REVIEW ARTICLE

Self-Monitoring of Blood Glucose in Diabetes Mellitus

Arguments for an Individualized Approach

Michael A. Nauck, Andrea El-Ouaghli, Irfan Vardarli

SUMMARY

Background: The utility of glucose self-monitoring in different types and stages of diabetes is controversial, as there is only sparse relevant evidence from randomized controlled clinical trials. In this analysis, the authors aim to develop individualized recommendations based on clinical needs and the available literature.

Methods: The PubMed database was searched for articles that appeared up to 30 September 2008 containing the terms "measurement," "control," "monitoring," and "hypoglycemia"; the retrieved articles were supplemented by other articles that were cited in them. A directed search was also made for the recommendations of the German, European, American, and international diabetological societies. Conclusions were then drawn about the useful modalities and extent of glucose self-monitoring on the basis of the clinical features of the major types of diabetes and the main treatment strategies for them.

Results: With the exception of intensified treatment strategies (which rely on blood-sugar regulation with insulin), only a few evidence-based recommendations can be derived from randomized clinical trials and meta-analyses. Nonetheless, a strategy for self-monitoring according to the patient's individual needs can be derived from the characteristics of therapeutic regimens: depending on the type of diabetes from which the patient suffers, the predicted number of glucometer strips required for self-monitoring will vary from almost none to roughly 400 per month.

Conclusions: The decision to use glucose self-monitoring, as well as the type and extent of self-monitoring that will be used, should be based on the individual patient's type of diabetes, treatment regimen, and clinical characteristics. Like any other type of therapeutic intervention, self-monitoring should have a well-documented, rational justification.

Key words: diabetes mellitus, blood sugar measurement, clinical research, self-monitoring, treatment

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Metabolic self-monitoring, such as urine and blood glucose self-measurement is a controversial topic. At the center of the discussions are the type, timing, and frequency of measures as well as issues of cost reimbursement. On the one hand, reliable findings from randomized clinical studies and meta-analyses are lacking. On the other hand, opinions are heavily influenced by personal experience and the individual researcher's interests and focus. For this reason, the aim of the present paper is to develop substantiated recommendations for blood glucose self-monitoring which reflect both the scientific literature and the practical needs of the major diabetes treatment regimens. Its purpose is to stimulate discussion on the topic of "sensible self-monitoring" which will give diabetes patients access to treatment based on current best practice, on the one hand, and on the other, will limit the costs for measuring devices and test strips to a reasonable amount.

Without a doubt, metabolic self-monitoring is the cornerstone of contemporary treatment of diabetes mellitus. One of the purposes of "intensified" therapy regimens is to allow rapid and effective corrections of blood sugar levels if they deviate from the set target range. If, for example, the blood sugar is too high, injection of additional rapid-acting insulin is indicated. If the blood sugar is too low, a carbohydrate snack may be effective in the short term; in the long term, reduction of insulin dosage may be necessary.

When using intensified conventional insulin therapy (ICT) for patients with type 1 or type 2 diabetes, regular self-measurement is an integral part of treatment (*Figure*) (e1, 2). Overall benefit in delay or prevention of complications has been demonstrated (1). It is less clear to what extent success is attributable to blood sugar self-monitoring and its consequences (i.e. blood sugar correction) and to what extent other properties of such treatment regimens contribute. Beyond the short-term correction of blood sugar, metabolic self-monitoring may have several other purposes (*Box 1*).

There is far greater uncertainty about the appropriate use, frequency, and pattern of metabolic self-monitoring at the expense of statutory health insurance in respect of other therapeutic regimens such as conventional insulin therapy, oral medication, a combination of bedtime insulin and oral hypoglycemic agents, or diet alone. Scientific investigations on this topic are rare, with only

Cycles through which blood sugar self-monitoring may contribute to the improvement of metabolic control

- a) Intensified conventional insulin therapy (ICT): immediate consequences: insulin dosage adjustment;
- b) Secondary adjustment: insulin dosage adjustment;
- c) Using conventional insulin therapy (CT) or oral hypoglycemic agents

few meta-analyses of studies of blood glucose self-monitoring demonstrating benefit (2, e3).

An evidence-based approach is impossible currently due to insufficient data. However, there is sufficient evidence to allow pragmatic recommendations (American Diabetes Association [3]; European Diabetes Policy Group [e1, 2]; International Diabetes Federation [e6]; Global Consensus Panel Conference [e7]). These are not, however, evidence-based guidelines based primarily on the results of randomized controlled studies, but rather consensus recommendations by the above associations (expert opinions). Of interest in this context is the ROSSO study that describes a connection between

blood glucose self-monitoring in type 2 diabetics and reduced cardiovascular complications (4).

The need for metabolic self-monitoring depends on the situation of the patient. When adjusting the dosage of insulin or oral hypoglycemic agents for the first time or changing the dosage, frequent measurements are needed for therapeutic safety. Increased self-monitoring is indicated during acute illness, fever, immobility, and surgery. These situations may require rapid treatment adjustments. In this article, however, we will not look at exceptional situations but rather consider measures that should be used routinely in self-monitoring to guarantee an acceptable long-term metabolic control.

Metabolic self-monitoring

Blood glucose self-monitoring can be carried out using urine or blood. Urinalysis strips use a color scale. Glycosuria suggests that the blood glucose has exceeded the "renal threshold" for several hours. This threshold value is about 160 to 180 mg/dL (9 to 10 mmol/L). We will not discuss the finer details of urinalysis and the limits of the method here, such as where the renal threshold for glucose is altered as during pregnancy. For this information we refer to the "Position Statement" of the International Diabetes Federation (5).

Hypoglycemia

Hypoglycemia may significantly disrupt daily routine and may be associated with acute risk. Many oral hypoglycemic agents may induce hypoglycemia. Fatal hypoglycemia has been described in connection with insulin or sulfonylureas (6, 7, 8–13). The risks of low blood sugar levels are recognized by patients in different ways. It is therefore important to always sensitize the patient to the danger associated with the prescribed drug when treatment is initiated. In principle, it must be possible to obtain certainty in various situations with the help of blood glucose measurements. It is also known that the risk of hypoglycemia in type 1 diabetics increases significantly with lower average blood glucose levels, i.e., with "better" diabetic control (14) (see *supplementary case report*).

Patients with "stable" type 2 diabetes will only use a small number of test strips. However, blood glucose self-monitoring should also be possible in this patient group as needed. The risks of hypoglycemia according to disease type and treatment are summarized in *Table 1*.

Treatment options

Intensified insulin therapy in type 1 diabetes

In the majority of patients with type 1 diabetes, the standard treatment is intensified insulin therapy (including insulin pump therapy), which is aimed at achieving a near normal metabolic state. An integral part of treatment is the immediate correction of high or low blood glucose levels by appropriate insulin dosage or the administration of additional carbohydrates. In patients with a normal diurnal rhythm and eating pattern, i.e., who eat three principal meals, insulin is usually administered before meals.

If regular insulin is injected with meals (the duration of action is about 4 to 6 hours), insulin should be administered before each of the three principal meals. This will avoid an overlap in the effects of insulin doses, and resulting hypoglycemia. While fast acting insulin analogs with a duration of action of about 2 to 4 hours are injected with meals, corrective insulin may also be given before snacks. Additional measurements are required at these times.

Additional measurements are essential if hypoglycemic symptoms occur, or before activities with a risk of hypoglycemia (i.e. before and during significant physical exertion as well as before or during driving [e15]) and before going to bed. On average, 4 to 7 blood glucose measurements per day are needed in patients receiving intensified insulin therapy (3, e16, e17). Fewer than 4 measurements per day over a long period of time are associated with a deterioration in glycemic control, as determined by HbA_{1c} (8).

Intensified insulin therapy in type 2 diabetes

Intensified insulin therapy for type 2 diabetes should be considered primarily in relatively young patients with ambitious treatment aims. Approximately 20% of patients with type 2 diabetes receive this type of treatment. The differences between this treatment for type 2 and type 1 diabetes are minimal (i.e. less elaborate long-acting insulin substitution). Blood glucose corrections with adjusted insulin dosages remain necessary but are usually less frequent due to smaller variations in blood sugar. Activities which affect blood glucose markedly such as sports or alcohol consumption induce less frequent and less pronounced blood glucose fluctuations in patients with insulin resistance, and in older patients, in whom critical challenges are rare. These patients will therefore need fewer test strips than patients with type 1 diabetes.

Conventional insulin therapy

Conventional insulin therapy should be considered primarily in patients with stable, well controlled type 2 diabetes. This is the case in about 10% of type 2 diabetics. This type of treatment is also indicated in exceptional patients with type 1 diabetes who do not meet the prerequisites for intensified insulin therapy. When using conventional therapy, a mixture of short- and long-acting insulin is administered twice daily, before breakfast and before the evening meal. With the morning injection of a higher dose, the insulin profile of the following 12 to 16 hours is thus set. Corrections of deviating blood glucose levels with additional insulin are not necessary.

The primary purpose of metabolic self-monitoring in conventional insulin therapy is to ensure that the individually set target blood glucose ranges (i.e. pre-prandial blood glucose levels of 80 to 140 mg/dL [4.4 to 7.8 mmol/L]) are achieved. This also allows for evaluation of spontaneous blood glucose fluctuations and to guide possible treatment improvements (*Figure*). Spontaneous blood glucose fluctuations are far less pronounced in type 2 than in type 1 diabetes.

BOX 1

Indications for metabolic self-monitoring

- As a measure for acute correction ("primary adjustment") if blood glucose levels are increased or decreased during intensive insulin therapy (including pump therapy); correction may be made with rapid-acting insulin (regular insulin or rapid-acting insulin analogues) or administration of carbohydrates.
- For evaluation and prevention of risks
 - Timely recognition of hypoglycemia
 - During driving or physical exertion
 - During occupational or recreational activities with the risk of injuries
 - After alcohol consumption
 - For evaluation of metabolic control as the basis for treatment changes ("secondary adjustment")
- For control of behavior with regard to diabetes (i.e. eating habits)
- For peace of mind
- Out of curiosity
- In the context of compulsive monitoring

The largest discrepancies in recommendations for metabolic self-monitoring are found in patients with type 2 diabetes who receive conventional insulin therapy. This is because widely varying conclusions can be drawn from available study results (9; e18–e20). These greatly diverging recommendations have effects on patient education. Considerable confusion is generated for patients if one clinician says that regular monitoring is a "must," while another one informs him that the costs of test strips are no longer covered by the insurance. This may be the case for type 2 diabetic patients on conventional insulin regimens.

In this case, it is recommended that blood glucose be measured about twice a week at the time of insulin injection (in the morning after fasting overnight and before the evening meal) (e20, e21). In addition, a diurnal profile of 4 blood glucose readings around every 2 to 4 weeks helps to identify any postprandial glucose spikes. If necessary, this may be complemented by urine glucose readings. Blood glucose levels read in the morning and before lunch are most sensitive to hypoglycemia. Readings before the evening meal and before bed time are best for detecting high blood glucose levels (e19). If the patient has symptoms of hypoglycemia, or in special situations such as sporting events or an acute illness, additional measurements are required as needed.

A combination of bedtime insulin and oral hypoglycemic agents

Combination therapy with oral hypoglycemic agents and a daily injection of long-acting insulin (usually before going to bed) is a well-proven treatment method for type 2 diabetics whose blood sugar control is insufficient despite a healthy life style and oral treatment. Approximately 20% of patients with type 2 diabetes are

TABLE 1

Hypoglycemic agents and risk of hypoglycemia

Diabetes type/ drug or therapy regimen	Patients with episodes of hypoglycemia		
	Patients with mild hypoglycemia (including symptomatic episodes only)* ¹ (%/year)	Patients with severe* ² hypoglycemia (%/year)	Deaths due to hypoglycemia
Type 1 diabetes			
ICT* ³	~ 100% (clinical experience)	~ 25% (18)	Up to 15% of total mortality (7)
CT* ⁴	~ 100% (clinical experience)	~ 10% (18)	Not reported
Type 2 diabetes			
Oral antidiabetic agents			
Metformin	0–10% (e34, e35)	Near 0% (36), one published case report (e37)	
Glibenclamide	~ 20% (19)	0.6–4% (19; e38)	Up to 20% after admission to hospital (20)
Glimepiride	13% (e35)	0.9–2% (e35, e38)	Not reported
Repaglinide	2–11% (21; e39)	Near 0% (e40), one published case report (e41)	Not reported
Nateglinide	0–13% (22; e42)	0–0.6% (22; e42), one published case report (e43)	Not reported
Acarbose	0–1% (e44)	Not reported	Not reported
Miglitol	0% (e45)	Not reported	Not reported
Rosiglitazone	0–4% (e46, e47)	Only in combination with sulfonylureas (e48)	Not reported
Pioglitazone	0–2.2% (e34, e49)	0% (e50)	Not reported
Combination therapy (long acting insulin and oral antidiabetic agents)			
Metformin	33–75% (10; e23, e51, e52)	About 2% (e52)	Not reported
Glimepiride	35–75% (23; e53)	0.7–2.6% (23; e53)	Not reported
Insulin therapy			
CT* ⁴	51–56% (24,25)	5.5–18.4% (24,25; e54)	
ICT* ³	93% (24)	20% (24)	Rare (e9)

*¹ Hypoglycemia that could be treated by self-therapy (intake of glucose/carbohydrates);

*² Hypoglycemia with impaired consciousness that had to be treated with help;

*³ ICT, intensified conventional (insulin) therapy (basis-bolus principle);

*⁴ CT, conventional (insulin) therapy (twice daily mixed insulin)

treated with this method. Compared with conventional insulin therapy, the therapeutic effort is smaller, and some combinations (i.e. NPH insulin and metformin) are associated with fewer instances of weight gain and hypoglycemia (10).

The success of combination therapy depends on consistent dose titration of long-acting insulin. Fasting blood sugar levels around 100 mg/dL (5.5 mmol/L) can be targeted without great risk of nightly hypoglycemia (22, 23). Therefore, the fasting blood glucose is the decisive criterion for the appropriate insulin dosage. A useful self-monitoring strategy would therefore be regular measurements of fasting blood glucose about twice a week (24, 25) and occasional determination of a blood glucose diurnal profile with postprandial levels 1 to 2 hours after breakfast, lunch, and dinner.

Treatment with oral hypoglycemic agents or with diet only

Approximately 40% of patients with type 2 diabetes are treated with oral hypoglycemic agents alone (no insulin). Approximately 10% of patients do not need any hypoglycemic agents ("life style modification," "dietary treatment"). Prescription of oral hypoglycemic agents is only meaningful if satisfactory metabolic control can be achieved. Such an achievement is essential. If medication that may induce hypoglycemia is used, occasional blood glucose measurements are useful in situations that may be associated with hypoglycemia or if symptoms occur (11). The number (%) of hypoglycemia episodes in patients treated with various oral hypoglycemic agents is listed in *Table 1*. The number of these episodes per affected patient is low (a few per year [12]). Nevertheless, the patient should be equipped with a blood glucose self-monitoring device. It is, however, controversial whether regular self-monitoring contributes to an improvement in glycemic control (13, e26–e28). Few studies suggest benefit (14, e29, e55).

There is little risk of hypoglycemia for patients not receiving drug treatment. These patients should not need blood glucose self-monitoring, and its use for them is controversial.

The authors are convinced that occasional measurements at negligible cost help ensure adequate metabolic control. Fasting and postprandial measurements are likely to be most appropriate. If monitoring is limited to HbA_{1c} levels and the levels are not within the target range, additional measurements must be made.

Diabetes during pregnancy

A distinction must be made between diabetes present before conception (predominantly type 1 but increasingly also type 2) and gestational diabetes (onset usually in the 24th to 28th week of pregnancy). Gestational diabetes occurs in about 4% to 6% of all pregnant women (e56).

Preexisting diabetes will require insulin treatment (ICT) in virtually all cases, either prior to or during pregnancy. Complications can only be avoided via excellent glycemic control. The target levels are: fasting and preprandial 60 to 90 mg/dL (3.3 to 5.0 mmol/L), 1

BOX 2

Individual patient related determinants of the frequency of metabolic self-monitoring

- Stability or instability of glycemic control (diabetes type, other individual factors)
- Initial adjustment or re-adjustment (initiation of treatment with oral hypoglycemic agents or insulin, dose increase/titration)
- Proneness to hypoglycemia
- Insufficient recognition of hypoglycemia (hypoglycemia unawareness)
- Fear of hypoglycemia and its consequences
- Occupation/leisure activities with risk of hypoglycemia
- Changing situations (irregular meals, physical stress, shift work)
- Planned or current pregnancy
- Willingness of a patient to participate in treatment (including self-monitoring)

hour postprandial <140 mg/dL (<7.8 mmol/L), 2 hours postprandial <120 mg/dL (<6.7 mmol/L) (15). For this reason, daily preprandial and postprandial blood glucose measurements are needed in such cases; even measurements during the night are sometimes appropriate. Monitoring during pregnancy is needed approximately twice as often as at other times (e30).

Gestational diabetes can often be controlled by diet alone, and is relatively stable. Blood glucose profiles every 2 to 3 days may be sufficient. If insulin therapy is needed, daily preprandial and postprandial measurements are indicated (e31–e33). In these patients, a diet appropriate for their diabetes is particularly important to prevent blood glucose peaks after meals.

New hypoglycemic agents

Medications of the new substance class incretin mimetics (i.e. exenatide and liraglutide) and dipeptidyl peptidase–4 inhibitors (DPP-4 inhibitors, i.e. sitagliptin and vildagliptin) cannot induce hypoglycemia when given alone. When administered in combination with sulfonylureas or insulin, hypoglycemia may occur. We therefore do not provide any detailed description of these drugs in *Table 1*.

Individualized self-monitoring

It is important to define individual therapy regimens and suitable self-monitoring concepts clearly. The above suggestions provide a framework for selecting useful self-monitoring regimens based on specific treatment approaches. Rigid usage is, however, unhelpful. Instead, it is necessary to define individual treatment objectives and suitable blood glucose and HbA_{1c} target levels for each patient and to record them in writing. Metabolic self-monitoring will only be meaningful if patients are familiar with the objectives and understand them completely. Patients must understand that if readings are

TABLE 2

Suggestions for self-monitoring strategies for the two diabetes types and various treatments

Diabetes type / therapy regimen	Regular blood glucose profile			Additional blood glucose measurements		Blood glucose test strip usage (per quarter)
	Frequency per day	Frequency per week	Fasting	Hypoglycemia (risk)* ¹	Particular situations* ¹	
Type 1 diabetes						
ICT or insulin pump	4–6* ²	Daily	See profile	2–10 ×/week	7–14 ×/week	484–863
During pregnancy	7–8* ³	Daily	See profile	4–20 ×/week	7–14 ×/week	785–1177
Type 2 diabetes						
ICT	4* ²	Daily	See profile	1–2 ×/week	3–7 ×/week	418–483
CT	2* ⁴ and 4* ²	2 ×/week 1 ×/2 weeks	See profile	1–2 ×/week	3–7 ×/week	130–196
Combination therapy (oral hypoglycemic agents and long-acting insulin)	4* ⁵	1 ×/2 weeks	2–3 ×/week	0–1 ×/week	1–3 ×/week	65–117
Oral hypoglycemic agents						
With risk of hypogl.	4* ⁵	1 ×/2 weeks	See profile	1–2×/week	1–5 ×/week	13–52
Without risk of hypogl.	4* ⁵	0–1 ×/2–4 weeks	See profile	–	0–2 ×/week	13–51
No drugs	–	0–1 ×/4 weeks	See profile	–	–	0–26
Gestational diabetes						
No drugs	4* ⁵	3–4 ×/week	See profile	–	1–3 ×/week	169–247
ICT	6* ⁶	Daily	See profile	1–4 ×/week	3–7 ×/week	601–692

^{*1} See Box 2;

^{*2} fasting (morning) and preprandially (with regular insulin: before major meals; with fast-acting insulin analogs: if needed, also before snacks) as well as before going to bed;

^{*3} fasting (morning), preprandially, each time 2 hours postprandially (after major meals), before going to bed and sometimes during the night;

^{*4} fasting (morning) and before the evening meal;

^{*5} fasting (morning) and 1 to 2 hours after each major meal;

^{*6} fasting (morning), preprandially and 2 hours postprandially each time;

ICT, intensified conventional therapy;

CT, conventional therapy; hypogl., hypoglycemia;

See profile means: the fasting glucose is planned as part of the blood glucose profile

frequently above or below the target range, this means that changes are needed to improve treatment. If target levels are defined explicitly, an individual self-monitoring regimen can be directly defined based on these values. This concept must include the frequency of self-monitoring measurements according to individual criteria. (Box 2). Table 2 summarizes suggestions related to frequency and type of metabolic self-monitoring for typical patient groups. These suggestions may be derived from the requirements of the respective treatment regimen, according to the method described in this article.

The results of self-monitoring measurements should always be recorded, preferably together with the treatment resulting from them (insulin dose, carbohydrate content of meals if applicable) and other factors influencing treatment (physical activity, acute illness, alcohol, hyperglycemic and hypoglycemic levels). Only by following these guidelines will the patient understand the situation as a whole, and will his recordings be available to the physician for analysis. With additional parameters such as HbA_{1c} and body weight, a decision can be made as to whether treatment should be continued unchanged or whether changes are needed. The target is not self-monitoring so much as rapid correction of diabetes therapy. Metabolic self-monitoring may be very useful in this. Unfortunately, therapy often requires intensification in patients with progressive type 2 diabetes (16, 17), and adjustment in patients with type 1 diabetes and poor glycemic control is also often necessary.

Key messages

- Blood glucose self-monitoring is meaningful if it leads to short or long term improvement of glycemic control.
- Blood glucose self-monitoring is expensive—the extent of use should be justified by the expected benefit.
- The need for blood glucose self-monitoring varies significantly depending on diabetes type, treatment, and individual patient factors.
- Both excessively frequent and infrequent blood glucose self-measurement can be problematic.
- The self-monitoring regimen should be explained explicitly to the patient and prescribed in the same way as other components of treatment.

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Conflict of interest statement

Prof. Dr. M. Nauck is the head of the "Clinical Studies of the German Diabetes Association Commission" (Kommission Klinische Studien der Deutschen Diabetesgesellschaft) that is conducting a prospective study on benefits of blood glucose self-monitoring in type 2 diabetes patients treated with conventional insulin therapy. This study is sponsored by the German Diabetes Association (Deutsche Diabetes-Gesellschaft) and Bayer Diagnostics.

Prof. Dr. M. Nauck has received lecture honoraria from companies that distribute blood glucose measurement devices and test strips (Berlin-Chemie, Lifescan, Bayer Diagnostics), and conducted studies on the measurement accuracy of devices for quick blood glucose measurement as part of his assignment (Bayer Diagnostics; Bionime, Taiwan).

Dr. El-Ouaghli and Dr. Vardarli declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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For e-references please refer to:
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Supplementary case report:
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REVIEW ARTICLE

Self-Monitoring of Blood Glucose in Diabetes Mellitus

Arguments for an Individualized Approach

Michael A. Nauck, Andrea El-Ouaghli, Irfan Vardarli

Case reports

Patient with hypoglycemia

A patient with diabetes who injects insulin ate a smaller meal than intended. While driving after the meal, he noticed beads of perspiration on his forehead and felt tremulous. He had to stop the car, check his blood sugar and correct it (with carbohydrates, for example, dextrose or fruit juice). The diabetic patient must wait until his condition improves and ensure that the blood glucose value lies in a safe range before he continues to drive.

Patient with severe hypoglycemia

In patients with severe hypoglycemia, orientation and consciousness are severely impaired due to neuroglycopenia; therefore, help from family members, caretakers or medical personnel is needed. Glucose must be injected or infused intravenously. For educated laypersons, glucagon for injection (1 mg intramuscularly or subcutaneously) is available.