Diagnosis of diabetes mellitus: reiterated responsibilities for the clinical laboratory

Diabetes mellitus is a global burden for public health worldwide. The number of diabetic patients in 2012 was 371 million, and the expected number in 2030 is 552 million, which represents an increase of more than 50%. As specifically regards the US, 25.8 million children and adults (i.e., 8.3% of the population) are currently suffering from this condition [1]. The diagnosis of diabetes mellitus is therefore a key event for patient and society, owing to the severe consequences of the disease, which lead to an impaired quality of life for patients and high healthcare expenses for society.

For decades the diagnosis of diabetes mellitus was only based on the assessment of venous blood glucose, more specifically plasma glucose. The current World Health Organization (WHO) criteria indicate that diabetes mellitus is diagnosed by a concentration of fasting plasma glucose higher than 7.0 mmol/L (i.e., 1.26 g/L) repeated twice, or by random glycemia higher than 11.1 mmol/L (i.e., 2.0 g/L). Recently, hemoglobin A1c (HbA1c) has been proposed as a valuable tool for diagnosing this condition, in the presence of values higher than 48 mmol/mol (i.e., 6.5% of total Hb) [2]. This last criterion has then been endorsed by several international and national organizations (including the WHO), although some doubts remain [3].

However, the approach, the determination of glucose or HbA1c has to be performed by clinical laboratories. This implies that the means devoted by the clinical laboratory for glucose and HbA1c assays are well fitted to the goal. Glucose assay seems to be a simple and straightforward procedure. However, the need to use validated techniques is still required, and methods have to be carefully calibrated and traceable to reference measurement procedures [4]. Point of care testing (POCT) instruments have also been recently suggested as valuable tools for the diagnosis of this condition, as well as for a number of other human disorders [5]. In this issue, Freckmann et al. clearly show that these devices must be strictly evaluated and related to reference procedures like laboratory methods [6].

Besides, a classical but still critical topic is the preanalytical phase of glucose assay(s). In a paper published in this issue, Chan et al. show that the decrease of glucose concentration in blood samples was not proportional to the initial glucose values, as suggested by other studies, but that this reduction was constant [7]. The alteration of glucose concentration due to the action of glycolytic enzymes is significant and could substantially impair glucose values, thus leading to misclassification of patients with respect to the (real) diabetic status. Further support to this evidence comes from another study by Fobker, who shows that the stability of glucose varies widely using different types of tubes and additives [8]. A recently published article by García Del Pino et al. confirms previous data on the straightforwardness and effectiveness of citric acid as an immediate inhibitor of glycolysis [9]. The authors reported significantly lower measured glucose concentrations in sodium fluoride (NaF) specimens than in paired citrate tubes, and the implementation of the new additive improved the quality of the diagnosis, achieving a statistical significance for gestational diabetes mellitus (GDM) screening. In a previous Editorial, Gambino and Bruns highlighted the need for additional studies about the effect of prompt inhibition of glycolysis on the diagnosis of diabetes, because the epidemiological studies that defined the diagnostic thresholds were based on the use of NaF tubes for collecting samples [10]. Szoke and colleagues provided further support to the need for reevaluating the current cut-points derived from plasma glucose data using fluoride tubes. The leading take-home message is that compensatory changes in decision levels should be considered when clinical laboratories introduce commercially available collection tubes containing citrate buffer (VFC) [11].

The drawbacks of only using plasma glucose for diagnosing diabetes are well known to most working in the field of laboratory diagnostics, and are mainly attributable to the high vulnerability of this test to preanalytical variables, especially to the storage conditions and the
presence of spurious hemolysis [12]. This is also reflected by the recent findings of Nielsen et al., who showed that the percentage of undiagnosed patients with diabetes may be reduced by approximately 2% with replacement of fasting plasma glucose with HbA1c [13]. A new era is probably dawning for the diagnosis of diabetes mellitus [3, 14], but the responsibilities for the clinical laboratory remain virtually unchanged.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

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