Journal of Diabetes Science and Technology
Volume 6, Issue 3, May 2012

REVIEW ARTICLE

The Role of Self-Monitoring of Blood Glucose in Glucagon-Like Peptide-1-Based Treatment Approaches: A European Expert Recommendation

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Abstract

The role of glucagon-like peptide (GLP)-1-based treatment approaches for type 2 diabetes mellitus (T2DM) is increasing. Although self-monitoring of blood glucose (SMBG) has been performed in numerous studies on GLP-1 analogs and dipeptidyl peptidase-4 inhibitors, the potential role of SMBG in GLP-1-based treatment strategies has not been elaborated. The expert recommendation suggests individualized SMBG strategies in GLP-1-based treatment approaches and suggests simple and clinically applicable SMBG schemes. Potential benefits of SMBG in GLP-1-based treatment approaches are early assessment of treatment success or failure, timely modification of treatment, detection of hypoglycemic episodes, assessment of glucose excursions, and support of diabetes management and diabetes education. Its length and frequency should depend on the clinical setting and the quality of metabolic control. It is considered to play an important role for the optimization of diabetes management in T2DM patients treated with GLP-1-based approaches.

J Diabetes Sci Technol 2012;6(3):665-673

Introduction

In 2005, glucagon-like peptide (GLP)-1-based treatment approaches for type 2 diabetes mellitus (T2DM) were introduced and their role in the treatment of T2DM is increasing.[1] Glucagon-like peptide-1 is an incretin hormone with glucose-dependent insulinotropic and glucagonostatic effects. It stimulates the pancreatic β cells and inhibits gastrointestinal secretion and motility.[2] The actions of GLP-1 have been shown to be glucose dependent,[3] and therefore, a low rate of hypoglycemic episodes has been observed. It enhances satiety and has been shown to reduce food intake and weight.[2] Native GLP-1 is highly susceptible to enzymatic degradation [particularly by

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Abbreviations: (DPP) dipeptidyl peptidase, (GLP) glucagon-like peptide, (HbA1c) glycosylated hemoglobin, (IDF) International Diabetes Federation, (NIT) non-insulin-treated, (SMBG) self-monitoring of blood glucose, (STeP) Structured Testing Protocol, (T2DM) type 2 diabetes mellitus

Keywords: diabetes, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 analogs, hypoglycemia, self-monitoring, treatment

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dipeptidyl peptidase (DPP)-4].[2] Two classes of GLP-1-based therapeutic agents currently are available: first, GLP-1 receptor agonists ("incretin mimetics") that imitate the actions of GLP-1 and are not targeted by DPP-4 and, second, DPP-4 inhibitors that inhibit *in vivo* degradation of GLP-1.[2,4]

In T2DM, self-monitoring of blood glucose (SMBG) has been shown to be a beneficial approach to assess glucose responses related to medications, nutrition, and lifestyle modifications.[5] Its value with regard to the detection of postprandial glucose excursions and glycemic variability is increasing.[6,7] A 14-year follow up of more than 500 T2DM patients reported that 2 h blood glucose levels, but not fasting blood glucose, predict cardiovascular events and all-cause mortality.[8] The performance of SMBG is also associated with a more frequent detection of hypoglycemic events.[5]

The role of SMBG in non-insulin-treated (NIT) T2DM is increasingly recognized. In 2009, the International Diabetes Federation (IDF) guideline "Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes" was published.[9] According to these guidelines, there is currently no clear evidence regarding optimal SMBG regimens in NIT T2DM. It is mentioned, however, that, in these patients, it is often not necessary to perform SMBG on a daily basis.[9] The guidelines differentiate three levels of diabetes care depending on the regions where they are applied: minimal care, standard care, and comprehensive care.

The guidelines emphasize that SMBG should be considered also on an ongoing basis for people using oral glucose-lowering agents to provide information on hypoglycemia, to assess glucose excursions due to medications and lifestyle changes, and to monitor changes during intercurrent illness. The guidelines also advise annual structured assessment of self-monitoring skills, the quality and use made of the results obtained, and the equipment used.

Although SMBG has been performed in numerous studies on GLP-1 analogs and DPP-4 inhibitors, the potential role of SMBG in GLP-1-based treatment strategies has not been elaborated.

The aim of this article is to discuss individualized SMBG strategies for GLP-1-based treatment approaches also on the schemes, which have been introduced by the IDF guidelines. Clinically relevant SMBG schemes are addressed, which also may be applied in future studies, and are presented in this setting.

Glycemic Effects and Hypoglycemia in Monotherapy with Glucagon-Like Peptide-1 Receptor Agonists

Currently, three incretin mimetics are available: exenatide, liraglutide, and exenatide long-acting release,[4] while the latter has not yet been approved by the U.S. Food and Drug Administration. In summary, a very low rate of hypoglycemia is seen in monotherapy with GLP-1 agonists.

Exenatide twice-daily monotherapy has been reported to reduce glycosylated hemoglobin (HbA1c; 0.7–0.9%), fasting blood glucose (17.5–18.7 mg/dl), and postprandial glucose excursions (21.3–24.7 mg/dl).[10] Hypoglycemia occurred in 4–5% of patients, with a zero rate of severe hypoglycemia.[10] Patients with higher baseline HbA1c presented with greater reductions in HbA1c.[11]

Compared with twice-daily formulation, exenatide QW (once weekly) has been reported to be associated with further reduction in HbA1c (-1.9% versus -1.5%) and fasting blood glucose (-41.5 versus -24.6 mg/dl), with no increased risk of hypoglycemia.[12–14] The switch from twice-daily to once-weekly regimen has been reported to be accompanied by a transient increase in mean fasting plasma glucose, followed by a rapid decrease within 2 weeks.[13] By 3–4 weeks after treatment switch, fasting glucose levels had returned to the previous range.[13]

Liraglutide monotherapy has been reported to reduce HbA1c by 0.75 and fasting serum glucose by up to 47 mg/dl,[15] with a 5.19% rate of hypoglycemic symptoms.[15,16]

Glycemic Effects and Hypoglycemia in Combination Therapies Using Glucagon-Like Peptide-1 Agonists

Glycosylated hemoglobin reductions ranging from 0.79% to 1.50%, zero rates of major hypoglycemia, and very low rates of minor hypoglycemia are reported in combination therapies of GLP-1 agonists with noninsulin secretagogues such as metformin[17–19] or thiazolidinedione.[19,20]

Combination treatment with insulin secretagogues such as glimepiride has been reported to be associated with higher rates of hypoglycemia, ranging from <10% to 36%.[21,22] Glycosylated hemoglobin reductions between 0.46% and 1.1% have been observed, while fasting plasma glucose has been reported to be reduced by 5–29 mg/dl.[21,22]

The combined use of GLP-1 agonists and insulin is expected to be approved soon. During a 24-month follow-

up on exenatide plus insulin glargine (mean HbA1c reduction 0.7%), 11–12% of patients experienced at least one hypoglycemic episode.[23] Five of 32 patients treated with liraglutide plus insulin detemir reported seven hypoglycemic events.[24] In a 52-week trial, insulin detemir as an add-on to a combination of metformin and liraglutide demonstrated improved glycemic control (HbA1c –0.5%) with 0.23 minor hypoglycemic events per patient year.[25]

Glycemic Effects and Hypoglycemic Episodes in Monotherapy with Dipeptidyl Peptidase-4 Inhibitors

Currently, four DPP-4 inhibitors are available in the United States and Europe. Efficacy and safety of sitagliptin, vildagliptin, saxagliptin, and linagliptin are reported to be largely comparable.[1] Summarizing various studies on DPP-4 inhibitor monotherapy, reductions of HbA1c (0.53–0.94%), fasting glucose (17.1–19.8 mg/dl), and postprandial blood glucose (26–52 mg/dl) has been reported.[25–30] Patients with higher baseline HbA1c, however, presented with larger placebo-subtracted reductions in HbA1c.[26,31] Low rates of patients experiencing hypoglycemic episodes with a maximum of 8.1% have been referred.[25–30]

Glycemic Effects and Hypoglycemic Episodes in Combination Therapies Using Dipeptidyl Peptidase-4 Inhibitors

Combined treatment with DPP-4 inhibitors and the noninsulin secretagogue metformin has been reported to reduce HbA1c by 0.58–0.90%, fasting plasma glucose by 12.7–31 mg/dl, and postprandial glucose by 31–63.9 mg/dl.[32–38] Zero rates of major hypoglycemia and very low rates of minor hypoglycemia are reported in dual therapies using DPP-4 inhibitors and noninsulin secretagogues such as metformin[16,17,32–37,39–42] or thiazolidinediones.[43–45]

Higher rates of hypoglycemia are reported in combinations with insulin secretagogues. Reductions in HbA1c (0.54–0.74%) and fasting plasma glucose (7–20.1 mg/dl) have been reported to be accompanied by hypoglycemic events in 3.6–16.7% of patients.[37,46–48]

Combined treatment with DPP-4 inhibitors and insulin seems to cause a higher risk of hypoglycemia.[49] In patients inadequately controlled on long-acting, intermediate-acting, or premixed insulin, the addition of a DPP-4 inhibitor has been associated with a reduction of HbA1c (-0.6%) and fasting plasma glucose (-15 mg/dl) as well as a 16% rate of hypoglycemic episodes.[49] In patients poorly controlled on high doses of insulin, the addition of vildagliptin has been observed to improve glycemic control with zero rates of severe hypoglycemia and approximately two hypoglycemic events per patient year.[50]

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

Self-monitoring of blood glucose in T2DM is essential for the achievement of long-term glycemic control.[5] It enables the identification of responses to behavioral and treatment modifications and also supports the prevention of acute and chronic complications.[5,51] Self-monitoring of blood glucose also enables the visualization of hypoglycemic episodes[52,53] and is seen as a potential tool identify risk scenarios for hypoglycemia.[54]

The clinical role of SMBG in T2DM is also supported by the growing evidence that glycemic variability, which can be visualized by SMBG, is associated with an increased risk of endothelial dysfunction, cognitive impairment,[55,56] microvascular and macrovascular complications, and mortality.[57,58] Glucose spikes and variability have been demonstrated to play an important role in long-term development of microvascular and macrovascular damage.[58] Improvement of blood glucose excursions, mainly in the postprandial phase, have been hypothesized to be beneficial for the outcome.[58]

The St. Carlos Study studied more than 160 newly diagnosed T2DM patients. In the study, the group with SMBG-based educational and pharmacological intervention achieved significantly greater reductions in median HbA1c (6.6% to 6.1%; $p < .05$) and body mass index (29.6–27.9 kg/m^2; $p < .001$ as compared with the group with a conventional HbA1c-based treatment algorithm.[6] The SMBG group ($n = 99$), but not the control group, has been reported to obtain significant reductions in HbA1c and body weight within 12 months.[6] The SMBG-based structured educational and pharmacological program is considered to empower patients to achieve treatment goals, particularly those regarding physical activity and nutrition.[6]

The Structured Testing Protocol (STeP) study, which enrolled 483 poorly controlled (HbA1c ≥ 7.5%), insulin-naïve people with T2DM, demonstrated significantly greater reductions in mean HbA1c in the structured testing group compared with the active control group.[7] The data confirmed that appropriate use of structured SMBG

significantly improves glycemic control and facilitates more timely/aggressive treatment changes in NIT T2DM.[7] The STeP study demonstrated that structured SMBG does not increase the frequency of testing as compared with conventional testing.[7]

The rationale for the potential role of SMBG in GLP-1-based treatment approaches encompasses five aspects:

1. Early assessment of treatment success or failure: There is evidence that reductions in HbA1c caused by GLP-1-based treatment are less pronounced in patients with baseline levels of 7–8%.[11,31] In order to assess the glycemic effects as well as a potential treatment failure as early as possible, treatment effects may be visualized by SMBG before they can be detected by HbA1c. While the latter is reflecting the glucose concentration over the previous 4–8 weeks,[59] SMBG is providing day-to-day information.[60]

2. Early modification of treatment: Treatment strategies in T2DM are frequently initiated too late.[61] On the continuum from nonpharmacologic to insulin treatment, a hypothetical patient accumulates approximately 5 HbA1c years of total burden >8.0% and approximately 10 HbA1c years of total burden >7.0%.[61] As demonstrated by the STeP study and the St. Carlos study, appropriate use of structured SMBG facilitates more timely/aggressive treatment changes in NIT T2DM.[6,7]

3. Detection of hypoglycemic episodes: GLP-1-based treatment approaches are reported to be associated with very low rates of hypoglycemia in monotherapy settings[62] and in combination therapies using noninsulin secretagogues.[17–19,39–45]

   Combination treatment, which includes sulfonylurea or insulin, however, has been linked with hypoglycemia rates up to the level of 36%.[21–24,46–49,63,64]

   In the DURATION-1 trial, reduction of sulfonylurea dosage along with the switch from exenatide twice daily to exenatide QW was accompanied by a temporary increase in fasting plasma glucose followed by a rapid decrease within 2 weeks.[13]

   A further aspect supporting SMBG use might be renal impairment due to its association with a decreased insulin clearance.[65,66] This may translate into higher insulin levels and the need for dosage adjustment of insulin and insulin secretagogues.[66,67] Absolute or relative insulin excess is an important risk factor regarding hypoglycemia.[66]

4. Assessment of glucose excursions (glycemic variability): Glucose variability, characterized by extreme glucose excursions over a daily period, is suggested to play an important role in diabetes complications independently of HbA1c levels.[58,68,69] To assess such glucose excursions, SMBG has been established as an appropriate tool.[70,71] Glucagon-like peptide-1-based treatment approaches are reported, however, to reduce postprandial glycemic excursions. Significant glucose excursions, however, frequently remain present.[27,68,72,73]

5. Support of diabetes management and diabetes education: Assessment of changes in blood glucose due to medications, lifestyle changes, physical activities, and meals by SMBG may improve patients' awareness of the disease and, thus, patients' compliance to lifestyle modification and treatment.[52]

Recommendations for Schemes of Self-Monitoring of Blood Glucose in Glucagon-Like Peptide-1-Based Treatment Approaches

A European expert panel, which was formed by experts in diabetology and endocrinology in July 2010, suggested SMBG schemes of varying intensity across the T2DM continuum.[5] Two SMBG schemes were suggested: scheme 1 (less intensive testing; **Figure 1**) and scheme 2 (intensive testing; **Figure 2**). The lengths of the periods of testing should depend on the individual situations and may range from an intermittent 3-day monitoring once per month to a continuous and daily performance of structured SMBG.[5]

In the following, the expert panel takes a further step on SMBG schemes and suggests schemes of SMBG for GLP-1-based therapies based on the previous publication.

These recommendations consider those recommendations of the IDF guideline "Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes."[9] The new IDF guidelines on postmeal glucose management include postprandial targets of <9.0 mmol/liter (160 mg/dl) taken 1–2 h after a meal.[74]

	Breakfast		Lunch		Dinner		
	pre	post	pre	post	pre	post	night
Mon	×	×					
Tue			×	×			
Wed					×	×	
Thur	×	×					
Fri			×	×			
Sat					×	×	
Sun	×	×					

Figure 1. Scheme 1, less intensive testing in T2DM. The scheme focuses on paired meal testing (preprandial and postprandial) once per day to identify dynamics of glucose levels in response to a meal. Frequency/duration of testing, according to individual aspects: one paired meal testing monthly/1 week monthly/3–7 days weekly/ continuous paired testing.[5]

	Breakfast		Lunch		Dinner		
	pre	post	pre	post	pre	post	night
Mon	×	×	×	×	×	×	×
Tue	×	×	×	×	×	×	×
Wed	×	×	×	×	×	×	×
Thur	×	×	×	×	×	×	×
Fri	×	×	×	×	×	×	×
Sat	×	×	×	×	×	×	×
Sun	×	×	×	×	×	×	×

Figure 2. Scheme 2, intensive testing. Seven tests per day over a minimum of 3 days up to 7 days for educational purposes or for adjustment of therapy or diet. The scheme focuses on the dynamics of glucose levels per day to identify the variability of glucose levels. Frequency/duration of testing: minimum 3 days weekly to 1 week monthly/continuous SMBG.[5]

The two schemes are allocated to various clinical scenarios in GLP-1-based treatment approaches (**Figure 3**):

- Initiation of GLP-based monotherapy and combination therapies using GLP-1 analogs or DPP-4 inhibitors as an add-on to noninsulinotropic agents such as metformin or thiazolidinedione: SMBG scheme 1 is suggested in order 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.

  Instable/poor metabolic control: 3 days to 1 week monthly.

- Switch from short-acting to long-acting GLP-1 analog: SMBG scheme 1 is suggested to facilitate the transition phase, which may be accompanied by a temporary increase in blood glucose levels. Duration/frequency of testing: 1–3 days weekly for 2–4 weeks, to be followed by a scheme according to the quality of metabolic control.

- Initiation of a combination therapy of GLP-1-based treatment approaches and insulin secretagogues, e.g., sulfonylureas and glinides: SMBG scheme 1 is recommended to detect hypoglycemic episodes and to facilitate diabetes education, understanding, and behavioral changes.

  Duration/frequency of testing: 1–3 days weekly for 4 weeks.

  Stable/good metabolic control: 1–3 days monthly to be considered.

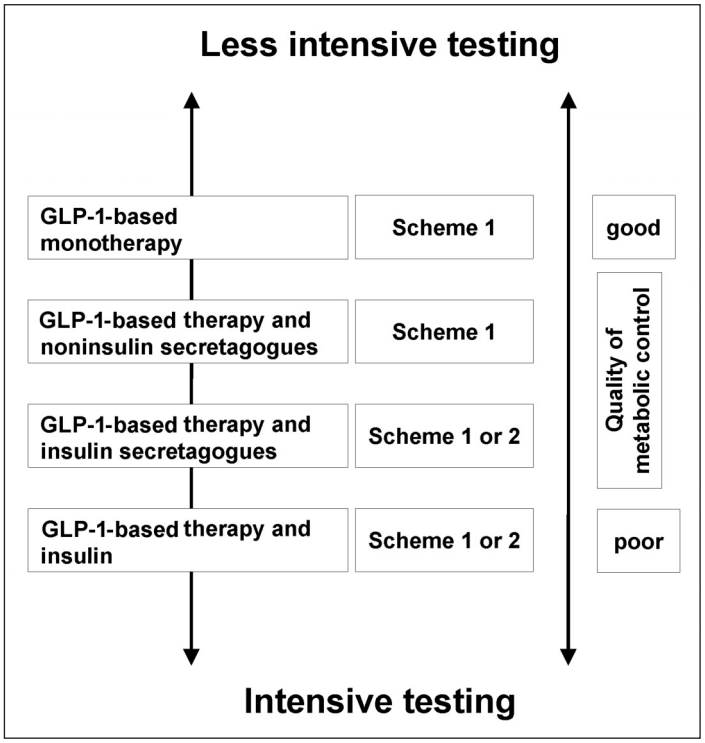

Figure 3. Allocation of scheme 1 and scheme 2 to different clinical scenarios. Intensity of testing is increasing with treatment escalation and deterioration of glycemic control. Declining intensity of testing with treatment de-escalation and improvement of glycemic control.

Instable/poor metabolic control: 3 days to 1 week monthly.

Very short-term performance of SMBG scheme 2 may be considered in case of poor glycemic control and the need to reach treatment targets rapidly. Return to scheme 1 as soon as the individual metabolic goals are reached.

- Initiation of a combination therapy of GLP-1-based treatment approaches with insulin: SMBG scheme 1 is recommended to depict hypoglycemic episodes and glycemic variability. It is recommended to facilitate diabetes education, understanding, and behavioral changes. Frequency of performance of SMBG scheme 1 also depends on the type of insulin treatment.

  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.

  Instable/poor metabolic control: continuous paired testing.

  Performance of SMBG scheme 2 may be considered in those with intensive insulin therapy according to the level of glycemic control and the variability of glucose.

Conclusions

The role of both GLP-1 analogs and DPP-4 inhibitors in the treatment of T2DM is increasing. Both approaches are efficacious in lowering HbA1c, preprandial glucose, and postprandial blood glucose.

In monotherapy and in combination therapy with noninsulin secretagogues such as metformin, GLP-1-based treatment approaches are associated with a very low risk of hypoglycemic episodes. In combination with combination insulin secretagogues and insulin or insulin secretagogues, higher rates of hypoglycemic episodes have been observed.

Structured SMBG is increasingly recognized to play an important role for successful diabetes management also in NIT T2DM without increasing the frequency of testing. In most studies that assess GLP-1-based treatment approaches, SMBG is used to visualize effects on preprandial glucose, postprandial glucose, and glucose variability. Self-monitoring of blood glucose may have a role in five clinical scenarios with GLP-1-based treatment approaches: (1) early assessment of treatment success or failure, (2) need for timely modification of treatment, (3) detection of hypoglycemic episodes, (4) assessment of glucose excursions, and (5) support of diabetes management and diabetes education.

The length and frequency of SMBG should depend on the clinical setting and the quality of metabolic control. A less intensive and a more intensive scheme for SMBG meets the needs of individualized approaches in T2DM. In GLP-1-based treatment strategies, the performance of simple, clinically meaningful, and standardized SMBG strategies may have the potential to further optimize diabetes management and education in the patients.

Disclosure:

Peter Diem has received funds from Roche Diagnostics. The expert panel was supported by an unrestricted educational grant from Bayer HealthCare.

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