

## Measurement of Circulating Glucose Concentrations: The Time Is Now for Consistency among Methods and Types of Samples

Diabetes mellitus was first described in the Egyptian papyrus of Ebers in 1552 BC by people who noted the attraction of insects to the "sweet urine" of those who produced abnormal amounts and later by tasters of urine who could fashion a diagnosis by recognizing the "sweet taste". The name "diabetes", initially used in the 1st century AD, comes from the Greek word meaning "to pass through". "Mellitus", a Latin word meaning "sweet as honey", was added in the 18th century. The first chemical tests to measure sugar in urine were developed in the early 19th century. Early in the last century, whole-blood colorimetric analyses became available to clinicians, despite complexities in the preparation and analysis of samples. The term "blood glucose" remains a prominent feature to describe the state of glycemia in patients with diabetes, whether as a fasting value, during a glucose tolerance test, or in monitoring glucose values to determine the insulin dose. Measurements of glucose in venous whole blood, capillary whole blood, or plasma still define diabetes mellitus by WHO criteria (1), with the American Diabetes Association (ADA) referring only to concentrations in plasma (2).

Modern applications of glucose assays practically diverge in the diagnosis vs monitoring of treatment(s) of diabetes. Thus, diagnosis is best made in a certified laboratory with the measurement of glucose in plasma after a fast of at least 8 h (3). The benefits of relating closely monitored glucose concentrations to treatment decisions have become feasible and practical with the availability of small devices capable of measuring with precision and accuracy glucose from low to high concentrations in very small quantities of blood or extracellular fluid. The fact that most devices sample whole blood presents a dilemma when expressing values in plasma vs whole blood.

In this issue, D'Orazio et al. (4) have admirably and directly addressed these conundrums with a strong recommendation to report all measured glucose concentrations (whether assayed in plasma, whole venous blood, whole capillary blood, or serum) as if they were assayed in plasma. Their commentary (and importantly, Fig. 1 in their report) suggests a constant to convert values in whole blood to comparable units in plasma. They aver that uniform application of their recommendations will rationalize the use of glucose measurements for diagnosis and monitoring of treatment. Certainly the consistent reporting of all values in plasma equivalents will reduce the 11% bias when values are reported in whole-blood equivalents but interpreted as equating to values in plasma. In addition, they recommend expressing glucose values in SI units.

During the usual course of managing their disease, patients with diabetes mellitus will experience glucose measured on different samples by different techniques. For example, they may encounter the healthcare system in

the emergency department or otherwise in a hospital or clinic and have venous blood collected and processed for measurement of glucose in plasma. Alternatively, if treated with insulin, they will quite frequently determine glucose concentrations with some kind of hand-held device, which most likely measures glucose in whole blood obtained from capillaries (5). Harmonization of the values reported by these two sets of instruments remains an imperative for clinical medicine in general and the management of diabetes in particular. Thus, the clinician may (and usually does) review the results with the expectation that the glucose values derived from measurement of whole blood or plasma are equivalent. However, that may not always be the case. D'Orazio et al. (4) have proposed a sensible solution with values reported exclusively as equivalents in plasma. This is not the first time these recommendations have been placed before the community of laboratory professionals. In 2001, an IFCC working group in a report (6) very similar to that of D'Orazio et al. (4) (and with several authors in common) recommended that glucose meters be harmonized to the concentration of glucose in plasma, regardless of the technology or type of sample. Two of the authors presented the same recommendation in a still earlier article (7). Similarly, the Clinical and Laboratory Standards Institute (formerly NCCLS) guidelines for point-of-care blood glucose testing published in 2002 recommend that institutions reporting plasma glucose results from instruments in the clinical laboratory should use point-of-care devices that report plasma-equivalent results (8).

The practical applications of these recommendations remain somewhat uncertain. D'Orazio et al. (4) emphasize that the WHO guidelines for the diagnosis of diabetes mellitus quote glucose concentrations in plasma, venous whole blood, and capillary whole blood. If one were to use the contrasting concentrations to discriminate "normal" vs impaired glycemia vs diabetes mellitus according to the WHO guidelines, manufacturers of instruments/assays may feel they need to provide algorithms in instruments to address the several requirements. On the other hand, if the recommendations of D'Orazio et al. (4) are sustained, reporting only in plasma equivalents may harmonize most instruments and methods, whether they be in the clinical laboratory or a small device used by the patient. However, the issue of measuring glucose in extracellular fluid needs to be reviewed to assure that values are equivalent to those in plasma. Although devices that continuously monitor glucose in extracellular fluids are routinely calibrated to blood glucose meters reporting values in plasma equivalents (9), there are no uniform analytical standards for calibrating these devices.

Although used in many countries, the reporting of plasma glucose concentrations only in SI units (i.e., mmol/L) remains a monumental challenge for the medical community in the United States. In our experience,

most clinicians do not wish to convert to a new system of values, emphasizing the possibilities of misinterpreting results with the new units and thereby placing patients at risk. In likely a positive mode, the concentration of fasting plasma glucose defining diabetes (126 mg/dL for both WHO and the ADA) is a bow (although slight in practice in the US) to SI units (7 mmol/L). Hopefully the next iteration of the ADA Expert Committee will strongly consider the recommendations of D'Orazio et al. (4) to express glucose values only in SI units.

Despite progress in our comprehension of the mechanisms of insulin action and the pathophysiology of diabetes, increased glucose concentrations in plasma or whole blood constitute the sole criterion for the diagnosis of diabetes (1, 2). In this context, the use of glycohemoglobin is appealing. Although still speculative, the application of glycohemoglobin measurements to the diagnosis and/or screening of diabetes mellitus will link diagnosis, long-term monitoring, and monitoring the efficacy of therapy. If glycohemoglobin is accepted as a diagnostic criterion, the use of glucose for diagnosis will be reduced. From the experience of one of us (M.S.) on the last iteration of the ADA Expert Committee, the movement toward diagnosis with glycohemoglobin may gain more support in North America, joining the Japanese, who currently include hemoglobin A<sub>1c</sub> as a diagnostic criterion.

However, for day-to-day management of patients receiving insulin, frequent monitoring of glucose remains an imperative to the goal of optimal glycemic control. The need for consistent reporting of circulating glucose concentrations among all techniques, as proposed by D'Orazio et al. (4), demands action. Thus, the IFCC and other similar organizations must find ways to implement these sensible recommendations in the clinical setting, for all patients with or evaluated for diabetes mellitus. In our experience these goals must be addressed through the relevant organizations of clinical medicine. It therefore is not sufficient to state guidelines without a plan to promulgate them. Having addressed similar issues of disseminating guidelines concerning the use of laboratory tests into the practice of medicine, we realize the complexity and challenges of implementing the recommendations of D'Orazio and various collaborators (4, 6, 7) across all providers of medical care. Nevertheless, in our view, another report of recommendations without a concerted effort to introduce them into practice serves little purpose.

Rather, we eagerly anticipate successful, pragmatic application of these recommendations with the ultimate goal of enhancing patient care.

#### References

1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2005;28:S37-42.
3. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436-72.
4. D'Orazio P, Burnett RW, Fogh-Andersen N, Jacobs E, Kuwa K, Kulpmann WR, et al. Approved IFCC recommendation on reporting results for blood glucose (abbreviated). *Clin Chem* 2005;51:1573-6.
5. The Diabetes Research In Children Network (Direcnet) Study Group. A multicenter study of the accuracy of the One Touch Ultra home glucose meter in children with type 1 diabetes. *Diabetes Technol Ther* 2003;5:933-41.
6. Burnett RW, D'Orazio P, Fogh-Andersen N, Kuwa K, Kulpmann WR, Larsson L, et al. IFCC recommendation on reporting results for blood glucose. *Clin Chim Acta* 2001;307:205-9.
7. Fogh-Andersen N, D'Orazio P. Proposal for standardizing direct-reading biosensors for blood glucose. *Clin Chem* 1998;44:655-9.
8. Sacks DB, Bernhardt P, Dunka LJ Jr, Goldstein DE, Hortin GL, Mueller P. Point-of-care blood glucose testing in acute and chronic care facilities; approved guideline-2nd ed. NCCLS document C30-A2. Wayne, PA: NCCLS, 2002.
9. Diabetes Research in Children Network (DirecNet) Study Group. Accuracy of the GlucoWatch G2 Biographer and the continuous glucose monitoring system during hypoglycemia: experience of the Diabetes Research in Children Network. *Diabetes Care* 2004;27:834-6.

Michael W. Steffes<sup>1\*</sup>

David B. Sacks<sup>2</sup>

<sup>1</sup> Department of Laboratory Medicine and Pathology  
Medical School  
University of Minnesota  
Minneapolis, MN

<sup>2</sup> Department of Pathology  
Brigham and Women's Hospital  
and  
Harvard Medical School  
Boston, MA

---

\*Address correspondence to this author at: Department of Laboratory Medicine and Pathology, Medical School, University of Minnesota, Minneapolis, MN 55455.

---

DOI: 10.1373/clinchem.2004.044867

---