Importance of Blood Glucose Monitoring to Achieve Short- and Long-Term Glycemic Control

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OBJECTIVE: To review the importance of short- and long-term glucose monitoring in people with diabetes, emphasizing the relationship between elevated fasting and postprandial glucose levels and their association with hemoglobin A1c (HbA1c).

DESIGN: Literature review

RESULTS: Numerous epidemiologic and interventional studies have demonstrated that lowering blood glucose to normal or near-normal levels for several years prevents the onset and delays the progression of microvascular complications including retinopathy, nephropathy, and neuropathy. Based on a substantial amount of data, the American Diabetes Association recommends that treatment of all individuals with diabetes be aimed at lowering blood glucose to normal or near-normal levels.

CONCLUSIONS: Frequent self-monitoring of blood glucose (SMBG), if used properly, can be effective at improv-

ing glycemic control on a day-to-day basis. SMBG should be done daily and should include measurement of both fasting and postprandial blood glucose levels. Routine measurements of HbA1c are used for measuring long-term control (90 to 120 days) and highly correlate with the incidence and progression of diabetic complications. This makes HbA1c a valuable clinical tool for both assessing long-term glycemia and predicting risk for the development of chronic complications. Achieving glycemic control through an interdisciplinary, comprehensive diabetes care program is beneficial to the patient and may be cost-effective within an integrated health care system. Diabetes should be identified as a target for disease state management programs.

KEYWORDS: Diabetes, Glucose monitoring, Student education, School of pharmacy

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Point-of-care testing and self-monitoring of blood glucose (SMBG) have dramatically enhanced the ability of both patients and clinicians to improve glycemic control. Results of blood glucose testing are used to assess the efficacy of medication therapy, enforce behavior modification in medical nutrition therapy and exercise, and facilitate changes in lifestyle. SMBG also can minimize chronic hyperglycemia, reduce the frequency and magnitude of hyperglycemic excursions, and alert patients to the signs of impending diabetic ketoacidosis or hypoglycemia. The importance of achieving target blood glucose values to minimize or prevent microvascular complications has led to more patients performing day-to-day testing. This paper reviews the importance of short- and long-term glucose monitoring in people with diabetes, emphasizing the relationship between elevated fasting and postprandial glucose levels and their association with hemoglobin A1c (HbA1c).

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TARGETING BLOOD GLUCOSE LEVELS TO ACHIEVE GLYCEMIC CONTROL

Due to an overwhelming amount of epidemiologic and interventional data, the American Diabetes Association (ADA) recommends that treatment of individuals with diabetes aim at lowering blood glucose to normal or near-normal levels (see Table 1), and advises that most patients on insulin should follow intensive treatment programs that include frequent

Table 1. Target Levels of Glucose Control

Biochemical Measurement	Normal	Acceptable
Preprandial glucose (mg/dL)	<115	70–120*
Bedtime glucose (mg/dL)	<120	100–140
Postprandial (90 min) glucose (mg/dL)	<140	<180*
Glycated hemoglobin (%)†	<6	<7

*DCCT goal for intensive therapy; †Normal reference range: 4%–6%

SMBG.^{1,2} Further, these guidelines state that patients with Type 1 diabetes should use premeal and bedtime glucose levels of 70 to 120 mg/dL (4.44–6.67 mmol/L) and 100 to 140 mg/dL (5.50–7.78 mmol/L), respectively, as targets. To achieve these levels, comprehensive treatment programs that include intensified insulin therapy, nutritional counseling, behavior modification, measurements of glycosylated hemoglobin, and SMBG have been devised.

The control of postprandial blood glucose levels is also important in the overall management of persons with diabetes. The Diabetes Control and Complication Trial Research Group (DCCT) published data on the relationship between the glycosylated hemoglobin value and the risk of complications. The DCCT concluded that mean HbA1c may not express the degree of hyperglycemia and that the risk of complications may depend on the extent of postprandial glucose excursions.³

Postprandial glucose excursions are synonymous with the acute rise of blood glucose that occurs after a meal. The report of the six-year United Kingdom Prospective Diabetes Study (UKPDS) showed that “despite continuing dietary advice, and increasing doses of sulfonylureas, metformin, and insulin, by six years after the diagnosis of diabetes, 53%, 59%, and 47% respectively of patients in the intensive group had fasting plasma glucose (FPG) levels above 140 mg/dL.” Four to six years after initiating therapy with metformin, sulfonylureas, and insulin, HbA1c levels generally returned to the higher values that existed before therapy.⁴ These increased HbA1c levels may be attributable to increasing postprandial glucose excursions.

IMPROVED GLYCEMIC CONTROL IN TYPE 1 AND TYPE 2 DIABETES

In 1993, the results of the DCCT study in 1,440 patients with Type 1 diabetes demonstrated that intensive therapy over a nine-year period effectively prevented the onset and delayed the progression of diabetic retinopathy, nephropathy, and neuropathy relative to conventionally treated patients.⁵ Although the DCCT was conducted in patients with Type 1 diabetes, other studies have provided evidence that reductions in hyperglycemia to DCCT-recommended levels (HbA1c = 7.2%) will produce favorable effects on microvascular and macrovascular

disease in patients with Type 2 diabetes.^{6,8} In the DCCT, one of the drawbacks to intensive insulin therapy was a threefold increase in hypoglycemic reactions.

Recent data from Vijan et al. demonstrated that reducing HbA1c from 9% to 7% results in a 2.3% decrease in lifetime risk for blindness due to retinopathy.⁹ Eastman et al. analyzed the health benefits and cost effectiveness of treating Type 2 diabetes with the goal of normoglycemia, and showed that comprehensive treatment that maintains an HbA1c of 7.2% is predicted to reduce the cumulative incidence of blindness, end-stage renal disease, and lower extremity amputation by 72%, 87%, and 67% respectively.¹⁰

The UKPDS was a multicenter randomized controlled trial comparing different therapies in newly diagnosed Type 2 diabetic patients that lasted for 20 years.¹¹ The UKPDS was designed to determine if intensive therapy to achieve near-normal glycemia would reduce microvascular and macrovascular complications in Type 2 patients. The study evaluated 3,867 newly diagnosed Type 2 patients over a 10-year period. It compared conventional therapy (diet plus medications to achieve an FPG of 15mmol/L) to intensive therapy (diet plus medications to achieve an FPG of 6mmol/L).

The medications used in the study were chlorpropamide 500 mg/day, glibenclamide 2.5–20 mg/day, glipizide 2.5–40 mg/day, insulin therapy (both intermediate and short-acting), or metformin 500–2550 mg/day. Results showed that the intensive therapy group was able to achieve and maintain a 0.9% reduction in HbA1c (11% reduction). This reduction led to a 12% lower risk of any diabetes-related endpoint, 10% lower risk for any diabetes-related death, and 6% lower risk for all-cause mortality. Intensive therapy also yielded a 25% risk reduction in microvascular endpoints. All medications were equally effective. Patients in the intensive therapy group had more hypoglycemic episodes and gained significantly more weight.

Before the DCCT and UKPDS studies were completed, the results of animal and human studies predicted a strong relationship between the duration and severity of hyperglycemia and the occurrence and progression of diabetic complications. Hyperglycemia has been shown to cause comparable morphologic abnormalities in retinopathy,^{12–14} nephropathy,^{15–17} and neuropathy¹⁹ in Type 1 and Type 2 patients. In one study of patients with incipient diabetic nephropathy, two years of strict metabolic control prevented the development of clinical nephropathy.¹⁸ Strict control of blood glucose as assessed by short- and long-term measures has been found to be critically important during pregnancy and has a positive effect on fetal outcome.^{20–23}

BENEFIT OF MONITORING BLOOD GLUCOSE

Multiple studies have been conducted evaluating the impact of SMBG on glycemic control. Most of the studies evaluated SMBG within the context of a comprehensive diabetes care program that included nutrition and exercise counseling. Dudley et al. evaluated 29 Type 2 diabetics over 12 months.²⁴ These

patients participated in a comprehensive program that included dietary intervention, education, routine follow-up, and SMBG seven times per day. Twenty-seven of the 29 patients had an improvement in HbA1c from a mean of 11.4% to 8.7%. Routine clinic visits, emergency room visits, hospital days, and telephone calls decreased by 79%, 54%, 87%, and 70% respectively. This decrease in utilization of services equated to an estimated savings of \$364 per patient in the first year.²⁴

A recent criteria-based literature review from 1976-1996 found only four studies that met their quality criteria.²⁵ Rutten et al. conducted one of the four studies that demonstrated a significantly positive result with SMBG.²⁶ Rutten conducted a randomized control trial in 100 patients to determine the efficacy of SMBG, using HbA1c and weight as efficacy measures. The mean change in HbA1c was -0.4% in the SMBG group versus +0.5% in the control group ($p < 0.05$). The patients in the SMBG group lost weight, whereas the control group gained weight (nonsignificant). At this point compelling data exists that clearly demonstrates the need to incorporate SMBG as an integral part of the comprehensive care of the persons with diabetes. This fact needs to factor into the decision-making process related to hypoglycemia therapy, insulin or oral antidiabetic medication adjustment, nutritional instruction, exercise, and assessment of complications.

SHORT-TERM BLOOD GLUCOSE MONITORING

Short-term monitoring of blood glucose is used in the management of patients with diabetes either for a specific purpose or for a discrete period of time, as in the management of patients with impaired glucose tolerance (IGT) or gestational diabetes.

IGT refers to a metabolic stage between normal glucose hemostasis and diabetes. Many patients with IGT have normal fasting blood glucose values and may have normal or near-normal HbA1c levels. If these patients become ill and require hospitalization, they will require bedside monitoring of their blood glucose. Insulin may be required during the hospitalization and is usually given based on fixed-dose algorithms that are linked to monitoring of capillary blood glucose levels.

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. In the majority of cases of GDM, glucose regulation will return to normal after delivery. Deterioration of glucose tolerance occurs normally during the third trimester. Women with gestational diabetes require short-term use of SMBG. Keeping blood glucose levels as close to normal as possible is very important for these patients. Kitzmiller et al. evaluated preconception care of 84 GDM patients versus postconception care for 110 GDM patients and its effects on congenital anomalies.²⁷ All patients self-monitored their blood glucose at least four times a day, during fasting and one hour after meals. Goals for preprandial levels were 60–100 mg/dL; one-hour postprandial goal was 100–140 mg/dL. Results from the study showed that the rate of congenital anomalies was

reduced when intensive management of blood glucose was instituted before or early in pregnancy.

Adjusting therapy based on postprandial glucose monitoring has been shown to be more effective than basing therapy on preprandial monitoring when the goal is improved glycemic control. De Veciana et al. randomly assigned 66 GDM patients to adjust their insulin based on preprandial or postprandial levels.²⁸ The target for preprandial levels was 60–105 mg/dL and postprandial levels was <140 mg/dL. When the postprandial or premeal glucose was evaluated to determine treatment effects, greater reduction in glycosylated hemoglobin occurred when the postprandial value was used ($-3.0 \pm 2.2\%$ versus $0.6 \pm 1.6\%$, $p < 0.001$). The patients in the postprandial monitoring group had a 70% reduction in all the complications of gestational diabetes. The study concluded that adjusting insulin treatment based on postprandial rather than premeal monitoring of blood glucose may be more effective in improving glycemic control in GDM patients and may decrease the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery.

Avignon et al. also demonstrated the importance of postprandial glucose levels.²⁹ This study evaluated the relative value of plasma glucose measurements at different times of the day in comparison with HbA1c measurements in 66 Type 2 patients and found that post-lunch (two hours) and extended post-lunch (five hours) measurements are better predictors of glycemic control than fasting plasma glucose.

Short-term monitoring of blood glucose can be achieved by measuring the glycosylation of serum proteins that occurs during periods of hyperglycemia. The measurement of serum fructosamine (a glycosylated protein) has been used to monitor short-term control in patients with diabetes. Measurement of fructosamine levels reflects average glucose control for two to three weeks and therefore allows earlier identification of adverse glycemic events and fosters earlier therapeutic intervention. HbA1c is measured as a percentage of glycosylated hemoglobin relative to total hemoglobin, whereas fructosamine is measured as micromoles of fructosamine per liter of blood ($\mu\text{mol/L}$). The advantage of fructosamine is that the testing is standardized from one laboratory to another and is potentially more accurate in patients with anemia. Studies in the elderly and in diabetic outpatients have found fructosamine to have clinical validity as a short-term marker of glycemic control.^{30,31}

FREQUENCY OF TESTING

The ADA recommends that efforts be made to substantially increase appropriate use of SMBG. According to a national survey conducted by Harris et al., 67% of people with diabetes have never checked their blood glucose.³² Forty percent of Type 1 and 26% of Type 2 patients monitor at least once a day.

All treatment programs should encourage SMBG for routine daily monitoring in Type 1 patients. Frequency and timing should be dictated by the needs and goals of the individual patients, but most Type 1 patients should monitor their plasma glucose

before breakfast, one to two hours after each meal, before and after exercise, and at bedtime on a daily basis. For Type 2 patients the ADA recommends "a sufficient number of tests should be performed to reach glucose goals."³³ Generally, Type 2 patients should conduct at least two tests per day at various times throughout the day, before and after meals. Daily SMBG is especially important for Type 2 patients treated with insulin or sulfonylureas to monitor for and prevent asymptomatic hypoglycemia.

In the DCCT, the glycemic goals for intensive therapy included premeal, 90-minute post-meal, and weekly 3 a.m. blood glucose levels of 70 to 120 mg/dL (3.9–6.7 mmol/L), <180 mg/dL (10 mmol/L), and >65 mg/dL (3.61 mmol/L), respectively. The DCCT study results also suggested that these targets be further adjusted in patients with a history of recurrent severe hypoglycemia or in those with hypoglycemia unawareness.^{1,2}

LONG-TERM GLUCOSE MONITORING

Fasting or postprandial blood glucose testing is useful for day-to-day monitoring of glycemic control. However, these tests cannot provide an accurate measure of glycemia over an extended period of time. Measurement of glycosylated proteins is a means of determining average glycemia over a period of weeks to months, thereby complementing day-to-day testing. HbA_{1c}, one of several glycosylated hemoglobins that reflect glycemic status, has been studied extensively. HbA_{1c} is the stable product of nonenzymatic glycosylation of the eight chain of hemoglobin by plasma glucose; it is found at concentrations that increase with increasing plasma glucose levels.

Because erythrocytes are freely permeable to glucose, the level of glycosylated hemoglobin in a blood sample provides an estimate of the degree of glycemia over the previous 90–120 days, which is the average erythrocyte life span.² Measurement of glycosylated hemoglobin has been available since the late 1970s. It is recommended for routine testing of long-term glycemic control in all patients with diabetes, 1) to document the degree of glycemic control at the initial assessment; then 2) as part of continuing care, since it can quantify average glycemia over the previous 90–120 days.¹ Interpretation of HbA_{1c} test results requires an understanding of the relationship between the test results and average blood glucose, the kinetics of HbA_{1c} formation, specific assay limitations, and patient factors that can affect the results.

In light of the DCCT and UKPDS results, HbA_{1c} testing is recommended for use in routine monitoring of all patients with diabetes.^{1,2} These studies showed that HbA_{1c} levels can be used clinically to assess long-term glycemic status and to predict risk for development of the chronic complications of diabetes.^{1,5,12} Some studies suggest that treatment strategies utilizing HbA_{1c} testing can improve, per se, glycemia in Type 1 diabetes.^{2,34}

Glycosylated hemoglobin values in diabetic patients represent a continuum, ranging from normal to elevations of two- to three-fold, making it difficult to relate the HbA_{1c} test result to average blood glucose values; however, general guidelines

can be suggested.³⁴ Data analysis from the DCCT has revealed that when HbA_{1c} and 24-hour seven-point blood glucose profiles were measured quarterly for one year in 278 subjects, a linear relationship existed between average glycemia and glycosylated hemoglobin level ($r = 0.80$, $p < 0.0001$). Approximately each 1% increase in glycosylated hemoglobin was related to a 30 mg/dL (1.99 mmol/L) increase in average blood glucose.^{5,34} In addition, if one multiplied the HbA_{1c} by approximately 23, the resulting number would represent the average blood glucose, assuming that the usual range for HbA_{1c} is 4%–6%.

COST OF COMPREHENSIVE DIABETES CARE IN A MANAGED CARE SETTING

Many integrated health care systems are looking at the cost of comprehensive care of their patients with diabetes. Gilmer et al. examined the relationship between glycemic control and medical care charges for 3,017 adults with diabetes enrolled in a large health maintenance organization over a four-year period, and found that for a person with an HbA_{1c} value of 6%, successive 1% increases in HbA_{1c} resulted in cumulative increases in medical charges of approximately 4%, 10%, 20%, and 30%.³⁵ These researchers concluded that for economic as well as clinical reasons, lowering HbA_{1c} when it is >8% is beneficial.

Selby et al. estimated the excess costs of medical care of patients with diabetes in a managed care population to determine the proportion of costs spent on treating the complications of diabetes.³⁶ This study compared 1994 medical costs of medical care among the 85,209 members of the diabetes registry of Kaiser Permanente Northern California, and in 85,209 age- and sex-matched nondiabetic control subjects.

Expenditures for members with diabetes were 2.4 times those for matched controls (\$3,494). Nearly 38% of the excess was spent treating the long-term complications of diabetes, predominantly coronary heart disease and end-stage renal disease. The researchers concluded that disease state management programs that aim to prevent complications could potentially lead to cost savings.³⁶

Eastman et al. analyzed the health benefits and cost effectiveness of treating Type 2 diabetes with the goal of normoglycemia, using an incidence-based simulation model of noninsulin-dependent diabetes mellitus and estimated treatment costs from national survey data and clinical trials.¹⁰ An estimated incremental cost per Quality Adjusted Life Years (QALY) was calculated comparing comprehensive to standard treatment of Type 2 diabetes. QALY is a single comprehensive indicator of health improvement resulting from a medical intervention within an individual. Technologies or interventions that cost less than \$20,000/QALY are considered an acceptable expenditure of health care system resources.^{37,38} The results of this study demonstrated that comprehensive treatment of Type 2 diabetes that maintains an HbA_{1c} value of 7.2% reduces the incidence of blindness, end-stage renal disease, and lower extremity amputations. Life expectancy increased by 1.39 years and the estimated incremental cost/QALY gained is \$16,002.¹⁰

SUMMARY AND CONCLUSIONS

Intensive treatment of diabetes mellitus requires effective blood glucose monitoring methods, including SMBG. Due to wide fluctuations in blood glucose levels, the frequent practice of periodic monitoring of fasting glucose levels has been questioned, and there is evidence that postprandial glucose levels may provide a better measure of short-term glycemic control.

The most comprehensive method of monitoring glycemic control over an extended period of time is the assessment of HbA_{1c}, which is formed in direct proportion to the ambient glucose concentration. A definitive positive correlation has been found between HbA_{1c} levels and the incidence and progression of diabetic complications. HbA_{1c} levels, therefore, can be used clinically to assess long-term glycemia and to predict risk for development of chronic complications in diabetes. Through the use of an interdisciplinary team approach, focusing on patient education on diabetes management and monitoring blood glucose levels, the test results from SMBG and HbA_{1c} can be used to achieve target levels. At this time it appears that achieving glycemic control through a comprehensive diabetes care program is cost effective. The goal of the program should be to prevent the long-term complication of diabetes and improve quality of life.

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