Limitations of blood glucose monitoring in type 2 diabetes

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Self-monitoring of blood glucose levels by people with diabetes is useful to guide decisions by the individual and healthcare professionals. However, it is important to understand and allow for the intrinsic and remediable limitations of blood glucose monitoring and know how to assess and correct causes of excess inaccuracy and variability.

Key points

- **Blood glucose monitoring (BGM) is useful to guide decisions by patients and healthcare professionals but its intrinsic and remediable limitations should be understood and allowances made for them.**
- **Problems with the BGM system affecting results include interference by ambient conditions, the haematocrit, medications, postprandial samples and reliability of blood glucose strips.**
- **Problems associated with the BGM user affecting results include errors in coding, strip storage, recording results and sample contamination.**
- **BGM variability is assessed by the coefficient of variation; components include measurement and biological variabilities.**
- **BGM results vary in their accuracy and variability but US and international standards are that 95% of BGM test results lie within 5% or 15%, respectively, of the true BGL value.**
- **The reliability of BGM results can be assessed by performing BGM immediately before and after a blood sample is taken for laboratory measurement of BGL: the lower the difference between the average of the two BGM results and the laboratory value, the higher the accuracy; and the lower the difference between the BGM results, the lower the variability.**

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Blood glucose monitoring (BGM) is recommended for all people with type 1 diabetes and those with type 2 diabetes taking medications that could cause hypoglycaemia (i.e. insulin or sulfonylureas).[1,2] People who self-monitor their blood glucose levels rely on it for short-term decisions about their management, and their health care professionals rely on it to assess the pattern of blood glucose levels (BGL) through the day, and use this to suggest changes in the person's lifestyle and/or medication schedules that may help with glycaemic control.

It is important for all those interpreting BGM results to understand the limitations of this management tool so appropriate therapeutic decisions can be made. The limitations of BGM relate to inaccuracy and variability. Some of these limitations have to be accepted as intrinsic to physiological glycaemic control and the current processes of BGM, but often the problems are largely remediable. This article outlines the extent and causes of the intrinsic and remediable inaccuracies and variabilities of blood glucose measurements, explains how accuracy and variability can be measured and minimised in individual patients and uses a case study to show how to assess BGM results before changing therapy based on them.

Accuracy and variability of BGM

Difference between accuracy and variability

A series of BGM measurements will give different values. The closer the average of the BGM test values to the true value, the greater the accuracy, and the larger the difference between the measurements, the greater the variability. Ideally, monitoring results have both high accuracy and low variability; unfortunately, however, they can sometimes have low accuracy and high variability. As noted, some of the inaccuracy and variability has to be accepted, but often there are remediable causes.

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Table. Accuracy and variability[3,4]*

Value	A High accuracy High variability	B Low accuracy Low variability	C (the ideal) High accuracy Low variability	D Low accuracy High variability
True value	8.1	8.1	8.1	8.1
Test values	10.4 and 6.0	6.2 and 6.0	8.3 and 8.1	8.3 and 3.9
Average of tests	8.2	6.1	8.2	6.1
Difference from true value	+0.1	–2.0	+ 0.1	–2.0
Difference between tests	4.4	0.2	0.2	4.4

* All measurements are in mmol/L.

Blood glucose monitoring standards: The American Diabetes Association and the International Organization for Standards require that 95% of blood glucose monitoring results lie within 5% and 15% of the true value respectively.[3,4]

1. Blood glucose monitoring: sample contamination

The effects of sugar contamination of the blood sample (0.3 μL) on the results of BGM can be spectacular. For example, one speck (1 μg) of glucose is 18.5 mmol/L, as shown in the calculation below.

1 μg of glucose = 1 ÷ molecular weight of glucose (μmol)

$= 1 \div 180$

$= 0.0056$ μmol

0.0056 μmol glucose in 0.3 μL of blood

0.0056×10^{-3} mmol glucose in 0.3×10^{-6} L of blood

$= (0.0056 \times 10^{-3}) \div (0.3 \times 10^{-6})$ mmol/L

$= 18.5$ mmol/L

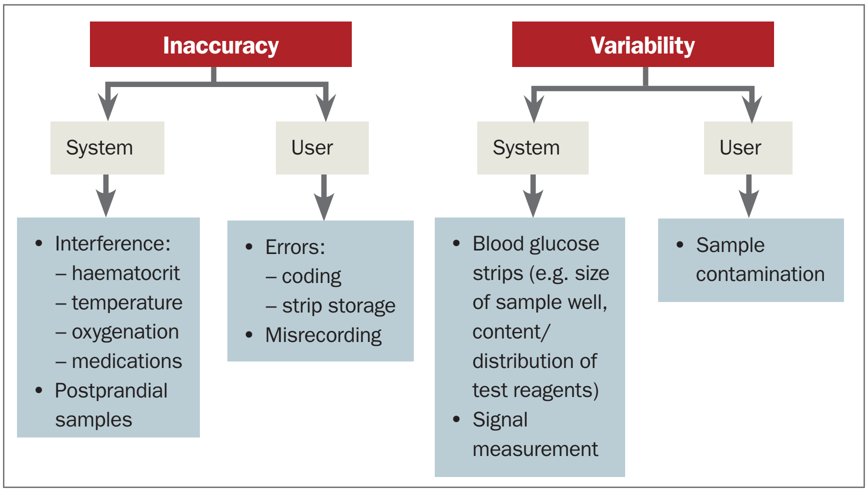

Figure 1. Sources of blood glucose monitoring inaccuracy and variability[5]

Four combinations of example values from two BGM measurements are shown in the Table to illustrate accuracy and variability.[3,4] The averages of the test values in columns A and C in the table are closer to the true value than those in columns B and D, indicating they are more accurate. The differences between the test values in columns A and D are larger than those in columns B and C, indicating they have greater variability. The test values in column C have both high accuracy and low variability – this is the ideal. The test values in column D, however, have both low accuracy and high variability.

The sources of inaccuracy and variability in BGM are associated with problems with the system and/or the user (Figure 1).[5]

Problems associated with the BGM system

The BGM system measures the capillary whole blood glucose concentration by chemical reactions in the blood glucose strip generating a signal that the meter converts into the displayed blood glucose reading. Problems with the BGM system affecting BGM results can occur at any stage in the procedure – the blood sample, the strip, the chemical reaction and the meter – and causes include interference by ambient conditions, the haematocrit, medications, use of postprandial samples and the reliability of the strips.[5]

Blood factors

The signal generated in the strip relates to the capillary whole blood glucose concentration but the meter is calibrated to give readings close to the fasting venous plasma glucose concentration. Glucose concentrations in whole blood are lower than in plasma (because red cells have a lower glucose concentration than plasma) and the glucose concentrations in venous plasma are less than in capillary plasma (because glucose moves from the capillaries into the tissues, especially after meals when tissue glucose uptake is stimulated by insulin).

Because the glucose concentration in red blood cells is less than that in plasma, increases and decreases in the percentage of red cells in the blood (the haematocrit) can result in misleadingly low or high BGL readings, respectively, unless, as in some BGM systems, the haematocrit is assessed and readings are adjusted accordingly.

Measuring capillary blood glucose concentration after a meal gives misleadingly high values because the system is adjusted to allow for the usual difference between fasting capillary blood and fasting venous blood but does not allow for the increased difference that occurs after meals.

Contamination of the skin with sugar at the site where the blood sample is taken can significantly increase the blood glucose concentration: a speck of glucose (1 μg) in a blood sample for BGM (0.3 μL) will increase the blood glucose by 18.5 mmol/L (Box 1).[6] Thorough cleansing of the sample site (hand washing) before BGM is therefore essential.

Strip, chemical reaction and meter factors

The chemical reaction between the glucose and the strip and its interpretation by the meter can be affected by the conditions of storage of the strips, the ambient temperature of their use, the

2. Blood glucose monitoring: variability[3,4,6-8]

- **The day-to-day variability in BGM results in one person include biological and measurement variability.**
- **The coefficients of variation for BGM in an individual (CV_i) are:**
  fasting BGL CV_i = 15%
  2-hour postprandial BGL CV_i = 18%
- **The least significant change (LSC) is the smallest change between measurements that is considered statistically significant:**
  LSC = 2 x CV_i
  LSC fasting BGL = 30%
  LSC 2-hour postprandial BGL = 36%

For details, see below.

Assessing the variability of laboratory test results

The distribution of repeated test results is described in absolute terms by measures of centrality (usually the arithmetic mean) and dispersion (usually the standard deviation [SD] from the mean value). The reference interval (RI), the range within which 95% of measurements lie, spans ± 2 SDs.

In practice, variability is usually described in relative terms as the coefficient of variation (CV), which is the ratio of the SD to the measured value, expressed as a percentage:

$CV = SD \div \text{test result} (\%)$

Measuring variability of blood glucose levels[6,7]

The total variability of the BGLs obtained from repeated BGM in an individual (CV_t) includes measurement variability (CV_m) and biological day-to-day variability within that individual (CV_b).

Biological variability[7,8]

BGLs measured at the same time of day in an individual under the same lifestyle and medication schedules and with perfect blood glucose measurement still vary from day to day. Also, postprandial biological BGL variability is considerably greater than preprandial – or fasting – BGL variability.

For example:[5,8]

CV_b for fasting BGL = 7%

CV_b for postprandial BGL = 13%

Measurement variability

To meet the American Diabetes Association (ADA) and the International Standards Organization (ISO) recommendations the CV_m is required to be below 2.5% and 7.5% respectively.[3,4] In the real world, using the average meter, the CV_m is approximately 13%.

This means that 95% of measurements where the true value is, for example, 4 mmol/L will lie between:

ADA: 3.8 to 4.2 mmol/L

IOS: 3.4 to 4.6 mmol/L

Real world: 3.0 to 5.0 mmol/L.

Total variability

The total variability of the results from an individual (the total CV, or CV_i) includes the biological variability within that individual (CV_b) and the measurement variability (CV_m). The formula to combine the measurement and biological variabilities is:

$CV_i = \sqrt{(CV_m^2 + CV_b^2)}$

For example:

Using a CV_m of 13% (the 'real-world' value) and the biological variabilities for fasting and postprandial BGLs quoted above:

For fasting BGL, $CV_i = \sqrt{(13^2 + 7^2)} = 15\%$

For postprandial BGL, $CV_i = \sqrt{(13^2 + 13^2)} = 18\%$

BGL variability from day to day – least significant change

The overall variability of the difference between two measurements in an individual is greater than the variability of the individual measurements:

CV of the difference between two measurements = $\sqrt{2} \times CV_i$

The more confident one wishes to be that the change in a measurement is a 'signal' rather than a 'noise', the greater the change needs to be relative to this – this is the least significant change (LSC):

$\sqrt{2} \times CV_i \times z$ (where the z value varies from 1.28 for 80% confidence to 2.6 for 99% confidence)* (Note that this is the standardised one-sided probability where the difference is not the result of chance – the background 'noise' of test variability)

Generally, 80% confidence is used: (z = 1.28):

$LSC = \sqrt{2} \times CV_i \times 1.28 = 1.4 \times CV_i \times 1.28 = 1.8 \times CV_i$

which approximates to 2 CV_i

Continuing the example above:

Using 80% confidence,

The LSC for fasting BGL is 2 CV_i = 2 x 15 = 30%

The LSC for postprandial BGL is 2 CV_i = 2 x 18 = 36%

This means that to be 80% sure that the difference between two daily results is a true difference, the actual change as a percentage must exceed 30% of the initial value for fasting BGL and 36% of the initial value for postprandial BGL.

Abbreviations: BGL = blood glucose level; BGM = blood glucose monitoring; CV = coefficient of variation; CV_b = biological variability; CV_m = measurement variability; CV_i = total variability of measurements in one individual; LSC = least significant change; RI = reference interval; SD = standard deviation.

* The z value is a measure of the distance of a particular normally distributed value from the mean in terms of numbers of SDs; the further from the mean (i.e. the greater the z value), the less likely a result has occurred by chance.

Blood glucose monitoring: check the whole system

Comparing self-monitoring and laboratory monitoring results

BGM result 1: ___________

BGM result 2: ___________

Average BGL on BGM: ___________

BGL on laboratory measurement: ___________

Accuracy and variability

- Accuracy is indicated by the difference between the average of the two BGLs on BGM and the laboratory value for BGL
- Variability is indicated by the difference between the two BGLs on BGM

Abbreviations: BGL = blood glucose level; BGM = blood glucose monitoring.

Figure 2. Blood glucose monitoring – check the whole system[9,10]

oxygenation of the sample (i.e. altitude), medications (such as L-dopa) in the blood and contamination of the blood sample by substances such as sugars on the skin.

Some meters automatically readjust the BGM system if a different batch of strips is used, but others require the user to calibrate the system. Users may not appreciate or remember the need to recalibrate their meter.

Avoiding these problems

Although some of the above sources of inaccuracy and variability can be avoided (e.g. incorrect strip storage and inadequate cleansing of the sample site), others cannot and can only be anticipated if the potential for problems in a particular patient are appreciated (e.g. in the cold or hypoxic/hyperoxic conditions, postprandially or in patients taking particular medications). In patients in whom BGM results are anticipated to be misleading, different ways of assessing glycaemic control are required, such as laboratory measurement of glucose, glycosylated haemoglobin (HbA_{1c}) or fructosamine levels.

Since their introduction in the 1980s, BGM systems have become simpler to use and less prone to some of these sources of inaccuracy. However, even when operated under the best possible conditions, results still vary considerably because so many factors interact in the BGM system in generating the BGL results.

Problems associated with the BGM user

Users of BGM can affect the results in several ways, including making errors when coding meters, incorrectly storing strips and recording results and contaminating samples. The incorrect recording of results, possibly with fabrication of results or omitting of some real results, is a common cause of inaccuracies that is often underestimated by health professionals. Apart from the variability of results associated with incorrect usage of the BGM system, blood glucose concentrations vary considerably within an individual even when lifestyle and medications are constant (Box 2). This variation is considerably greater for postprandial BGLs than for preprandial BGLs.

The inaccuracy and variability associated with the BGM system and the user should always be considered if BGM results are unexpected, different from those predicted by other measurements of glycaemia (e.g. HbA_{1c}) or would prompt a significant change in glycaemic management. The measuring of variability between BGM results within an individual is discussed in Box 2, including when a difference is a true signal of change (i.e. is statistically significant) – which is termed the ‘least significant change’ (LSC).[3,4,6-8]

Assessing reliability of BGM results

Assessment of an individual’s BGM results may be prompted by noticing considerable variability in BGLs at the same time on different days or a difference of more than about ±2 mmol/L between the average recorded fasting BGL value and that predicted by the current HbA_{1c} % – as a rough rule, the average fasting BGL in mmol/L is $2\ \text{HbA}_{1c} - 7$.[9,10]

Both accuracy and variability can be checked by arranging for the patient to perform a capillary BGL test (BGM) immediately before and after a blood specimen is taken for laboratory BGL analysis. The patient’s BGM results are then compared with each other and the laboratory value (Figure 2).[10] This is usually best done after an overnight fast because fasting BGL values are likely to be the lowest in the day and incorrect results of lower BGL values are more likely to prompt management changes that can cause significant problems (i.e. hypoglycaemic or hyperglycaemic episodes if BGM results are spuriously high or spuriously low, respectively).

Ideally, both BGM results will be within 5% of the laboratory value and separated from each other by less than 10%. As noted, the ideal rarely applies in practice but the BGM technique should be reviewed if the results of the two BGM tests taken within minutes of each other are separated by more than 26% of their mean value (the LSC, $2 \times \text{CV}_m$; Box 2) or if the mean of these two BGM results is separated by more than 15% from the laboratory value (the International Standards Organization [ISO] standard).[4,6,7]

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Using BGM to guide glycaemic therapy

Case study

Debbie is 59 years old, has had type 2 diabetes for eight years and is taking gliclazide modified release 60 mg in the morning and metformin 850 mg with breakfast and the evening meal. Her current HbA$_{1c}$ is 8.2% (66 mmol/mol). Her recorded fasting BGL values on BGM over the past six days have been 6.0, 7.2, 6.1, 5.9, 7.1 and 14.2 mmol/L, and the reading today is 6.9 mmol/L.

- *What would account for the unusually high fasting BGL?*

Excluding the high result yesterday, Debbie's average fasting BGL is 6.5 mmol/L.

- *Does this fit with the fasting BGL value predicted by the HbA$_{1c}$?*

You refer Debbie to a diabetes nurse educator to advise her on the appropriate use of her blood glucose meter. A few weeks later, you arrange to check her BGM results against the laboratory value.

Debbie's results before and after the laboratory sample was taken were 7.5 and 8.9 mmol/L and the laboratory value was 9.1 mmol/L.

- *Are Debbie's BGM results satisfactory?*

A month later, Debbie asks what is likely to have caused her fasting BGL to decrease from 7.1 mmol/L yesterday to 5.6 mmol/L today.

- *Is the apparent decrease a true signal or reflecting background measurement variability?*

Discussion of case

The unusually high value

Debbie's BGM result of 14.2 mmol/L the day before her presentation at the start of the case study is very different from the average (excluding this high result) of 6.5 mmol/L and probably results from a measurement or recording error. Debbie's finger may have been contaminated with a sugar when she pricked it, or she may have performed the measurement after breakfast rather than before.

Average fasting BGL and HbA$_{1c}$ prediction

The fasting BGL predicted by Debbie's HbA$_{1c}$ of 8.2% is 9.4 mmol/L (from 2 HbA$_{1c}$ – 7), whereas her average fasting BGL on BGM (excluding the high value) is 6.5 mmol/L. In the absence of a recent clinical event causing hyperglycaemia (e.g. illness), this discrepancy suggests either a systematic error in BGM testing (e.g. incorrect meter coding) or a laboratory problem in measuring HbA$_{1c}$ in Debbie's blood (e.g. a haemoglobinopathy affecting the HbA$_{1c}$ assay).

It is important to sort this out because if the HbA$_{1c}$ is correct, Debbie's hypoglycaemic therapy should be intensified but if the average fasting BGL of BGM testing is correct, such an intensification may well cause hypoglycaemia.

Debbie's BGM results vs laboratory value

Both the accuracy and the variability of Debbie's two test BGM values (7.5 and 8.9 mmol/L) after having had her BGM technique reviewed are within recommended limits. The mean of her two BGM results is 8.2 mmol/L, which is 0.9 mmol/L lower than the value measured in the laboratory of 9.1 mmol/L; at 9.9%, this is within the ISO standard of 15%. Debbie's two BGM results are separated by 1.4 mmol/L (17% of their mean value), which is within the recommended 26% separation (LSC).

The later two fasting BGL results

The difference between Debbie's fasting BGLs some time later is likely to be the result of BGM measurement variability. The second value (5.6 mmol/L) is 1.5 mmol/L (21%) lower than the first (7.1 mmol/L), which is within the LSC of 30%.

Summary

Self-monitoring of BGLs is useful to guide decisions by the patient and healthcare professionals but it is important to understand and allow for the intrinsic and remediable limitations of BGM and know how to assess and correct causes of excess inaccuracy and variability. Arranging for self-BGM testing immediately before and after a laboratory sample is taken for BGL analysis can assess the reliability of BGM results. **ET**

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