The Accuracy and Interferences in Self-monitoring of Blood Glucose

Diabetes mellitus affects an estimated 20.8 million individuals in the US, approximately 7% of the population. Diagnosed in only 14.6 million individuals, 6.2 million are unaware of their condition and remain untreated as a result. Extensive research has clearly shown that improved glycemic control can impede the development and progression of diabetic complications, but many patients with diabetes still do not achieve or maintain these glycemic goals. In recent years, there has been a focus on self-monitoring of blood glucose (SMBG) as one modality that can help people with diabetes improve glycemic control.

The Benefits of Self-monitoring of Blood Glucose

The development of SMBG has revolutionized the management of diabetes by allowing patients to monitor glycemic responses to their diet, activity, oral medications, and insulin therapy. Indeed, SMBG has been shown to be associated with improved glycemic control in both type 1 and type 2 insulin-treated diabetes. Although the role of SMBG in non-insulin-treated type 2 diabetes remains less defined, a meta-analysis of studies that compared a diabetes management strategy with SMBG to one without SMBG has demonstrated the benefit of SMBG on glycemic control in non-insulin-treated type 2 diabetes patients. Moreover, a large-scale study tracking the use of SMBG over a span of almost seven years showed an association between SMBG use and decreased diabetes-related morbidity and mortality in these patients; this and other recent evidence supports the use of SMBG in non-insulin-treated type 2 diabetes.

SMBG profiles help healthcare providers (HCPs) better understand the individualized antihyperglycemic regimens and provide an educational feedback tool to inform patients of the effects of modulating their diet, physical activity, or intake of oral antidiabetic agents or insulin. Such active involvement in their care helps empower patients and has been shown to facilitate the achievement of glycemic targets.

Appropriate use of SMBG will allow patients to identify, prevent or manage episodes of hypo- and hyperglycemia. Furthermore, SMBG can help minimize fluctuations in blood glucose levels that have been shown to signal the imminent occurrence of severe hypoglycemia in 58–60% of cases and may independently contribute to diabetic complications.

Increasing evidence of the benefits of SMBG has been associated with increased HCP and patient awareness about the importance of self-monitoring of blood glucose: 63.4% of all adult patients and 86.7% of those treated with insulin now carry out SMBG at least once a day.

The Functionality of Glucose Meters

To date, the US Food and Administration Agency (FDA) has approved at least 25 commercially available glucose monitors and the ADA reviews a number of them annually, the majority of which use test strips containing either glucose hexokinase or oxidase chemistry. The most common test involves obtaining a small blood sample (<1µL for most meters) through a finger prick and applying the sample to a test strip for a series of chemical reactions. The strip is then inserted into a meter that displays a measure of the glucose concentration, by a variety of means, including colorimetry, photometry, and electrochemistry. Patients with diabetes can manually record these test results or utilize the meter’s built-in memory and/or computer software.

Accuracy in Self-monitoring of Blood Glucose—Improving Patient Technique

Since patients and their HCPs rely on SMBG results to identify hyper- and hypoglycemia and modify treatment accordingly, it is important for glucose meter readings to be accurate and reliable. However, an ADA consensus panel reported that up to 50% of all SMBG readings may vary from their true value by more than 20%. One study found that of 111 patients using glucose monitors, 53% were in compliance with ADA guidelines with SMBG readings showing less than 10% of variation, while 16% had SMBG readings that varied in excess of 20% of the control values. The performance of patients regarding SMBG was also evaluated using a checklist of steps deemed critical in the proper calibration and operation of their glucose monitors. The patients scored poorly in critical quality control, as many of which used improper techniques when collecting blood samples. Only one (0.9%) of the 111 patients scored perfectly on the evaluation checklist. In spite of the poor techniques and performance errors, a large proportion of glucose values obtained were still clinically acceptable.

Despite the increasing simplification of blood glucose meters over the years, they are still not foolproof. Almost half of patients trained appropriately in SMBG can still obtain inaccurate readings through poor technique. Patients of various ages and social classes have also been found to falsify their results, omitting high glucose readings, and recording extra results to indicate more frequent testing than in reality. Such cases emphasize the importance and necessity of educating a patient in proper SMBG, not only in the technical aspects of correct usage and interpretation of a blood glucose meter, but also about the supporting role of SMBG in their antidiabetic regimens.

Many aspects can alter the accuracy of a glucose meter reading, including patient characteristics, variances in manufacturing of the glucose test strips, and interfering substances. Most importantly, the adequacy of training available to the patient will affect their ability to use the meter and, crucially, tell if they are using it correctly.
Variances in the reactivity of the glucose test strips mean that some SMBG devices require the patient to enter a unique code to calibrate the meter. This is another aspect of the process that is open to error, and miscoded meters lead to an insulin dose error. However, certain newer meters have automatic coding, thus eliminating this potential problem.

In terms of patient characteristics, the cleanliness of the finger, the quality and size of the blood sample, and the technique used (for example in terms of wicking time in the well and complete filling of the well) can all influence the reading. Similarly, there are differences and variances in strip design and well size across manufacturers, and the cleanliness of the meter can also affect results. Some meters allow for these inaccuracies and others do not. Interfering substances are discussed below.\textsuperscript{21,30}

Sources of Interference

Factors that cause erroneous readings on the blood glucose meters can be categorized into two groups: sugars and interfering substances. Cross-reactivity can occur between enzymes on the test strip and substances in the blood similar to glucose—such as maltose, galactose and xylose—while non-sugar molecules interfere by different methods.

Maltose, Galactose, and Xylose

Maltose is a disaccharide formed from two glucose molecules and is found in certain immunoglobulin products. Additionally, icodextrin used in peritoneal dialysis metabolizes to maltose. Galactose and xylose are found in certain foods, herbs, and nutritional supplements, and are also used in diagnostic tests. In clinical doses, these sugars can interfere with some blood glucose monitoring systems.\textsuperscript{29} Inaccurate glucose readings can place a patient at risk for a number of complications, either masking hypoglycemia or giving false indications of hyperglycemia. In the past, some patients receiving products containing maltose, galactose, and xylose showed falsely elevated glucose readings, and were treated with aggressive insulin therapy as a result. However, the administration of this excess insulin caused these patients to suffer hypoglycemic shock or irreversible brain damage and death.\textsuperscript{24}

In systems using test strips containing the enzymes glucose dehydrogenase (GDH), pyrroloquinolinequinone (PQQ), or glucose dye oxidoreductase, the maltose, galactose, and xylose sugars are mistaken in the inclusion of a warning in the limitations section of the product's labels to alert users. Overall, it is important to stress that both physicians and patients should carefully review the package inserts of all test strips. This will ensure that that type of glucose-testing system being used is appropriate for the patient.

Oxygen

In glucose oxidase test strips, oxygen acts as a competing electron acceptor. The corresponding reaction will vary depending on the pO\textsubscript{2} in blood samples. High partial pressure of oxygen (pO\textsubscript{2} (400torr)) is most common in the critically ill, or in patients receiving oxygen therapy or undergoing surgery. These patients will show pronounced decreases in blood glucose level. Low pO\textsubscript{2} (40torr) is common in neonates or patients at high altitudes, in which glucose readings will be anomalously high. However, both situations are extremes, and unless the average patient prolongs exposure of their blood sample to air prior to testing (e.g. >15 minutes), the effect of oxygen should be negligible.\textsuperscript{21,32}

Paracetamol

Paracetamol is the active metabolite in certain analgesics, is significantly oxidizable, and is known to interfere with glucose measurements.\textsuperscript{35,36} Typical therapeutic levels (1–2mg/dl) are too low to have any significant effects,\textsuperscript{35} but overdosing on paracetamol would be capable of inducing a clinically significant overestimation of blood glucose.\textsuperscript{35,36}

Ascorbic Acid

Vitamin C is a potent antioxidant and easily oxidized. However, ascorbic acid is readily excreted in the urine and even large doses are quickly normalized within the body. Although ascorbic acid has the potential to interfere with results from glucose monitors,\textsuperscript{37} normal levels (1–2mg/dl) are not at high enough concentrations to significantly affect the readings.\textsuperscript{36}

Uric Acid

Uric acid is a natural by-product of purine catabolism. At normal levels, uric acid has an insignificant effect on glucose meter readings. However, poor clearance from kidneys or overproduction of uric acid can cause hyperuricemia. If oxidized, the uric acid can lead to falsely lowered values on glucose meters.\textsuperscript{36}

Bilirubin

Bilirubin is a product of hemoglobin breakdown, and normal levels do not affect glucose meter readings in a significant manner. Bilirubin can be elevated in jaundiced neonates, or patients with liver disease, hepatitis, or
certain forms of anemia to create positive interference in meters using test strips with GDH-based chemistry.84

**Hematocrit**

Hematocrit counts vary depending on age and gender. Low hematocrit can be caused by a number of factors, such as anemia and sickle cell anemia, blood loss, malnutrition, or leukemia. In contrast, hematocrit can often increase under conditions of dehydration, but will normalize upon the restoration of fluid balance. Other causes of high hematocrit, though rare, include certain bone marrow disorders and tumors, lung diseases, and living at extremely high altitudes. Glucose meters are generally calibrated towards the normal hematocrit levels of 40–50%. Erythrocytes living at extremely high altitudes. Glucose meters are generally calibrated towards the normal hematocrit levels of 40–50%. Erythrocytes and living at extremely high altitudes. Glucose meters are generally calibrated towards the normal hematocrit levels of 40–50%. Erythrocytes living at extremely high altitudes. Glucose meters are generally calibrated towards the normal hematocrit levels of 40–50%. Erythrocytes

**The Effect of Interference on Accuracy**

Maltose, galactose, and xylose are likely the most serious causes of interference in glucose meters. However, the effect of these extraneous sugars on glucose readings can easily be negated with proper information and by choosing to only use meters that will not cross react with non-glucose sugars such as those using glucose oxidase or GDH-NAD test strips. In spite of the various interfering substances that can potentially confound the accuracy of glucose meters, these factors actually have little bearing in the average patient with diabetes.82,83

**Conclusion**

The increasing prevalence of diabetes illustrates the importance of proper disease management through successful use of SMBG. The glucose meters available on the market are similar in terms of functionality, yet vary in accuracy depending on multiple factors including variance in strip design and manufacturing, the patient’s technique in testing and finger cleanliness, appropriate calibration of the meter with strip code, and the chemistry and cross-reactivity with interfering substances. When selecting the optimal glucose meter, not only must aspects from the patient’s lifestyle and other health treatment regimes be taken into account, but also the glucose meter systems must also be assessed in detail to ensure the minimum risk of interference.

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