Sensing in Electroanalysis

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Possible Errors in Electrochemical Detection of Blood Glucose

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Abstract: The need of dosage of glucose concentration required to develop test methods that allow rapid and accessible even at home. It is necessary to follow a simple protocol that minimizes errors and interferences using some functions of these devices. We have identified possible errors in obtaining experimental data: lower sample volume, consume of different foods in the evening and the morning of blood collection, type of sample analysed (serum/plasma, venous/capillary blood). The data obtained using commercial biosensors were compared with spectrometric methods and good report was obtained.

Keywords: Blood glucose; Electrochemical detection.

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Introduction

Blood glucose measurement is important in the screening, diagnosis and monitoring of diabetes mellitus, the most common disorder of the carbohydrates metabolism, with a rapid worldwide increasing incidence and prevalence (Table I).

There are many available methods for glucose determination, but yet there is no international consensus about a reference/standard method for the measurement of blood glucose, especially taking into account that since the introduction of the first glucose point-of-care system (in 1970s), blood glucose assay has changed from a solely central laboratory-based procedure into a usual practice in hospital wards, emergency and primary care settings, and home self-monitoring in diabetic patients [1].

Table I*: Diagnostic criteria for diabetes and prediabetes (adapted from American Diabetes Association [2]).*

Test	Prediabetes (increased risk for diabetes)	Diabetes
FPG	100 mg/dL – 125 mg/dL (5.6 mmol/L – 6.9 mmol/L) [Impaired Fasting Glucose, IFG]	≥ 126 mg/dl (7 mmol/L)
2-hours plasma glucose on 75g OGTT	140 mg/dL – 199 mg/dL (7.8 mmol/L – 11.0 mmol/L) [Impaired Glucose Tolerance, IGT]	≥ 200 mg/dL (11.1 mmol/L)
Hb A1c (ADA criterion, 2011)	5.7 – 6.4%	≥ 6.5%
RPG	---	≥ 200 mg/dL (11.1 mmol/L)

Legend: FPG, Fasting Plasma Glucose, i.e., no caloric intake for at least 8 hours; *OGTT*, Oral Glucose Tolerance Test, using a glucose load that contain the equivalent of 75 g anhydrous glucose which is dissolved in water; *HbA1c*, A1c isomer of glycated haemoglobin (glycohaemoglobin); *RPG*, Random Plasma Glucose in patients with classic symptoms of hyperglycaemia or hyperglycaemic crisis; *ADA*, American Diabetes Association.
Note: In the absence of unequivocal hyperglycaemia, criteria 1–3 should be confirmed by repeated testing.

Moreover, differences have been reported both in the central laboratory and at the point of care measurements, depending sometimes on specimen types used, i.e., whole blood (capillary, venous, or arterial), plasma, or sample matrices such as interstitial fluid.

Since in diabetes mellitus medical decision making is most based on the information provided by laboratory tests, the attempt to develop an internationally recognized reference method for blood glucose measurement or a reference material is a real key challenge that would dramatically improve both diabetes prophylaxis and care.

Hyperglycemia and Hypoglycemia

Dosage of glucose is used as screening for diabetes, insulin requirements calculation, islet diagnosis, evaluation carbohydrate metabolism disorders. To determine fasting glucose is mandatory patient not to eat at least 8 hours.

Hypoglycemia occurs in severe liver disease, malabsorption syndrome, alcohol consumption, pituitary insufficiency, and Addison's disease. To prevent hypoglycemia is recommended to not exceed 16h food item and before harvesting not be oral antidiabetic medication or insulin. These drugs can cause blood sugar low values: acetaminophen (Tylenol), alcohol, clofibrate, oral contraceptives, disopyramide, enalapril, erittromicina, fenfluramine, gemfibrozil, glyburide, guanethidine, monoamine oxidase inhibitors, insulin, nitrazepam, oxandrolone, oxymetholone, pentamidine, promethazine, propranolol, steroiri anabolic sulfonylurea, tolazamide, tolbutamide, verapamil [3].

Hyperglycemia occurs in diabetes, stroke, pregnancy, gestational diabetes, Cushing's syndrome. Elevated blood sugar can give tricyclic antidepressants, beta-blockers, clonidine, oral contraceptives, corticosteroids, diuretics, estrogens, furosemide, salbutamol, salicylates. Failure fasting can give falsely elevated blood glucose levels [3]. Characteristics of people who use blood glucose tests are indicated in Table II.

Table II: *Description of some characteristics of people using glucose tests*.

Characteristics	Description	Ref.
Users	Groups of patients with diabetes. Physician’s offices. Intensive care units (icus) and hospital wards. Rescue services emergency response units. During dialysis. Aged care facilities.	[4]
Volume sample/time for analysis	Large volumes of blood (> 20 μl) - several minutes to carry out the full measurement. Small blood samples (< 1 μl) - few seconds.	[5]
Costs	Significantly reduced over time.	[4]

Continuous Glucose Monitoring

Glucose monitoring is a very important part of the management of glycaemia in people with type 1 diabetes. Some of the patients don't monitor the concentration of glucose levels either postprandial or overnight, which may leave undetected situations of hyperglycaemia and hypoglycaemia respectively.

There have been developed systems using continuous monitoring of glucose (subcutaneous sensors), which measure interstitial glucose levels. These systems are generally only considered for use by patients who experience particular difficulties in maintaining normal glucose levels or who have been transferred to continuous subcutaneous insulin infusion therapy. The accuracy of current devices is sometimes poor and one possible explanation is the low performance of used calibration algorithm [6].

Some studies developed a new adaptive calibration algorithm based on a population local-model-based intercompartimental glucose dynamic model. The novelty consists in the adaptation of data normalization parameters in real time to estimate and compensate patient's sensitivity variations [4]. For blood glucose testing were used by various devices over time [7-12] are summarized in Table III and are illustrated in Fig. 1.

Table III: *Examples of devices for measuring blood glucose*.

Year	Example	Company
1957	Clinistix	Ames
1964	Dextrostix	Ames
1970	Ames Reflectance Meter	Ames
1973	Eyetone	Ames
1974	Reflomat	Boehringer Mannheim
1980	Dextrometer	Ames
1980	Glucochek/Glucoscan	Lifescan
1981	Glucometer I	Ames
1986	Glucometer M	Ames
1987	OneTouch	Lifescan
1987	Exactech	Medisense
1997	Glucometer	Esprit Bayer
2001	OneTouch Ultra	Johnson & Johnson
2002	AccuChek Voicemate	Roche
2003	Freestyle Freedom	Abbott
2003	Ascensia Breeze	Bayer
2005	AccuCheck Compact	Roche
2008	SensoCard Plus	BBI

Fig. 1: *Devices for rapid monitoring of glucose*.

Sources of Errors

The International Organization for Standardization (ISO) standard describes a distribution for several production lots of meters and test strips, blood matrices and environmental conditions. Other references or organizations established some specific requests concerning the analytical accuracy and errors (Table IV).

Table IV: *Requests for analytical accuracy*.

Year	Standard reference/organisation	Details	Ref.
	International Organization for Standardization (ISO) standard	Maximum observable error for a specific glucose meter, test strips etc., for a specific need to be significantly lower than the specified ± 20 %.	[4]
1987	American Diabetes Association	Total error < 10 % in 100 % of cases.	[4]
1993	American Diabetes Association	Analytical accuracy < 5 %.	[4]
	Standards development organization in the United States (CLSI)	Analytical accuracy < 20 % in 95 % of cases for glucose concentrations > 100 mg/dl and < 15mg/dL below this concentration.	[4]
2011	New ISO 15197 standard	System accuracy in the range < 100 mg/dl to be within ± 15 mg/dl (0.83 mmol/L) of the manufacturer's reference and > 100 mg/dl within ± 15 % for 95 % of measurements	[13]

Several sources of errors interfere during the analysis and cause wrong results of glycaemia (Table V).

Table V: *Sources of errors for blood glucose detection*.

Parameters	Sources of errors	Ref.
Total system accuracy	Interference with other drugs/sugars/substances. System limitations: - Temperature. - Height above sea level. Safety features of the system. Quality assurance. Labelling of the devices and insert details. Associated support for patients. Training of persons who use the systems. Blood-glucose monitoring was less accurate for situations within or near the hypoglycemic range (*e.g.* patients with variable hemodynamics or receiving insulin treatment).	[4,14]
False positive and negative results of hypo/hyperglycemia	Medications. Food consumption before blood drawing. Time before drawing and the last meal.	[3]
Type of sample	Arterial blood samples may be used rather than capillary blood sample (for critically ill patients).	[14]

Pre-Analytical Errors

Pre-analytic laboratory testing errors can lead to highly inaccurate test results, placing patients at risk for their health status [15].

As a result of a range of pre- and post-analytical sources of error (cleanliness of hands, dimension of the blood drop), the data obtained during daily practice can be significantly worse. Pre-analytical errors that could increases/decreases the glycemia, may appear due to incomplete submission of sample to the active site of the sensor, errors in testing/calibration/ sensor control, if the sensor was at high temperatures during storage, if the test has expired, if testing is done at high altitude (increases glucose oxidase) [9,16].

Inadequate storage conditions of test strips could introduce error on measurements [17-19]. In order to avoid pre-analytical errors and to limit/diminish them, the laboratories need indirect methods to identify these errors [15].

Errors Due to Operator/Patient

Errors due to operator or patient are important for the final results of detection [9,16]. Diet or medication containing galactose, maltose and xylose increases the activity of GDH (glucose dehydrogenase)-PQQ (pyrroloquinoline quinone). Specimen contamination with small amounts of dextrose or total parenteral nutrition–containing fluid may result in substantially elevated glucose results [20,21].

Diets containing high concentrations of ascorbic acid (vitamin C) determine the changes of GDH (glucose dehydrogenase) biosensor. Dietary measures to increase plasma concentration of vitamin C may be an important strategy for reducing the prevalence of diabetes of people [22].

Glucose oxidase activity is modified due to the changes of other different biochemical parameters: lowers of blood triglycerides, increases of blood oxygenation, high level of uric acid in the blood. Increased hematocrit decreases glucose concentration.

Studies indicated that are groups of patients who consider that the complexity of steps to perform a measurement might be more important than the situation when the number of working steps is higher [19].

Analytical Errors

Several errors of analysis of glucose could appeared due to some erroneous coding to testing/calibration, or due to contamination sampling site with fruit juice or other compounds, or if insufficient blood is applied to the active test area, or if the reactive band is not completely inserted into the meter. If test is overloaded, increased levels of blood glucose could be observed. Washing and drying hands are also incriminated as possible sources of errors [23].

Post-Analytical Errors

Post-analytical errors could be when the results (displayed results) obtained by the patient are wrongly interpreted. The relative decreases of handling steps was required for the fully integrated system (Accu-Check Mobile) compared with other systems (partly integrated and conventional systems) [19].

Conclusions

The aim of several researchers and companies is to increase the analytical accuracy of this electrochemical analysis of blood glucose, thorough and systematic training of patients/users. Regular refresher training and permanent updating of the protocols are important to minimize errors.

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