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Recommendation on Reporting Results for Blood Glucose (From an IFCC Stage 1 Document) IFCC Scientific Division Working Group on Selective Electrodes

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****For purposes of this document, direct reading biosensors are defined as sensors which detect analyte without requiring dilution of the sample.**

Different devices for the measurement of glucose detect and report fundamentally different analytical quantities. In man, glucose distributes like water between erythrocytes and plasma, carried by the erythrocyte glucose transporter. Therefore, molality of glucose (amount per unit water mass) is equal in plasma and erythrocyte fluid. Different water concentrations in calibrator, plasma, and erythrocyte fluid can explain some differences dependent on sample type, methods requiring sample dilution, and "direct reading" biosensors** detecting molality. The original intention of the IFCC Document was to recommend reporting of plasma equivalent glucose concentrations for direct-reading biosensors in blood gas/electrolyte/metabolite analyzers. However, an isolated recommendation will not lead to globally commutable results, which require a consensus on reporting results from all analyzers. The IFCC-SD Working Group on Selective Electrodes recommends harmonizing to the concentration of glucose in plasma (with the unit mmol/L), irrespective of sample type or measurement technology used.

Glucose permeates the erythrocyte membrane quickly, by passive transport (facilitated by the erythrocyte glucose transporter, which catalyzes the uniport movement of D-glucose down its concentration gradient). Therefore, glucose distributes between erythrocytes and plasma like water. The activity (or molality) of glucose inside erythrocytes equals that in plasma, providing equivalent results for blood and plasma when measured with a direct reading glucose biosensor. Activity (of symbol a, without unit) is related to the chemical potential ($\mu = \mu 0 + RT\ln a$ of unit kJ/mol) used in calculations of free energy changes, reaction affinity etc. The activity of glucose is assumed equal to molality, or amount per unit water mass, m of unit mmol/kg H_2O. Activity is the physiologically relevant quantity, determining enzymatic reaction rate, direction of chemical processes, transport, binding to receptors etc. The activity (or molality) of glucose in blood is physiologically relevant, but not recommended as a quantity for clinical use in this document. A new quantity like activity or molality of glucose in plasma would only increase the present risk of clinical misinterpretation and add to the confusion regarding sample type and measurement technology.

Various types of instruments now detect and report fundamentally different glucose quantities. Inexpensive instruments with direct-reading biosensors are widely available for self-monitoring or point of care glucose testing (1-3). For the foreseeable future, the clinical chemistry laboratory is expected to perform glucose determinations by direct reading sensors concurrently with other routine instruments. Unlike direct reading glucose biosensors that detect molality, sensors that require diluted samples produce results that depend on water concentration of the sample. On a concentration basis (amount of glucose per liter of sample), glucose in plasma is higher than glucose within erythrocytes, because the water concentration is higher in plasma than in erythrocytes. Therefore, biosensors relying on sample dilution will produce higher results for plasma than the corresponding blood, by approximately 11% for blood of normal hematocrit. Furthermore, the clinical staff in general does not know whether the laboratory results are for blood or plasma glucose (4).
The World Health Organization (WHO) (5, 6) and American Diabetes Association (ADA) (7) define diabetes mellitus by more than one fasting plasma glucose concentration > 7.0 mmol/L. As an alternative, a casual 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. The new category of "impaired fasting plasma glucose concentration" has a narrower interval of 6.1-6.9 mmol/L than the previous fasting interval of 5.6-7.7 mmol/L between normal and diabetic classifications. With the present use of multiple methods providing different results, there is a serious risk for clinical misinterpretation. The WHO and ADA categorize patients based on their plasma glucose concentration. The ADA further recommends no more than 5 % analytical error for future glucose monitors, with a maximum of 15% total error and 10 % imprecision (8, 9). The systematic 11 % difference between normal blood and plasma glucose concentration alone exceeds the maximum analytical error. We recommend always reporting the concentration of glucose

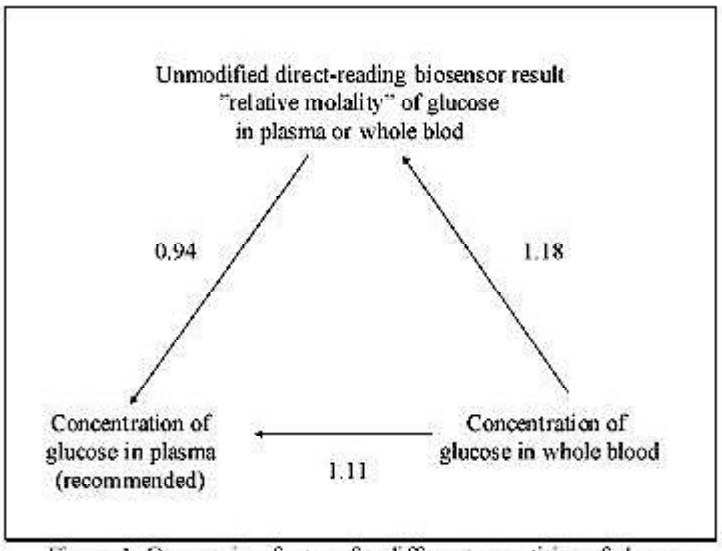

Figure 1. Conversion factors for different quantities of glucose.

Figure 1 illustrates the relationships among the various methodologies and sample types currently used for glucose analysis. We recommend converting and reporting results from systems and devices using direct-reading glucose biosensors as the equivalent concentration of glucose in normal plasma. The advantage of direct-reading glucose biosensors detecting molality (rather than conventional concentration, which may be less physiologically relevant) will not be lost. The converted results of direct reading glucose biosensors will be proportional to molality and activity of glucose due to the constant factor relationship. The ratio of molality to conventional concentration of glucose in plasma is dependent on the ratio of water concentrations of normal to actual plasma, which is close to one. Thus, a lower water concentration, e.g. due to hyperlipidemia, will provide a slightly low 'conventional', but not 'equivalent' concentration of glucose

in plasma to avoid ambiguity. The choice of plasma instead of whole blood is somewhat arbitrary. However, leading practitioners in the field of diabetes management prefer plasma glucose concentration as the quantity of choice (from personal communication with KGMM Alberti). When whole blood glucose concentration is measured, a constant factor of 1.11 will convert whole blood to plasma glucose concentration. The factor 1.11 is the ratio of water and therefore, glucose concentrations in normal plasma and whole blood. We recommend always using a constant factor of 1.11. An individual conversion based on hematocrit may introduce additional imprecision (10), besides being less convenient and requiring additional information. The converted plasma glucose concentrations will have the same dependence on hematocrit as the presently reported whole blood glucose concentrations.

Consider, e.g., a blood specimen with a normal hematocrit (Hct) of 0.43. The water concentration of erythrocytes is ~ 0.71 kg/L. The water concentration of plasma is ~ 0.93 kg/L. The water concentration (kg H2O/L) of the blood specimen must be intermediate, (0.43)*(0.71)+(1-0.43)*(0.93) = 0.84. The ratio of water (and therefore, glucose) concentration between plasma and whole blood is 0.93/0.84, or 1.11. The ratio depends on hematocrit. A decreased Hct causes an increased glucose concentration in whole blood and vice versa. When hematocrit is known to be abnormal, whole blood glucose concentration may be "hematocrit adjusted" to a normal hematocrit of 0.43 by multiplication with 0.84/(0.93-0.22*Hct). Unfortunately, some methods may have additional erythrocyte or hemoglobin interference.

Direct-reading glucose biosensors detecting molality of glucose in whole blood are available on combined blood gas/electrolyte/metabolite analyzers from all the major manufacturers of these systems. Most of these systems presently correlate to the plasma equivalent concentration of glucose. However, one manufacturer calibrates with aqueous calibrators without considering the different concentrations of water in sample and calibrator, providing 'relative molality' of glucose in the sample. The predicted ratio of results for unmodified direct/diluted methods is 0.99/0.84 = 1.18 for whole blood and 0.99/0.93 = 1.06 for plasma, in harmony with results from the literature (10, 11). Most devices for point of care analysis of blood glucose also use direct reading biosensors, and some calibrate to the plasma equivalent concentration of glucose (1). Continued use of the variety of systems presently available for measurement of glucose without conversion to plasma results may cause confusion with conventionally measured and reported glucose concentrations, for example from the central laboratory. All reference intervals and clinical decision levels must accordingly reflect plasma results. **Figure 1**

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