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Improvement of therapeutic safety through standardized plasma calibration of blood glucose test systems at the point-of-care[1)]

Statement of the POCT Working Group of the German Society for Clinical Chemistry and Laboratory Medicine (DGKL)

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Abstract

Blood glucose measurements are performed mainly at the point-of-care in out-patient settings and in hospitals as well as for patient self-monitoring mainly by small hand-held devices. Generally, capillary or venous blood is used as a sample but results are variably reported, depending on the different calibration procedures of the test strips by the manufacturers, as either whole blood or as plasma glucose, accounting for a difference of ca. 11%. This can result in therapeutic misjudgments. To avoid the risk of confusion of whole blood and plasma results, in 2005 the IFCC has proposed to report all results only as glucose concentration in plasma, irrespective of sample type or measurement technique. This recommendation should be followed in Germany as soon as possible.

Keywords: blood glucose; plasma calibration; point-of-care testing (POCT); standardization.

Introduction

The majority of blood glucose measurements today are performed near patients as point-of-care-testing (POCT). This is achieved predominantly with the help of small mobile devices, but also with desk-type units, with which other additional parameters may be measured. These POC glucose measurements are an essential component of the treatment in accordance with guidelines [1], whether for the optimal metabolic regulation of patients with diabetes mellitus or with acute transitory disorders of glucose metabolism in connection with other diseases, such as acute heart failure.

In the last few years the need for glucose measurements has increased noticeably, both in the area of in-patient as well as out-patient care, and thus has stimulated the further and new development of suitable POCT measurement systems. With a market volume of €0.5 billion glucose test strips and devices for self-monitoring by the patient represent approximately two-thirds of the total market for POC test procedures in Germany [2].

Originally glucose measurement in venous plasma, venous whole blood and capillary blood of the finger tip, which consists of a mixture of arterial and venous blood, interstitial fluid and cellular fluid and whose composition can vary from specimen to specimen, had been established as the clinical standard. However, in the last few years POCT glucose measurements in intracutaneous and subcutaneous interstitial fluids, mainly in the context of continuous measurement procedures, have been added as well. Currently a multitude of non-invasive procedures for POC glucose testing in various extravascular compartments are in clinical development and testing [1, 3].

The question now is which glucose concentration is the most representative for diagnostic procedures and therapy and the most feasible for POCT from the aspect of day-to-day usefulness.

Physiologic fluctuation of the glucose concentration

It is well known that glucose concentrations in various parts of the organism differ at a given point in time for physiologic reasons: for example, in the blood there is a concentration gradient from the arterial system via the capillary bed to the venous system; in the acral capillary bed of the skin of trunk and extremeties fast changes in the arterial blood glucose

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concentration result in clinically relevant delays in comparison to the concentration in the finger tip; in the interstitium or in other compartments variable diffusion gradients also play a role for glucose in that they depend on the one hand on the concentration gradient versus capillary blood and on the other hand they change depending on the varying, hormonally and metabolically regulated glucose uptake of the surrounding tissue.

The development of test systems requiring very low amounts of blood allows us to also obtain capillary blood from the skin areas of the arms, legs and the abdomen. This relieves the sensitive finger capillaries and blood collection is less painful. Even if glucose values between these areas and the finger do not differ with a patient at rest and fasting, fast changes in concentration (>2 mg/dL/min) in both directions, e.g., following a meal rich in carbohydrates, an injection of a large amount of insulin, intensive physical work or exercise, result in a clinically relevant and on average 30 min delay in the adjustment of the glucose concentration in the alternative areas to the values in the finger [4].

Glucose in the blood

Glucose passes through the erythrocyte membrane by passive transport and divides itself evenly between plasma and erythrocytes. Theoretically the concentration of free glucose in the aqueous compartment is the suitable, because biologically effective characteristic value, whose concentration is stated in mmol/kg water. So far, however, only the measurement of glucose concentration in whole blood and in venous plasma (stated in mmol/L or mg/dL) has prevailed in the clinical practice.

While the molality of glucose (=mg glucose/kg water) is the same in the aqueous compartment, its molarity (=concentration) in erythrocytes is lower than in plasma, since the typical water content of erythrocytes is 0.71 kg H_2O/L, that of plasma, however, is 0.93 kg H_2O/L. A hematocrit (HCT) of 43% results in a factor of 1.11 for the conversion of whole blood into plasma glucose. However, in specimens with deviating hematocrit values this factor is not exact. In cases of extreme hematocrit concentrations it might make sense to employ a ''hematocrit correction'' for the conversion factor based on the equation $f=0.84/(0.93–0.22\times HCT)$. The correction factor calculated in this way should then be multiplied with the conversion factor 1.11 [5, 6].

A distinction must be made between this physiologic hematocrit dependence of the whole blood-plasma difference and a technology related hematocrit interference, which – to a varying degree – occurs in nearly all POCT glucose measuring instruments and in general has the result that the glucose values measured are too low when hematocrit values are high and when hematocrit values are low the glucose values measured are too high. Especially in newborns with high hematocrit values this makes it difficult to reliably diagnose neonatal hypoglycemia. In a number of newer systems the hematocrit value is measured conductometrically on a special test strip field and used for correction of the hematocrit interference. To a large extent it is thereby possible to achieve independence of the results from the hematocrit value of the specimen in a range of 20–70% hematocrit.

Technical influences on measured glucose concentrations

Modern test systems for blood glucose POCT ex vivo are mainly designed for use of whole blood (capillary or venous). However, since the automatic processing of the whole blood specimen is different in the various test procedures, the actual measurement occurs in varying specimen media, e.g., in hemolysate or in different plasma-like filtrates, but also in unchanged whole blood. During the analysis glucose is converted enzymatically and the reaction product is detected electrochemically or photometrically. Test systems for continuous subcutaneous glucose measurements in vivo are geared to use either the subcutaneous interstitial fluid or a dialysate there from as the base specimen material that is similar neither to plasma nor to whole blood. Nevertheless the method of measurement does not differ fundamentally from the one described above.

These procedures make use of glucose oxidase or glucose dehydrogenase as enzymes, FAD or PQQ as coenzymes and most frequently atmospheric oxygen, hexacyanoferrate or nitrosoaniline as mediators. The combination of the individual components is responsible for the specificity of the reaction and explains interferences that occur in some systems and that are of particular clinical importance in the in-patient sector, e.g., through oxygen, maltose, galactose or certain medications. Additional electrodes can compensate for the effect of temperature, humidity and hematocrit on the result [5].

Since with these test procedures the particular actual glucose concentration is not measured directly, but is detected indirectly via measured quantities like flow or color changes, the procedures must be calibrated and the measured quantities must be converted into the corresponding glucose values. Calibration is performed by the manufacturers by means of varying company- and instrument-specific procedures, whose details are not usually published. The results can be applied to whole blood as well as plasma, i.e., can be stated either as whole blood or plasma concentrations [1].

Even independent of the calibration to whole blood or plasma, however, measured values can vary greatly between different types of instruments or within model series – among other things because of quality deviations in instruments and test strips [7]. In addition, methodic inadequacies in the performance of evaluations and method comparisons contribute to uncertainty in the interpretation of systematic differences between measured values. Although there are various initiatives for a solution, e.g., by the ''Clinical and Laboratory Standards Institute (CLSI)'' or the ''STARD Initiative'', these have been implemented only insufficiently in many studies [5].

Diagnostics

Progress in technical development has reduced measurement errors of modern systems to a degree that, for example, makes it possible to fulfill the new guideline of the German Medical Association (Bundesärztekammer) for quality assurance (RiliBÄK 2008), which for glucose POCT specifies a maximum permitted total deviation of $\pm 11\%$ of the nominal value of a control sample [8]. According to the guidelines of the German Diabetes Association (DDG) the primary diagnosis of diabetes mellitus may be made only based on glucose measurement values that were obtained through a quality controlled *method* according to RiliBÄK.

In order to keep any errors that may result from the multitude of glucose measurement procedures as low as possible for primary diagnostics and therapy decisions and in keeping with international agreements, the guidelines of the DDG specify equivalent concentration ranges or limits for four different types of specimens (plasma glucose: venous or capillary; whole blood: venous or capillary) [3, 9].

For follow-up diagnostics and the resulting therapy decision as well as for comparative examinations between glucose POCT systems and a wet-chemical reference method in the clinical-chemistry laboratory (hexokinase/glukose-6-dehydrogenase method), which when measuring glucose from whole blood in Germany can lead to descriptions as whole blood or plasma glucose, the same principle applies implicitly: the glucose concentrations on which the respective therapy algorithms or comparisons are based must have been measured in the same way as the current follow-up value; at the very least, however, the result must be equivalent. This also applies to procedures for control inspections of glucose measuring instruments intended for self-monitoring by the patient which are used in medical practices focused on diabetes [1].

In other words, those measuring whole blood glucose values must also structure their therapy algorithms or comparative measurements on whole blood glucose values and those measuring plasma glucose values must also gear their therapy algorithms or comparative measurements to plasma glucose values.

Conclusions

A variety of factors can complicate the interpretation of glucose measurement values in the day-to-day work at the POC where as uniform as possible reference systems are needed for evaluating glucose concentration values when implementing therapy. Misjudging these circumstances can acutely endanger the patient, most particularly through hypoglycemic decompensation, while in the long-term insufficient therapy adjustments prevent an optimum regulation of the metabolism [1].

As trivial as this statement is, in the routine in-patient as well as out-patient treatment of persons with diabetes mellitus those affected often are as little aware of the circumstances described as the members of the attending diabetes team. On the one hand the theoretic difference between whole blood and plasma glucose values is not necessarily well known, on the other hand people with diabetes frequently do not know what their therapy algorithms are based on or in the course of their treatment they change the glucose test system without realizing that it entails a change of the method of measuring [10].

In Germany test systems for glucose POCT are available commercially with calibration for whole blood values (e.g., Bayer Vital) as well as for plasma values (e.g., Abbott Diabetes Care or Ortho-Clinical Diagnostics, LifeScan).) Roche Diagnostics started in September 2009 to change its test systems from their previous calibration for whole blood values to plasma values stepwise over a period of several months.

When traveling to countries in which neither measuring systems nor test strips calibrated to whole blood glucose values are available, e.g., the USA and many other parts of the world, this can lead to problems and faulty therapy.

With a therapy target of long-term normoglycemia, as well as with faster and more effective therapeutic means (e.g., intensified conventional insulin therapy or continuous subcutaneous or intravenous insulin infusion) the risk of a wrong decision at the step-wise limits of glucose concentration-dependent insulin or carbohydrate portion algorithms increases if the described problems are ignored. The resulting consequences are an increased risk of acute hypoglycemic decompensation and hyperglycemia-related long-term complications.

To end the risk of confusing whole blood and plasma glucose values, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) proposed as early as 2005 to state glucose results exclusively as plasma values, independent of the type of specimen or the method of measurement [11]. This proposal has been implemented successfully and without noticeable problems in the USA in agreement with the American Diabetes Association as well as most other parts of the world and Europe. So far Germany, Austria and Spain have not complied with this proposal.

Against this background the working group POCT of the DGKL endorses a new initiative with the goal to also implement the recommendation of the IFCC in Germany, both for glucose measurements at the POC as well as in the clinical-chemistry laboratory. The working group is ready 1) to support the preparation of the necessary transitional regulations and informational concepts within the framework of the DGKL and in cooperation with diabetes DE, the new German joint diabetes organization, the healthcare providers in Germany and the industry and 2) also to participate in the transmission of information at all relevant levels.

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