

Approved IFCC Recommendation on Reporting Results for Blood Glucose (Abbreviated)

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In current clinical practice, plasma and blood glucose are used interchangeably with a consequent risk of clinical misinterpretation. In human blood, glucose, like water, is distributed between erythrocytes and plasma. The molality of glucose (amount of glucose per unit of water mass) is the same throughout the sample, but the concentration is higher in plasma because the concentration of water and, therefore, glucose is higher in plasma than in erythrocytes. Different devices for the measurement of glucose may detect and report fundamentally different quantities. Different water concentrations in calibrators, plasma, and erythrocyte fluid can explain some of the differences. Results of glucose measurements depend on sample type and on whether methods require sample dilution or use biosensors in undiluted samples. If the results are mixed up or used indiscriminately, the differences may exceed the maximum allowable error of glucose determinations for diagnosing and monitoring diabetes mellitus, and com-

plicate the treatment. The goal of the IFCC Scientific Division Working Group on Selective Electrodes and Point of Care Testing (IFCC-SD, WG-SEPOCT) is to reach a global consensus on reporting results. The document recommends reporting the concentration of glucose in plasma (with the unit mmol/L), irrespective of sample type or measurement technique. A constant factor of 1.11 is used to convert concentration in whole blood to the equivalent concentration in the pertinent plasma. The conversion will provide harmonized results, facilitating the classification and care of patients and leading to fewer therapeutic misjudgments.

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The WHO and the American Diabetes Association (ADA) define the diagnosis of diabetes mellitus by at least 2 measurements of fasting plasma glucose concentration ≥ 7.0 mmol/L. As an alternative, a random venous plasma glucose concentration ≥ 11.1 mmol/L in the presence of symptoms or a 2-h post-oral glucose tolerance test result ≥ 11.1 mmol/L suffice to make a definite diagnosis of diabetes mellitus (1,2). The new classifications of "impaired fasting glucose" have narrower intervals [6.1–6.9 mmol/L (WHO) or 5.6–6.9 mmol/L (ADA)] for venous plasma glucose concentration than the previous fasting interval (5.6–7.7 mmol/L) for classifying normoglycemia and diabetes (3). The narrower diagnostic limits increase the need for reliable results to classify individuals correctly.

Currently, various types of instruments detect and report fundamentally different glucose quantities. Biosensors for glucose are "direct reading" when they measure glucose directly, i.e., without previous dilution of the sample. The new generation of direct-reading glucose sensors responds to the molality of glucose, which is identical in whole blood and plasma, whereas the glucose

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concentrations in these two systems are different. Methods requiring high sample dilution will produce results equivalent to concentration when calibrated against aqueous standards because the water concentrations in the sample and calibrator are almost identical after dilution.

The original intention of the IFCC Scientific Division Working Group on Selective Electrodes and Point of Care Testing (IFCC-SD WGSE) was to make a recommendation for direct-reading biosensors in blood gas/electrolyte/metabolite analyzers. However, an isolated recommendation would be meaningless and not lead to the goal of harmonized results, which requires a consensus on reporting results for all analyzers. Inexpensive instruments with direct-reading biosensors are available for self-monitoring or point-of-care testing of glucose (4–6). The clinical chemistry laboratory is expected to perform glucose determinations by direct-reading sensors concurrently with other routine instruments that measure substance concentration in diluted samples.

In current clinical practice, plasma and blood glucose are used interchangeably (7) with a consequent risk of misinterpretation. The two systems are frequently mistaken in the clinical literature, despite an average 11% difference in glucose concentration (plasma > blood). The ADA provides clinical decision limits for the concentration of glucose in venous plasma, but the WHO in addition provides the concentration of glucose in whole blood (1–3).

With the present use of multiple methods providing results of different quantities, there is a serious risk of clinical misinterpretation. For example, some blood gas/electrolyte/metabolite instruments with direct-reading glucose biosensors are calibrated with aqueous calibrators to provide results according to the “relative molality” of glucose in the sample. The predicted ratios of results obtained by such instruments to the results obtained by instruments that analyze diluted specimens are 1.18 (0.99/0.84) for normal whole blood and 1.06 (0.99/0.93) for normal plasma, in agreement with results from the literature (8, 9).

We recommend a constant factor of 1.11 for conversion between the glucose concentration in blood and the equivalent concentration in the pertinent plasma and reporting of only the glucose concentration in plasma to avoid misjudgments. The converted result equals the concentration of glucose in plasma when the hematocrit and water concentrations are normal. The recommendation includes point-of-care devices and methods that measure the concentration of glucose in whole blood. The conversion does not eliminate current preanalytical influences or hematocrit effects, which are specific to certain methods [see the summary by Chance et al. (4)]. However, the conversion will provide consistent harmonized results, facilitating the classification and care of patients and leading to fewer therapeutic misjudgments.

Activity and Molality of Glucose

Biosensors respond to activity of the pertinent analyte. The activity of glucose is assumed equal to molality, with a molal activity coefficient equal to 1. Activity is physiologically relevant for determining enzymatic reaction rates, direction of chemical processes, transport, and binding to receptors. Glucose permeates the erythrocyte membrane quickly via passive transport (facilitated by the erythrocyte glucose transporter); therefore, the molality of glucose (amount of glucose per unit mass of water) is identical in erythrocytes and plasma. Results obtained by a direct-reading glucose biosensor responding to molality are identical for whole blood and its separated plasma.

The converted results based on measured glucose activity and the average concentration of water in normal plasma are called the active concentration of glucose in normal plasma to distinguish them from the substance concentration of glucose in actual plasma. We recommend converting and reporting results from all systems and devices using direct-reading glucose biosensors as the active concentration of glucose in normal plasma (10, 11) and using the unit mmol/L. The converted results of direct-reading glucose biosensors are proportional to the activity and molality of glucose (contrary to the less physiologic substance concentration of glucose) because of the constant factor relationship. The advantage of direct-reading glucose biosensors responding to activity and molality is maintained. The ratio between the active and conventional concentrations of glucose in a given plasma sample equals the ratio of the average plasma water concentration to the actual plasma water concentration (with a mean of 1.00 and SD of 0.01 if the water concentration is normal). In practice, the two can be considered identical. Subgroups such as neonates or pregnant women may have slightly higher than average plasma water concentrations. A lower-than-average actual plasma water concentration attributable to, e.g., hyperlipidemia will lead to a lower conventionally used substance concentration but has no impact on the active concentration of glucose. The active concentration of glucose is unaffected by changes in water concentration, but the conventionally used concentration will change in proportion to the water concentration.

For the same reason, control materials with assigned glucose concentrations must have a normal water concentration of 0.93 kg/L to be valid for quality assessment of direct-reading glucose biosensors. Otherwise, the water concentration must be taken into account.

Concentration of Glucose

Most current photometric methods to measure glucose use enzymatic conversion with NADH or NADPH as coenzymes and absorbance measurements near or at 340 nm. The molar absorptivity permits direct calculation of the glucose concentration after complete reaction.

The concentration can also be determined by a kinetic measurement, comparing sample to a calibrator. A kinetic

measurement obviates subtraction of background, at the cost of introducing a small positive bias. Enzymatic reaction rates depend on substrate activity (or molality). The slightly lower water concentration in a diluted sample compared with a diluted calibrator provides a relatively (slightly) higher enzymatic reaction rate in the diluted sample. Methods that include protein precipitation also have a positive bias, depending on the degree of dilution and concentration of protein. Despite these (minor) theoretical queries, routine clinical chemical analyzers measure glucose concentration (amount of glucose per volume of sample) with sufficient trueness and precision.

Biosensors that require dilution provide results that closely resemble concentration. These devices report concentration based on the concentration of glucose in the calibrator.

Plasma and whole-blood glucose concentrations are not interchangeable because of the difference in glucose concentrations between plasma and whole blood (in contrast to current practice in many institutions). Different reference intervals and clinical decision limits apply. The recommendation here is to report only the concentration of glucose in plasma, irrespective of material investigated. Glucose and water distribute freely between erythrocytes and plasma; therefore, the molality (but not the concentration) of glucose is identical in erythrocytes and plasma. Because erythrocytes have a lower water concentration than plasma, the concentration of glucose in whole blood is lower than in plasma for a given concentration of glucose in plasma. The concentration of glucose in plasma is independent of hematocrit. Another reason for choosing plasma rather than whole blood as the system of reference is the relationship between glucose activity and concentration. Glucose activity and concentration are practically proportional in plasma, where the water concentration varies relatively little, but not in whole blood, where hematocrit may vary considerably and confound the relationship. The concentration of glucose in plasma (rather than the concentration in whole blood) therefore more closely reflects the activity of glucose. For most purposes, the concentration of glucose in plasma is physiologically more relevant to measure and report than the concentration in whole blood.

Serum should not be used because the glucose concentration decreases $\sim 0.6 \text{ mmol} \cdot \text{L}^{-1} \cdot \text{h}^{-1}$ as a result of glycolysis during its preparation (12). Likewise, the concentration of glucose in capillary whole blood should not be used as a substitute for the concentration in venous plasma (13).

The system of reference and type of specimen have not always received the attention they deserve. The ADA recommends for self-monitoring a maximum allowable CV of 10% at glucose concentrations of 1.7–22 mmol/L and a maximum bias of 15% from a reference method value (14, 15). In other words, the ADA accepts no more than 5% analytical error for self-monitoring of blood glucose (14). The recently proposed quality criteria for

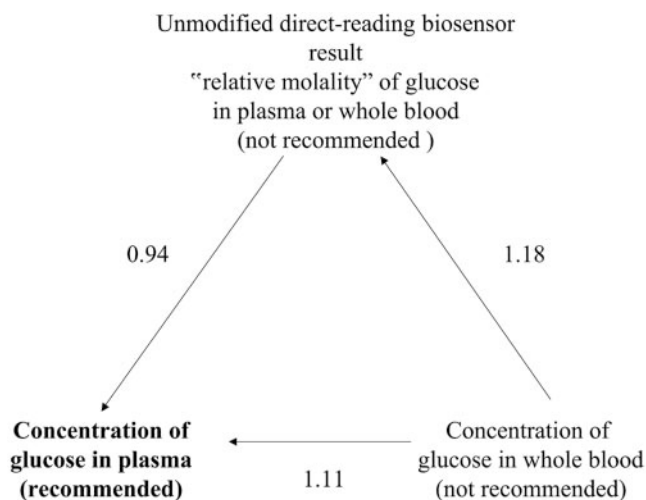


Fig. 1. Conversion factors for different glucose quantities.

laboratory analysis of The National Academy of Clinical Biochemistry (NACB) (12), based on intraindividual biological variation (16), are even more demanding. The maximum allowable imprecision (CV) according to the NACB Laboratory Medicine Practice Guideline is 3.3%, the maximum bias is 2.5%, and the maximum total error (difference from the true value) is 7.9%. The systematic 11% difference between normal blood and plasma already exceeds the recommended allowable maximum error. Mistaking or not properly distinguishing sample type may lead to misinterpreting the result and a wrong diagnosis. According to an editorial on the subject (17), reporting whole-blood glucose values is anachronistic and comparable to reporting the whole-blood rather than the plasma concentration of potassium. Manufacturers and clinical chemists always should report the concentration of glucose in plasma to avoid this risk, irrespective of sample type and method of measurement.

The present IFCC document recommends using a constant factor of 1.11 (Fig. 1) for converting glucose concentration, based on water concentrations of normal whole blood and of normal plasma. The relationship has been supported experimentally (8, 9). Conversion based on measured hematocrit may introduce additional error (9), in addition to being less convenient and requiring additional information. Converted (whole blood \rightarrow plasma) glucose concentrations have the same dependence on hematocrit as the currently reported whole-blood glucose concentrations (18). With this recommendation, all results can be harmonized and reported as the concentration of glucose in plasma. The laboratory, however, must keep information about which sample type and measurement procedure were used.

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