Mini Review

Variability of capillary blood glucose monitoring measured on home glucose monitoring devices

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ABSTRACT

Self monitoring of blood glucose helps achieve glycemic goals. Glucometers must be accurate. Many variables affect blood glucose levels. Factors are analytical variables (intrinsic to glucometer and glucose strips) and pre analytical related to patients. Analytical variables depend on factors like shelf life, amount of blood and enzymatic reactions. Preanalytical variables include pH of blood, hypoxia, hypotension, hematocrit etc. CGMS has the potential to revolutionise diabetes care but accuracy needs to be proven beyond doubt before replacing current glucometer devices.

Key words: Self-monitoring of the blood glucose, Variability, continuous glucose monitoring

INTRODUCTION

Monitoring of the glycemic status by the patient and the health care provider is the cornerstone in providing optimum diabetic care. The concept that adequate glycemic control results in reduction in the diabetic complications took a stronghold after the Diabetes control and Complications Trial (DCCT) in type 1 diabetes and UK Prospective Diabetes Study (UKPDS) for type 2 diabetics and also by the follow up of the DCCT. Self-monitoring of the blood glucose (SMBG) helps patient and doctor achieve their glycemic goals. Given the paramount importance of SMBG to diabetes care, it is essential that the home glucose monitoring both glucometers and continuous glucose monitoring (CGMS) devices be accurate and values be as near as to the laboratory values. In this review, we will be discussing the various variables affecting the blood glucose levels. Factors can be broadly divided into analytical variables (which are intrinsic to glucometer and glucose strips) and pre-analytical variables (related to patient)

ACCURACY OF GLUCOMETERS

The 2011 American Diabetes Association position statements[1] on self-monitoring of blood glucose has recommended that glucose meter values an intermediate goal of limiting total error for 95% of samples to ≤ 15% at glucose concentrations ≥ 100 mg/dl and to < 15 mg/dl at glucose concentrations < 100 mg/dL. International Organization for standardization (ISO) recommendations in 2003[2] proposed that for test readings >75 mg/dL, the discrepancy between meters and an accredited laboratory should be < 20% for glucose readings ≤ 75 mg/dL, the discrepancy should not exceed 15 mg/dL in 95% of the samples. Also, the Clinical and Laboratory Standards Institute (CLSI) proposed that 95% of the samples, the difference between meter and laboratory measurements of glucose < 20% when the laboratory glucose value is >100 mg/dL and < 15 mg/dL of the laboratory glucose value when the glucose concentration is <100 mg/dL. The Clarke Error Grid Analysis (EGA)[3] was developed in 1987 to quantify clinical accuracy of patient estimates of their current blood glucose as compared to the blood glucose value obtained in their meter. The grid breaks down a scatter plot of a reference glucometer and evaluated glucometer into 5 regions; A, B, C, D, and E. In a recent study in 2012 of 43 glucose meters, only 34 systems met ISO standards.[4] A recent study in April 2012 of two new glucometers demonstrated high accuracy compared to...
previous glucometers. However, current meters exhibit superior performance compared to previous meters. CGMS is still in its infancy with many studies documenting its benefits and also guidelines recommending its use in adults and children as outpatients. Its future use is going to be determined by its cost relative to its benefits.

**Analytical variability**

**Detection Method**- Glucometers use predominantly 2 principles: Electrochemical (amperometry) and reflectance photometry. In glucometers, the enzyme used (glucose oxidase) induces an electric current through the strip, which is proportionate to the amount of glucose. In the reflectance glucometers, the strip changes color according to the amount of glucose in the sample. These glucometers quantify the color change by reflectance photometry. If the drop of blood does not cover the entire testing area of reflectance, glucometers can give falsely low value. Also, they are either automatic (non-wiping) or manual (wiping). The ambient temperature has shown to affect the glucose readings in the reflectance meters. In one study, it was demonstrated that the manual reflectance glucometer overestimated glucose concentrations by 14% at 44°C and underestimated by 12.7% at 25°C.

**Enzymatic reactions**- Glucose meters contain strips that contain two enzymes; glucose oxidase (GO) and glucose dehydrogenase (GDH) or hexokinase. Glucose oxidase meters require oxygen and water for their reaction and hence are susceptible to extremes of hydration or oxygenation. GO-mediated reactions result in generation of gluconic acid and hydrogen peroxide. Capillary blood glucose was measured in mountain climbers at 13500 ft by various glucometers. GO glucometers overestimated blood glucose by 6-15%, whereas the GDH meters were all within 5%. This is because the glucose oxidase biosensor strips are sensitive to the oxygen concentration. But, recent study shows no such difference. Also, patients on icodextrin peritoneal dialysis using GDH meters will result in falsely high values as it can be metabolized to maltose cross-reacting as glucose.

**Glucostrips**- Glucostrips are another potential source of variability of blood glucose levels. Glucostrips have a finite life; it is usually for 2 years in ideal storage conditions. Exposure of strips to light causes discoloration of test area resulting in falsely elevated glucose levels. Exposure of strips to humidity and temperature by open cap vials decreases their stability by day 14 due to exposure to heat and humidity.

**Pre-analytical variables**

**Operator error**- Patient education can have significant influence on the accuracy of the readings shown on the glucometer. Operator error such as differences as much as 14.5 mg/dl between lots of test strips has been reported. Most of the glucometers require coding to be done prior to use. A study by Raine *et al.* have suggested that up to 16% of patients in endocrine practice miscode their glucometers. This can lead to -37% to + 29% errors in clinical practice. The probability of giving additional 3 units of insulin dose when meters are miscoded was as high as 22.5%.

**Hematocrit**- Variation in the patient hematocrit can result in inaccuracies in the blood glucose reading. Low hematocrit can result in falsely elevated blood glucose levels. In one study, hematocrit effect was studied by adjusting the hematocrit of donor sodium heparin blood at glucose concentrations of 54, 247, and 483 mg/dl. At low glucose concentrations (54 mg/dl), the mean glucose difference changed by more than 10 mg/dl. At higher glucose concentrations, meters demonstrated more than 10% change in the mean glucose percentage difference between the lowest and highest hematocrit values.

**Whole vs. plasma**- The estimation of whole blood glucose levels are usually 10-15% lower than plasma glucose alone. The glucose concentration in the water that makes up plasma is equal to that of erythrocytes. Plasma has greater water content than erythrocytes and, therefore, exhibits higher glucose levels than whole blood. The World health Organization (WHO) has devised a conversion factor of 1.12, which has been mathematically derived assuming a hematocrit of 45% and red-cell to plasma ratio of ~ 0.8. In a critical care setting, multiple variables affecting the blood glucose may be present at one time. Hypotension, hypoxia, pH of blood, temperature are amongst the many variables affecting the blood glucose measurement.

**Hypotension**- Hypotension results in decrease in perfusion and increase in glucose utilization resulting in false results in capillary blood glucose. Atkin *et al.* assessed the validity of the finger stick glucose measurements in the hypotensive critically-ill patients. They found that the fingerstick glucose values were significantly lower than the values obtained by venous reagent strips or laboratory glucose measurements. Fingerstick glucose values in the hypotensive group were 67.5% of laboratory glucose values and were significantly lower than the values obtained in the normotensive group (91.8%, *P* less than 0.001). Juncia *et al.* aimed to compare the accuracy of capillary bedside glucometry with arterial samples in critically-ill patients with shock through a prospective case-control study. They studied 100 patients on vasopressor support, and the control group had 100 normotensive patients. Mean arterial and capillary sugars (mg/dl) in study and control groups
were 164.7 ± 70 and 157.4 ± 69.8 and 167.1 ± 62.2 and 167.5 ± 61, respectively. They concluded that arterial blood glucose is better measurement compared to capillary blood glucose in hypotensive patients. Venous blood glucose values are also stated to be significantly better than capillary blood glucose measurement and correlate better with the laboratory measurements in a critical care setting.[9] Also, the prandial state accentuated the difference between various measurements in hospital setting. Capillary blood glucose levels were 20-25% higher than venous plasma glucose level in prandial state, whereas it was only 2-5 mg/dl higher in fasting state.

**PH**- Like any other enzymatic reaction, change in pH is likely to affect the enzymatic reaction. However, in the range of pH 6.89 to 7.4, it is found to not have much effect on the blood glucose levels measured.[10]

**Alternate site**- Bina et al. studied the differences in the measurement of blood glucose at various site (forearm, palm, and thigh) with respect to the finger tip capillary blood glucose. Also, the effect of prandial state and moderate exercise at the blood glucose levels on the different sites were studied. Significant differences in BG at alternative sites were found 60 min post-meal (P < 0.0003) and post-exercise (P < 0.037). However, no significant differences were observed between sites in either the fasting state or at 90 and 120 min post-meal.[11] It has been observed that there is a considerable time lag in measurement at alternate sites. It can be particularly dangerous in hypoglycemia situations, and hence clinicians must be aware of this. The effect of oxygen concentration in the sample has already been discussed.

**Drugs**- There are various drugs affecting the capillary glucose readings. Of particular importance were the acetaminophen, dopamine, mannitol, and the ascorbic acid. Acetaminophen increased glucose readings with GDH meters but decreased readings with some, but not all, GO-based meters at therapeutic drug levels. Dopamine increased glucose values on GDH-based meters, primarily at high drug concentrations. Mannitol increased GO-based meter readings, possibly through detection by the analyzer or by a non-specific osmotic effect. At high doses, ascorbic acid increased GDH-based meter readings but decreased those that used glucose oxidase.

**Other interfering substances**- Some naturally occurring substances in the body tend to interfere in the blood glucose readings. High triglyceride levels cause falsely low blood glucose values as they tend to take up volume reducing the glucose levels. Also, bilirubin has also noted to cause pseudohypoglycemia

**Implications**

With such vast data regarding the various variables affecting the blood glucose reading in glucometer, the clinician must be alert while interpreting the values while treating a patient. Also, the patients need to be educated regarding their glucometers, which can prevent false readings and inadvertent admission of excess insulin resulting in severe hypoglycemia.

**Future**

Continuous glucose monitoring (CGM) has the potential to revolutionize the diabetes care. However, the data provided by it is both voluminous and complex. CGM devices measure the blood glucose in the interstitial compartment. The interstitial blood glucose levels are related to blood glucose through a diffusion process.[12] There are around 9 studies of CGM in ICU setting. Goldberg et al.[13] and Holzinger et al.[14] found that CGM had a high degree of accuracy, but a study by Rabice et al. found that CGM missed around 50% of the 30 hypoglycemic episodes as noted by Accu-Check glucometer, and hence the authors concluded that it is unsafe in ICU setting.[15] Before CGM replaces the home-based glucometer testing, various points need to be considered; firstly, maintaining direct access to blood for a prolonged period and its complications is quite cumbersome. Secondly, the accuracy needs to be proven beyond doubt before replacing the current glucometer devices. And lastly, the financial constraints of using the CGM need to be considered.

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