Glucose monitoring revisited: *Past – Present – Future*

A SATELLITE SYMPOSIUM AT THE 18TH INTERNATIONAL DIABETES FEDERATION CONFERENCE IN PARIS ON 28TH AUGUST 2003 SUPPORTED BY AN EDUCATIONAL GRANT FROM LIFESCAN.
A SPECIAL REPORT PRODUCED IN ASSOCIATION WITH DIABETES AND PRIMARY CARE.

CONTENTS

Produced by SB Communications Group, publishers of Diabetes And Primary Care.

Sponsored by LifeScan and printed by Pensord Press.

INTRODUCTION

A satellite symposium held in association with the 2003 International Diabetes Federation (IDF) conference in Paris presented the past, present and future of blood glucose monitoring.

The symposium was chaired by Dr Wim Wientjens, newly appointed President of the IDF European Region. He explained that, as someone who has had diabetes for 52 of his 65 years, his appointment was a sign of growing patient empowerment within the ranks of diabetes care. Dr Wientjens emphasised the vital impact self-monitoring of blood glucose had had both on his own life and that of so many other people with diabetes.

Dr Wim Wientjens Symposium Chair

He introduced four speakers during the course of the symposium, each of whom examined different aspects of blood glucose monitoring: from the rationale for monitoring through to the new, exciting developments that can be expected over the next few years.

Glucose self-monitoring: why and when?

Professor Louis Monnier

Self-monitoring of blood glucose (SMBG) is an important tool for assessing and improving the quality of diabetes control in both type 1 and type 2 diabetes. According to Professor Louis Monnier from the University of Montpelier, France, the frequency and timing of glucose testing should be a compromise between an optimal and minimal regimen of SMBG, that depends both on the type of diabetes, the clinical status (stable or unstable) and the degree of diabetes control.

SMBG recommendations

The last American Diabetes Association recommendations for SMBG stated that SMBG is useful for preventing hypoglycaemia and for adjusting medications, dietary treatments and physical activities. At present, testing is recommended 3 or more times daily in patients with type 1 diabetes and in pregnant women treated with insulin. The optimal frequency and timing of SMBG is not known in type 2 diabetes but should be sufficient to facilitate reaching blood glucose targets.

'Self-monitoring of blood glucose (SMBG) is an important tool for assessing and improving the quality of diabetic control in all types of diabetes.'

The two major questions addressed by Professor Monnier were therefore:

- *Is there a common rationale for SMBG in patients with type 1 and type 2 diabetes?*
- *Consequently, is it possible to define an*

optimal and/or minimal regimen for SMBG in each type of diabetes?

The physiology of intestinal absorption of carbohydrates illustrates that meal ingestion is followed by three periods corresponding to postprandial, post-absorptive and fasting states. The basis for an appropriate regimen of SMBG might therefore be to have one time-point of monitoring included within each of these three periods.

4- to 5-point daily profile

In stable type 1 diabetic patients, it is thought that a 4- to 5-point daily profile represents an optimal regimen. This type of SMBG includes four daily glucose determinations – three before each meal and one at bedtime – and one weekly monitoring at 3.00 am.

However, this programme does not include any marker of the 'real' postprandial state. Such states should be monitored after each meal when:

- Insulin treatments are initiated.
- Profound adjustments of insulin are required.
- Rapid insulin analogues or pump treatments are used.

In this case, at least three more determinations would be needed to cover the postprandial state, leading to the use of an 8-point daily profile.

In patients with type 2 diabetes it is thought that the testing of fasting plasma glucose in combination with HbA_{1c} levels probably does not provide a full picture of diabetic control:

- HbA_{1c} levels probably reflect both fasting and postprandial glycaemia.
- HbA_{1c} levels do not provide information on hypoglycaemic episodes.
- Variations in HbA_{1c} levels occur after a delay of several weeks.

This view is supported by the recent recognition that postprandial glucose is an important contributor to HbA_{1c} levels and a major influence in moderately controlled diabetes.

Analysis of 4-point diurnal profiles has also demonstrated that mid-morning hyperglycaemia is the 'weakest link' in the metabolic control of patients with type 2 diabetes who do not use insulin. Therefore, mid-morning glucose testing should be recommended when HbA_{1c} levels are not correctly controlled.

In addition, extended post-lunch glucose concentrations at 5.00 pm have been shown to have a better sensitivity and specificity for predicting HbA_{1c} <7% than fasting glucose values. Furthermore, in most patients, the lowest glucose values of the diurnal profile are at the end of the afternoon and the 5.00 pm value is approximately equal to the glucose nadir as observed during the early period of the night. For that reason, it appears that glucose monitoring at 5.00 pm can be helpful for checking both the quality (HbA_{1c} <7%) and the safety (risk of hypoglycaemia) in patients with type 2 diabetes who do not use insulin.

Two key conclusions in type 2 diabetes

Two key conclusions in type 2 diabetes can therefore be drawn, said Professor Monnier. The first is that the minimum regimen for these patients should be one of testing at 5.00 pm; this value can serve as a global assessment for both the quality and safety of diabetes control. This should be greater than 4.4 mmol/l (80 mg/dl) for minimizing the risk of hypoglycaemia and less than 7.0 mmol/l (126 mg/dl) for ensuring the quality of diabetes control (HbA_{1c} <7%).

The second conclusion is that the maximum regimen might be limited in a patient with type 2 diabetes to 3-point testing at 8.00am (fasting state), mid-morning (postprandial state and peak value of daytime) and at 5.00pm (postabsorptive state and nadir value of daytime).

'The maximum regimen might be limited in a patient with type 2 diabetes to a 3-point testing at 8.00am, mid-morning and at 5.00pm.'

Critical success factors for glucose self-monitoring

Self-monitoring of blood glucose (SMBG) is important for achieving specific glycaemic controls. However, according to Professor Dreyer from Bethanien Hospital, Hamburg, only 40–70% of patients practise SMBG according to guidelines.

He stressed the need to address the barriers to SMBG and explained that a key function of the healthcare professional is to help patients realise that the results of such tests represent real management tools rather than being just a string of measurements.

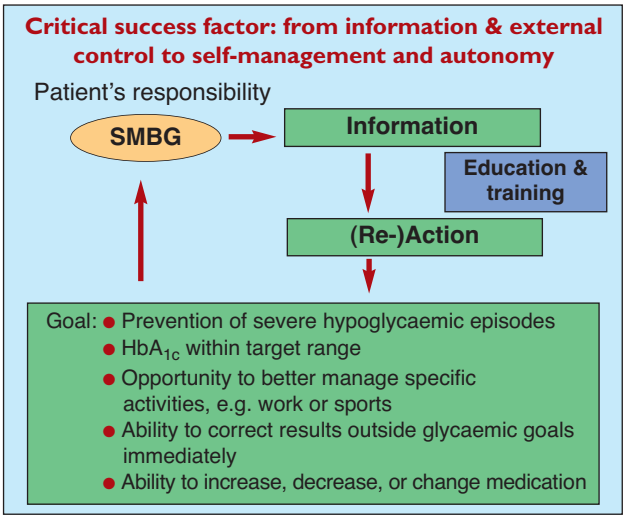
Based on appropriate training, education and advice from healthcare professionals, the patient's perception of SMBG needs to shift from a means of acquiring information and external control to becoming a vital tool for self-management and autonomy. Only then, said Professor Dreyer, can they assume their necessary position as 'captain of their diabetes ship.'

Barriers to SMBG

A study in the US showed that only 40% of patients with type 1 diabetes followed American Diabetes Association (ADA) recommendations for SMBG, i.e. 3–4 times per day. In addition, 30% tested 1–2 times per day and 30% less than once (Karter et al, 2000). For patients with type 2 diabetes, up to 60% followed ADA recommendations; the greater number may reflect the fact that the guidelines only recommend ≥ one test per day for such patients. Why do patients not perform SMBG more often?

There may be several reasons why patients fail to perform the

Professor Manfred Dreyer



recommended number of tests; these barriers are often divided into the following categories:

- *External physical, e.g. physical access or limited range of services.*
- *External psychological, e.g. unsatisfactory/inappropriate diabetes care or a lack of support.*
- *Internal psychological, e.g. health beliefs, motivation or priorities.*

In many cases, the patient's own beliefs and attitudes to their disease may constitute the greatest barrier to SMBG. It is necessary to understand where the patient is coming from: do they, for example, have particular worries about their diabetes, other health issues or the medications they are on? It will be difficult for them to move forwards if these remain unaddressed.

Behaviour change

Simply explaining the risk of late complications – often many years in the future – as a result of poor glycaemic control is not enough to change behaviour with regard to frequency of SMBG.

'The patient's perception of SMBG can shift from a means of acquiring information and external control to becoming a vital tool for self-management and autonomy.'

Many patients perform SMBG tests merely as a ritual; what they need is a reaction to this information with the help of education and training to get the opportunity to manage specific activities such as work and sports or to increase, decrease or change medication and by so doing prevent severe episodes of hypoglycaemia. The patient is thus able to self-manage their diabetes in a way that allows them to address the factors that are important to their own lives.

Different patients have different needs and should, following discussion with the healthcare professional, be allowed to select the meter that best suits them. Features that affect the selection criteria include the following:

- *Accuracy*
- *Easy handling*
- *Low blood volume*
- *Speed*
- *Pain*
- *Alternative site testing*
- *Design*

Most people agree, however, that accuracy is the most important – accuracy and the correct use of the meter should therefore be part of the quality management of the patient. It is recommended that three measurements be taken on a meter at different times in parallel with laboratory measurements. A mean of the difference in measurements of <20% is acceptable; if >20%, a re-check is required.

Involving the patient in all aspects of education and training – including SMBG techniques and the all-important accuracy issue – will increase the perceived value of these measurements as self-management tools. The most important factor though is that the patient is enabled to be the key decision-maker.

Karter et al (2000) Diabetes Care 23: 477

Options for reaching good metabolic control

Professor Geremia Bolli

Tight glycaemic control is often associated with a corresponsing increase in episodes of hypoglycaemia, explained Professor Geremia Bolli from the University of Perugia, Italy.

The DCCT and UKPDS studies have established that in both type 1 and type 2 diabetes long-term near-normoglycaemia strongly protects against the onset and/or progression of microangiopathic complications.

However, the simultaneous increase in the chance of hypoglycaemia is risky for the patient – not only because they cannot enjoy their lives but also because mild recurring episodes of hypoglycaemia can lead to loss of symptoms from hypoglycaemia through a complex mechanism of action on the brain. They also result in blunted responses of adrenalin to hypoglycaemia; a patient can therefore lose all hypoglycaemic symptoms which is of course a risk factor for the subsequent development of severe hypoglycaemia.

Thus optimum treatment strategies should aim to improve blood glucose control while avoiding the occurrence of hypoglycaemia.

To achieve this objective in type 1 diabetes, insulin therapy must mimic nature by providing a bolus of insulin at meal ingestion and by replacing basal insulin between meals and during the night. The need for mealtime insulin can be best met by subcutaneous injection of a rapid-

acting insulin analogue such as insulin lispro or aspart – these are preferred to human regular insulin because of:

- *Convenience: mealtime injection means better adaptation of insulin dose to carbohydrate content of meal.*
- *Lower blood glucose 2 hours after meals.*
- *Reduced risk of late postprandial hypoglycaemia.*

However, in patients with type 1 diabetes, the benefits of mealtime treatment with rapid-acting insulin analogues only become apparent if replacement of basal insulin is optimized at the same time. The interprandial need for basal insulin, particularly during the night, is best met by continuous subcutanaous insulin infusion (CSII) with an external minipump. CSII in the basal state is the insulin replacement of choice because it uses a rapid-acting analogue (with low variability in subcutaneous absorption and a peakless action profile).

A second option for basal insulin replacement is subcutaneous injection of the long-acting analogue insulin glargine, with its retarded action and nearly peakless action profile. Glargine is preferred to the peak preparation NPH (isophane insulin) in both type 1 and type 2 diabetes because it:

- *Reduces the risk of nocturnal hypoglycaemia.*
- *Lowers interprandial blood glucose.*
- *Reduces HbA_{1c} more than NPH if optimally combined with mealtime lispro or aspart.*

In type 2 diabetes, which is a disease primarily of the ß-cell, insulin must be initiated in an early phase possibly by-passing initial treatment with sulphonylureas. This is because:

- *Appropriate insulin treatment rescues the ß-cell by removing glucose and lipotoxicity.*
- *Insulin is better at maintaining good long-term blood glucose control.*

Insulin may be initiated by a single daily evening dose of insulin glargine and/or by mealtime rapid-acting analogues. Metformin should be added whenever possible to limit an increase in body weight. Over time, all patients with type 2 diabetes – and indeed type 1 diabetes – will require both basal and mealtime insulin substitution.

Importance of blood glucose monitoring

In terms of blood glucose measurement, checks need to be made before each insulin injection. It should also always be checked 2–3 hours after meals to assess the effects of rapid-acting insulin in patients with type 1 diabetes, and every other day in type 2. With insulin glargine or CSII, there is less need to measure the 3.00 am blood glucose compared with NPH because levels will be sufficient to limit the risk of nocturnal hypoglycaemia.

It is apparent, therefore, that in addition to rational insulin strategies, patients also need to receive appropriate education and training in why and how they should perform adequate self-monitoring of blood glucose.

'In addition to rational insulin strategies, patients also need to receive appropriate education and training in why and how they should perform adequate self-monitoring of blood glucose.'

Metabolic monitoring: a view into the future

The future of metabolic monitoring is exciting in terms of potential improvements in existing minimally invasive sensors, the development of new technologies, including non-invasive sensing, and the move from intermittent to continuous measurements, said Professor John Pickup from Guy's Hospital, London.

Current strategies have inherent problems. Three systems for *in vivo* glucose testing are presently in routine clinical use:

- *Implantable enzyme electrodes: impaired in vivo response and drift (need for mulitple calibration), better for trend than single-point accuracy, short-term use.*
- *Reverse iontophoresis: skips, skin rash, better for trend than single-point accuracy.*
- *Microdialysis: needs clinical evaluation, short-term.*

The future will see each system attempt to improve its functioning in terms of better stability, leading to fewer calibrations and enhanced accuracy.

Alternative technologies

Alternative technologies for probe-type or implanted sensors will probably enter clinical evaluation soon. Of these, fluorescence-based systems have several advantages for tissue sensing.

Truly non-invasive glucose sensing – currently not precise enough for clinical use – will further be explored over the next decade and technologies such as near-infrared spectroscopy, impedance measurement and photoacoustic spectroscopy will be optimised and interferences better defined and hopefully overcome.

Although short-term, closed loop insulin delivery has been achieved experimentally, work will continue on developing a portable system for everyday use, which has complete safety and reliability.

Further into the future, tissue engineering and nanotechnology may allow the construction of glucose-sensitive cells for implantation and interrogation.

For the moment, however, what is important is improving currently available systems while looking to develop some of the exciting new technologies being examined at present.

Professor John Pickup