop monitoring they would do so, regardless of an ability to adjust the self-monitoring frequency after a period of time. In addition, compliance with the minimal requested self-monitoring frequency was similar to other SMBG trials and marginally changed over time.

**Sample size and power**
To detect (clinical) relevant changes in distress and self-efficacy we aimed at including 100 patients per trial arm. With a sample size of 300 participants and a maximum dropout of 15% we would have been ensured to have adequate statistical power ($\alpha=0.025; \beta=0.85$) to detect 10 points difference in distress and 6 points difference in self-efficacy. To ensure sufficient power in case pre-stratification by oral treatment likely to cause hypoglycaemia was necessary, it was decided to double the sample size. In addition, a total of 600 participants was expected to be more than sufficient to detect a clinically relevant decrease of 0.5% in HbA1c. The final number of included participants was smaller ($n=181$) than we minimally aimed for ($n=300$). However, a post-hoc power calculation using the actual sample-size and standard deviation of the difference as detected, indicated that our sample had at least 80% power to detect substantial changes in distress ($d=10$ points, $\alpha=0.025$), but not for self-efficacy. Whether or not there was enough power to make conclusions on the effect of self-monitoring on HbA1c is a point of discussion. As mentioned earlier, HbA1c was a secondary outcome in this study and therefore sample-size calculations were not made.
Post-hoc power calculations using the HbA1c data of the trial confirmed a lack of power for the contrast SMUG vs. control, but clarified that the study was adequately powered for the comparison of SMBG vs. control ($\alpha=0.025; \beta=0.87$).

**Diabetes Glycaemic Education and Monitoring (DiGEM) cohort study (CHAPTER 7)**

The DiGEM trial \textsuperscript{1;22;26;27} was one of the first studies that addressed critiques on internal and external validity as made by Welschen and colleagues \textsuperscript{3} and McAndrew and colleagues (2005) \textsuperscript{28}. It included a representative group of well-controlled type 2 diabetes patients, which were followed up for one-year in a primary care system in the United Kingdom. Furthermore, it made use of a standardized programme to teach patients active self-management using the information acquired from self-monitoring of blood glucose and was grounded by the Leventhal’s Common Sense Model (CSM) \textsuperscript{29;30}. The cohort study as presented in **CHAPTER 7**, therefore provided an excellent opportunity to explore associations of the long-term impact of diabetes related hypoglycaemic events on beliefs about diabetes and on health status. Even though the findings are exclusive for patients using a blood glucose meter and only mild hypoglycaemic events were reported, we are of the opinion that this study and its results provide insight into how the distressing effects of (mild) hypoglycaemia impacts the way patients manage and think about their diabetes.

**Theoretical framework**

The primary reason for underpinning all studies described in this thesis with the CSM \textsuperscript{29;30} was the self-regulatory nature of self-monitoring. Within this model patients are viewed as active problem solvers who come to understand their illness by monitoring their efforts and outcomes in managing illness related tasks. This information is then used to develop coping strategies to manage their illness.

The use of this model provided a well-thought framework for our hypotheses, helped in selecting suitable outcome measures and provided a solid base for exploration of the theory underlying effects of self-monitoring of glucose levels. We hypothesized that self-monitoring of glucose leads to an increase of patients’ perceptions of self-control over their disease, which in turn
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would motivate self-care activities, resulting in changes in biochemical and psychological outcomes. For an extensive mediation analysis of the processes underlying the IN CONTROL-trial we chose to add the social-cognitive determinants self-efficacy\(^{31}\) and belief about perceived severity of diabetes\(^{32}\) to the model. Self-efficacy, or the perceived ability to perform self-care tasks, reflects the link between the constructed cognitive and emotional representations and coping strategies\(^{33}\). Perception of severity was added because of its association with self-care behaviours\(^{32}\).

Despite of the underlying theory, no significant and clinical relevant effects were found for the effect of self-monitoring on diabetes-specific emotional distress, self-efficacy (CHAPTER 5) and HbA1c (CHAPTER 4). This might be explained by the instruments not being sensitive enough to measure change, or the presence of a floor/ceiling effect for diabetes-specific emotional distress and self-efficacy, respectively. In CHAPTER 6 we showed that self-monitoring of glucose did not change patients’ illness perceptions and perceived severity of diabetes. This can be explained by the CSM assuming that feedback from self-monitoring was not sufficient to provoke changes in illness perceptions and perception of severity, and thus not sufficient to change diabetes-specific distress, self-efficacy and Hba1c.

Part 3: Possible explanations for our results

Regulating glycaemic control in type 2 diabetes patients who do not require insulin is a complex task and is mainly influenced by the effect of prescribed glucose lowering agents. In most countries only general practitioners (GPs) are used to prescribe or modify doses and types of glucose lowering agents and not the patients themselves. Therefore, mainly the GPs knowledge of the short and long-term effects of the prescribed agents and his responsiveness to observed changes in glucose levels is responsible for influencing glycaemic control. Self-monitoring of glucose may still have an important role in this regulatory process since regular patterns in glucose levels might contribute in the decision to modify doses or type of glucose lowering agents. However, besides a high motivation for both the patient and doctor, this requires an intensive patient-doctor interaction and ongoing guiding and support in self-monitoring.
Furthermore, besides training, diabetes education, adequate cognitive abilities and personal willingness are required for a patient to understand the self-monitoring readings and know how to respond. Embedding the IN CONTROL-trial into diabetes care systems ensured that all participants received structured diabetes education according to the most recent standard of the Dutch college of General Practitioners and all intervention groups ongoing guiding and support in self-monitoring of glucose. Our trial design was primarily focused on assessing effects of self-monitoring of glucose in a general population of non-insulin treated type 2 diabetes patients. Therefore, training GPs in effects of oral glucose lowering agents and modifying prescribed doses and motivating patients to discuss their monitoring results with their GP had no specific attention. Possibly, putting more focus on the conditions needed for an adequate patient-doctor interaction when self-monitoring, can stimulate the patient’s central role in his own care, leading to satisfying appraisal, increased patient beliefs of control and ultimately resulting into decrease in diabetes-specific distress and an increase in self-efficacy.

Part 4: Recent developments

As mentioned earlier, effects of self-monitoring of glucose in non-insulin treated type 2 diabetes patients have been researched extensively and have resulted into 6 published trials and 10 reviews in the past 6 years. All trials and reviews had a primary focus on the impact of self-monitoring of glucose on glycaemic control (Chapter 2).

Over the past 15 years a change in focus in self-monitoring of glucose studies in non-insulin treated type 2 diabetes patients could be noticed. The earliest studies assessed short-term effects on HbA1c and did not provide all included groups with standardized diabetes and/or self-monitoring education. Subsequent studies explored long-term effects on HbA1c and well-being and provided standardized diabetes education for all included groups in conjunction with ongoing education and advice in self-monitoring for the intervention groups. The latest development is seen in the recent St. Carlos Study and Structured Testing Program (STeP) study. The two randomised controlled studies offered a structured SMBG based treatment regimen with a central role for patients and GPs, collaborating in interpreting and acting on
SMBG results to assess long-term effects on HbA1c and well-being \(^{39;40}\). Both studies reported significant reductions ranging from 0.3 to 0.5% in HbA1c for the intervention group, compared to control. However, it has to be noted that the St. Carlos study included newly diagnosed patients only and the STeP study was performed in a newly initiated enhanced usual care setting. Thus, their results cannot be generalized to a general population of non-insulin treated patients with type 2 diabetes. Nevertheless, their results stress that very intensive co-operating teamwork may result into adequate changes in lifestyle behaviour and glucose lowering medications, leading to improved glycaemic control in certain subgroups. More research is needed to explore whether such intensive interventions can be cost-effective.

Another development is the intention of 6 SMBG trialists \(^{11;22;23;36;38;41}\) to perform an individual patient data meta-analysis of their SMBG in non-insulin treated type 2 diabetes trials \(^{42}\). Their work might be an opportunity to identify subgroups, most likely to benefit from SMBG. Possibly, their results will deliver more precise estimates of overall effect of SMBG and may help in developing future trials.

Finally, in the same time that we conducted our trial, the STeP study \(^{40;43}\) acknowledged the importance of assessing the impact of self-monitoring on diabetes-specific quality of life and included diabetes distress as a secondary outcome. In this study no between groups differences in diabetes distress were found. In addition, differences in onset of depressive symptoms were not found. Consequently, both the present results and results from the STeP study \(^{43}\) refute possible associations of self-monitoring of glucose with increased worries and depressive symptoms.

**Part 5: Future research & implications for practice**

It seems that the evolution in self-monitoring trials has a two-folded focus. On the one hand there is an urge to discover (sub)groups of patients in which self-monitoring is beneficial, and on the other hand there is a drive to explore the most ideal setting in which beneficial effects of self-monitoring of glucose can be reflected as much as possible.
Based on the latest developments and the results described in this thesis we conclude that:

- short-term and long-term self-monitoring of glucose in moderately controlled type 2 diabetes patients does not decrease diabetes related distress or increase self-efficacy (CHAPTER 5). Since in our study baseline levels of distress were low and did not exceed threshold level, it is still unknown how patients with higher levels of distress react on self-monitoring. Therefore, research on the impact of effects of self-monitoring on distress in patients with higher levels of distress is wanted.

- regular self-monitoring of glucose in blood or urine in a setting with easy access to education and information has minimal impact on glycaemic control when not using insulin (CHAPTERS 2 & 4) and therefore does not add to a clinical relevant long-term benefit. We therefore discourage future studies to (re)investigate glycaemic benefits of self-monitoring of glucose in a population of moderately controlled non-insulin using type 2 diabetes patients.

- the regular process of self-monitoring of glucose and the actions to influence glucose levels does not provide adequate feedback to change illness beliefs (CHAPTER 6). Presumably, feedback resulting from the self-monitoring process should fit expectations to reassure or increase beliefs about control (CHAPTER 7). Future research should embed self-monitoring of glucose in a system in which patients: i) are sufficiently guided in recognizing when a reading is high or low; ii) have the ability to make changes in oral medication, diet, or exercise in response to the reading; iii) can adequately evaluate the efficacy of these self-management behaviours with a subsequent reading for effective, volitional control.
Self-monitoring of glucose is a part of every day life for a majority of non-insulin treated type 2 diabetes patients. The monitoring results are intended to adjust behaviour in order to self-regulate blood glucose levels. However, the results from this thesis show that there is no evidence that self-monitoring of glucose in blood or urine in moderately controlled type 2 diabetes patients not using insulin helps them to constructively target emotional and biochemical outcomes of their illness. Hence, we currently advise non-insulin using type 2 diabetes patients not to self-monitor glucose levels.
References


