Self-Monitoring of Blood Glucose in Glucagon-Like Peptide-1–Based Treatment Approaches

The role for self-monitoring of blood glucose (SMBG) in type 2 diabetes has been recommended in recent publications. The Structured Testing Program (STeP),\(^1\) the Role of Self-Monitoring of Blood Glucose and Intensive Education (ROSES) study,\(^2\) and the St. Carlos Study\(^3\) have emphasized that, to optimize its efficacy, SMBG should be implemented in a structured and standardized approach.

A prerequisite is that both people with diabetes and their health care professionals receive education about how to respond appropriately to SMBG results.\(^4,5\) Information obtained from SMBG measurement has to be used to optimize treatment. Consensus and expert panel recommendations from Europe for using SMBG in patients with type 2 diabetes\(^4–7\) will be reviewed in this article, with a particular focus on SMBG for patients treated with glucagon-like peptide-1 (GLP-1)–based approaches.

A European expert panel was recently convened to further facilitate and enhance standardized approaches to SMBG. Its aim was to provide simple, clinically meaningful, and standardized SMBG strategies for people with type 2 diabetes.\(^4\) The panel recommended less or more intensive patterns (or schemes) of SMBG across the type 2 diabetes continuum. It was recommended that the selection of the adequate scheme, as well as the lengths and frequency of testing periods, should be oriented to individual patient situations.\(^4\)

Individualized SMBG management has also been proposed in a consensus document aimed at explaining how SMBG could be used in different patient populations.\(^6\) The recommendations focused on nine clinical scenarios addressing aspects of daily clinical practice: pediatric patients with type 1 diabetes, patients with gestational diabetes, patients with type 2 diabetes with elevated postprandial blood glucose levels, patients with a lack of motivation or poor adherence, type 2 diabetes patients at risk of hypoglycemia unawareness, obese type 2 diabetes patients taking oral glucose-lowering agents, patients with type 2 diabetes and coronary artery disease who are initiating insulin, patients with type 2 diabetes and nephropathy, and elderly patients \(\geq 80\) years of age with type 2 diabetes.\(^6\)

In addition to these clinical scenarios, the potential clinical role for SMBG in GLP-1–based treatment strategies has recently been elaborated in European expert recommendations.\(^7\) GLP-1–based treatment approaches for type 2 diabetes were introduced in 2005, and their role is increasing.\(^8\) The two classes of GLP-1–based therapeutic agents currently available are GLP-1 receptor agonists (“incretin mimetics”), which imitate the actions of GLP-1, and dipeptidyl peptidase-4 (DPP-4) inhibitors, which inhibit in vivo degradation of GLP-1.\(^8,9\) The actions of GLP-1 have been shown to be glucose dependent,\(^10\) and, therefore, a low rate of hypogly-
cemic episodes has been observed. The expert European recommendations for GLP-1 treatment approaches include simple and clinically applicable SMBG schemes to be applied temporarily to evaluate glycemic control and make adjustments to treatment plans.

Using SMBG in GLP-1–Based Treatment Approaches
To support the implementation of SMBG in type 2 diabetes in a more structured and standardized approach, SMBG schemes of varying intensity across the type 2 diabetes continuum were recommended. In a further step, schemes for SMBG in GLP-1–based treatment approaches have been proposed. Potential roles for SMBG in GLP-1–based treatment approaches have been identified for five clinical scenarios:

1. Early assessment of treatment effects
2. Early modification of treatment
3. Detection of hypoglycemia
4. Assessment of glucose excursions (glycemic variability)
5. Support of diabetes management and diabetes education

Early assessment of treatment effects
To aid in tracking blood glucose and identifying possible treatment failure as early as possible, SMBG performance can identify treatment effects sooner than A1C testing. The latter reflects glucose concentrations throughout the previous 4–8 weeks, whereas the former provides day-to-day information. There is evidence that reductions in A1C observed in GLP-1–based treatment are less pronounced in patients with baseline A1C levels of 7–8%.11,12

Early modification of treatment
In type 2 diabetes, pharmacological treatment strategies to optimize glycemic control are often delayed.13 Earlier adoption of treatment strategies is recommended.13 During the treatment continuum, a hypothetical patient accumulates ~ 5 A1C-years of total burden > 8.0% and about 10 A1C-years of total burden > 7.0%.13 The STeP and St. Carlos studies emphasize that structured SMBG, which is embedded in diabetes care plans, enhances earlier treatment modifications in noninsulin-treated type 2 diabetes.2,3

Detection of hypoglycemia
SMBG may be beneficial to detect patients at risk for hypoglycemic episodes.

GLP-1–based treatment approaches are associated with very low rates of hypoglycemia in monotherapy14 and in combination therapies using noninsulin secretagogues such as metformin or thiazolidinediones. Also, the switch from twice-daily exenatide to exenatide once weekly has been reported to be accompanied by a temporary increase in fasting plasma glucose followed by a rapid decrease within 2 weeks.18

Combination treatment with insulin secretagogues such as glimepiride has been reported to be associated with higher rates of hypoglycemia, ranging from < 10 to 36%.19,20 During a 24-month follow-up of patients using exenatide plus insulin glargine (mean A1C reduction 0.7%), 11–12% of patients experienced at least one hypoglycemic episode.21 In a 52-week trial, insulin detemir as an add-on to a combination of metformin and liraglutide resulted in a reported 0.23 minor hypoglycemic events per patient-year.22

In monotherapy, low rates of minor hypoglycemic episodes (not more than 8.1% of patients experiencing hypoglycemic episodes) have been observed.23–25 No major episodes of hypoglycemia and very low rates of minor hypoglycemia have been reported in dual therapies using DPP-4 inhibitors and noninsulin secretagogues such as metformin or thiazolidinediones.26–31 Higher rates of hypoglycemia are reported in combinations with insulin secretagogues.32,33 Combined treatment with DPP-4 inhibitors (vs. placebo) and insulin seems to increase the risk of hypoglycemia.34 In patients whose diabetes is poorly controlled on high doses of insulin, the addition of vildagliptin has been observed to improve glycemic control with no severe hypoglycemia and approximately two hypoglycemic events per patient-year.35

Patients with renal impairment who are on a combination of insulin and GLP-1–based treatment may also benefit from SMBG. In these patients, higher insulin levels, which may occur secondary to reduced elimination of insulin, may have a greater need for dosage adjustment of insulin and insulin secretagogues.36,37

Assessment of glucose excursions (glycemic variability)
Glycemic variability plays a key role in the pathogenesis of vascular abnormalities.38,39 SMBG has been established as an appropriate tool to analyze glucose fluctuation.40,41 GLP-1–based treatment approaches lower post-

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<th>Table 1. Scheme 1: Less Intensive SMBG Testing in Type 2 Diabetes7</th>
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<td>This SMBG pattern focuses on paired meal testing (pre- and postprandial) once daily to identify the dynamics of glucose levels in response to a meal. The frequency and duration of testing, adjusted for individual needs, is as follows:</td>
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Diabetes Spectrum Volume 26, Number 2, 2013
prandial glycemic excursions but may not fully prevent them.\textsuperscript{24,39,42,43} SMBG could assist patients in determining the effects of lifestyle and pharmacological treatment on their blood glucose levels.

Support of diabetes management and diabetes education
SMBG provides a means for visualizing changes in blood glucose resulting from medications, lifestyle changes, physical activity, and meals and, therefore, may improve patients’ awareness of the disease and thus their adherence to lifestyle modification and treatment regimens.

Recommendations for Schemes of SMBG in GLP-1–Based Treatment Approaches
A less intensive SMBG scheme, which includes paired testing, has been suggested for individualized approaches in type 2 diabetes (Table 1).\textsuperscript{7} In the large majority of patients with diabetes, a temporary regimen of SMBG will be applicable.

More intensive approaches may be warranted in regimens that combine GLP-1–based treatment and insulin therapy (Table 2). Examples of less and more intensive SMBG testing schemes, based on the types of pharmacological treatments used, are presented below.

- Initiation of GLP-based monotherapy and combination therapies using GLP-1 receptor agonists or DPP-4 inhibitors as an add-on to noninsulinotropic (oral) antihyperglycemic agents such as metformin or thiazolidinedione.\textsuperscript{7} SMBG scheme 1 is suggested to facilitate diabetes education, understanding, behavioral changes, and appropriate self-management.
  - Duration/frequency of testing: 1–3 days weekly for 2–4 weeks
  - Stable/good metabolic control: 1–3 days monthly
  - Instable/poor metabolic control: 3 days to 1 week monthly
- Switch from short-acting to long-acting GLP-1 receptor agonist, which may be accompanied by a temporary increase in blood glucose levels. SMBG scheme 1 is suggested.
  - Duration/frequency of testing: 1–3 days weekly for 2–4 weeks, followed by a scheme based on the quality and stability of metabolic control achieved
- Initiation of combination therapy of GLP-1–based treatment and insulin secretagogues (e.g., sulfonylureas and glinides). SMBG scheme 1 is recommended to detect hypoglycemia and to facilitate diabetes education, understanding, and behavioral changes.
  - Duration/frequency of testing: 1–3 days weekly for 2–4 weeks
  - Stable/good metabolic control: 1–3 days monthly to be considered
  - Unstable/poor metabolic control: 3 days to 1 week monthly
  - Very short-term performance of SMBG scheme 2 may be considered in cases of poor glycemic control and the need to reach treatment targets rapidly. Return to scheme 1 as soon as individual metabolic goals are reached.
  - Duration/frequency of testing: 3–7 days weekly up to continuous paired testing
  - Stable/good metabolic control: 3–7 days weekly up to continuous paired testing
  - Unstable/poor metabolic control: continuous paired testing
  - Performance of SMBG scheme 2 may be considered in those using an intensive insulin therapy regimen according to their level of glycemic control and glycemic variability. The duration may range from 1 day to longer periods.

Figure 1 summarizes these recommendations and shows appropriate schemes for different treatment regimens.

Conclusions
SMBG is a key pillar for the successful, professional management and self-management of type 2 diabetes. The need for structured implementation of SMBG is increasing with the emerging roles of GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes. SMBG may have a role in five different clinical scenarios with

### Table 2. Scheme 2: Intensive SMBG Testing in Type 2 Diabetes\textsuperscript{7}

This SMBG pattern includes seven tests per day for educational purposes or to aid in adjusting pharmacological therapy or diet. The pattern focuses on the dynamics of glucose levels throughout the day to identify glycemic variability. The frequency and duration of testing can range from a minimum of 3 days per week to daily for 1 week per month.

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GLP-1–based treatment approaches: 1) early assessment of treatment success or failure, 2) need for timely modification of treatment, 3) detection of hypoglycemia, 4) assessment of glucose excursions, and 5) support of diabetes management and diabetes education.

In GLP-1–based treatment strategies, the performance of simple, clinically meaningful and intermittent SMBG testing may further support diabetes management and education. The length and frequency of SMBG will depend on individual patients’ clinical situation and quality of metabolic control.

References

19. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, Zdravkovic M, Le Thi TD, Colagiuri S: Laglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone.
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