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References


Comparability of Blood Glucose Concentrations Measured in Different Sample Systems for Detecting Glucose Intolerance, Rainer Haackel2* Ute Brinck1, Dubravka Colic, Hans-Uwe Janka, Isabel Püntmann, Jörg Schneider, and Carsten Viebrock2 (1 Zentralkrankenhaus Bremen-Nord, 28755 Bremen, Germany; 2 Zentralkrankenhaus Sankt-Juergen-Strasse, 28205 Bremen, Germany; * author for correspondence: fax 49-421-4973334, e-mail info@zkh-bremen-mitte.de)

Glucose concentrations are usually measured in whole blood or plasma. Plasma values are influenced by the concentration of proteins, especially those with large volumes, such as lipoproteins. Blood values additionally depend on the total volume of the various blood cells, which is usually expressed as the hematocrit (1, 2).

The interconversion of glucose values for venous and capillary blood is further complicated by the arteriovenous difference. In the fasting state, the glucose concentrations in arterial, capillary, and (forearm) venous blood are supposed to be almost indistinguishable. In contrast, arterial blood glucose values may differ by 20% or as much as 70% in the postprandial state (3, 4). The mean arteriovenous differences are largest in lean nondiabetic individuals, smallest in diabetic individuals, and larger in deep veins than in superficial vessels (1, 5). Other factors can influence the differences in glucose concentrations among the various samples (6–9). Thus, the conversion of concentration values from one system (or sample type) to another is subject to unpredictable errors.

Several authors have already rejected the practice of converting glucose concentrations and have recommended that plasma be used for all glucose determinations (2, 10, 11). In a recent editorial, glucose measurement in whole blood was considered anachronistic (12), but only whole blood is used by home monitoring and near-patient monitoring devices. Many laboratories measure the glucose concentration in whole blood, especially in capillary whole blood, for therapeutic monitoring and for diagnosing hypo-, normo-, and hyperglycemia. However, the applicability of whole blood for determining glucose intolerance is still a matter of debate. Many practitioners tend to use capillary blood (CB) for diagnostic purposes (13, 14). The decision limits usually applied for whole blood are those recommended by WHO (15–17) and the American Diabetes Association (18), which are based on epidemiologic studies with venous plasma (VP). In practice, either measured values or decision limits are converted from one sample system to another. The present study was undertaken to reinvestigate the comparability of glucose determinations in venous blood (VB), VP, and CB.

The study group consisted of 147 individuals from outpatient departments (internal medicine and dermatology) who were able to walk to the laboratory for blood collection (age range, 25–76 years). Using values recommended by WHO (15, 16) for the classification of plasma glucose concentrations, we separated the individuals into three groups according to whether they displayed a “healthy” (n = 74), impaired (n = 36), or diabetic glucose tolerance (n = 37). Oral glucose tolerance tests (GTTs) were performed according to WHO recommendations (15, 16). Participants ingested 75 g of glucose as Dextro O.G.T. (Roche Diagnostics).

VB samples were drawn into 2.7-mL monovettes containing lithium heparinate (cat. no. 05.1553; Sarstedt AG). Capillary and VB samples were collected within 2 min of each other by separate medical staff. Plasma was prepared within 10 min of blood sampling.

Glucose concentrations were determined in 500 μL of hemolyzing reagent plus 10 μL of blood or plasma (collected in heparinized end-to-end glass capillaries; cat.
<table>
<thead>
<tr>
<th></th>
<th>VP/VB at time (min) after glucose load</th>
<th>VP/CB at time (min) after glucose load</th>
<th>CB/VB at time (min) after glucose load</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Nondiabetic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.122</td>
<td>1.14</td>
<td>1.132</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.262</td>
<td>1.442</td>
<td>1.352</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.859</td>
<td>0.736</td>
<td>0.913</td>
</tr>
<tr>
<td>SD</td>
<td>0.074</td>
<td>0.092</td>
<td>0.085</td>
</tr>
<tr>
<td>n</td>
<td>62</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Mean (±SD) of 0–120 min</td>
<td>1.140 ± 0.074 (n = 301)</td>
<td>0.997 ± 0.095 (n = 316)</td>
<td>1.173 ± 0.105 (n = 319)</td>
</tr>
<tr>
<td>Diabetic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.155</td>
<td>1.162</td>
<td>1.143</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.300</td>
<td>1.311</td>
<td>1.286</td>
</tr>
<tr>
<td>Minimum</td>
<td>1.052</td>
<td>1.044</td>
<td>0.969</td>
</tr>
<tr>
<td>SD</td>
<td>0.052</td>
<td>0.062</td>
<td>0.061</td>
</tr>
<tr>
<td>n</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Mean (±SD) of 0–120 min</td>
<td>1.154 ± 0.052 (n = 170)</td>
<td>1.089 ± 0.066 (n = 208)</td>
<td>1.055 ± 0.063 (n = 169)</td>
</tr>
<tr>
<td>Mean (±SD) of all groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.138</td>
<td>1.148</td>
<td>1.142</td>
</tr>
<tr>
<td>SD</td>
<td>0.067</td>
<td>0.079</td>
<td>0.072</td>
</tr>
<tr>
<td>Overall mean (±SD) of all groups</td>
<td>1.148 ± 0.067 (n = 674)</td>
<td>1.048 ± 0.099 (n = 730)</td>
<td>1.115 ± 0.096 (n = 680)</td>
</tr>
</tbody>
</table>
no. 19.414; Sarstedt AG) with an EBIO plus 6668 analyzer (Eppendorf AG) using glucose oxidase-containing electrodes (19) within 2 h of sampling. Glucose concentrations in hemolyzed samples were stable for at least 24 h. The results obtained with the glucose analyzer were referred to a glucose solution (11.11 mmol/L; certified primary reference material from NIST). All procedures were subjected to internal and external quality assurance programs. Control materials (Validate A and N) were purchased from Organon Teknika. The mean value (± SD) obtained for Validate A (lot no. 6B403; assigned value, 11.54 mmol/L) over 24 days was 11.55 ± 0.39 mmol/L glucose, and that for Validate N (lot no. 6B401; assigned value, 5.21 mmol/L) was 5.35 ± 0.20 mmol/L (obtained over 28 days).

All calculations were performed with mean values from duplicates. The relationship between concentration ratio (target quantity) and time-specific metabolic and disease duplicates. The relationship between concentration ratio over 28 days). The mean VP/CP ratio from all determinations during the tolerance tests was 1.148 (Table 1), increasing slightly but statistically not significantly (P = 0.37) from the healthy to the diabetic group (Table 1). This increase appeared to be constant throughout the GTT. The mean VP/CB ratio was 1.048. The VP/CB ratio was related to the nutritional state, being 1.084 in the fasted and 0.972 in the postprandial state in healthy nondiabetic individuals (P <0.001). In contrast, the VP/CB ratio remained almost constant after a glucose load in diabetic individuals (P = 0.92). The VP/CB ratio was higher in diabetic than in nondiabetic individuals (P <0.001). According to these results, the WHO recommendation for the 2-h postload CB cutoff should be reduced from 11.1 to 10.0 mmol/L. The clinical consequence would be the detection of more diabetic individuals. The CB/VB ratio (Table 1) increased during the GTT only in normotolerant individuals (P <0.001) and was lower in the diabetic than in the nondiabetic group (P <0.001). Individual ratios varied considerably. The ranges were 0.74–1.66 for the VP/VB ratio and 0.52–1.63 for the VP/CB ratio (Table 1).

Glucose concentrations are usually converted from one sample system to another by use of fixed factors. These factors are either derived from the water content of the different compartments (water distribution theory) or from the glucose concentrations determined with analytical procedures (ratio of mean values or equation of regression lines).

The considerable variation in the conversion factors was demonstrated by the range of conversion factors (Table 1). A large variation in the percentage difference between blood and plasma glucose concentrations has already been reported by others (2, 21–23). Mean VP/VB ratios reported in the literature (2, 10, 21–25) also vary from 1.04 (24) to 1.183 (2). The mean ratio in this study was 1.148. The even greater variation of the VP/CB ratio is probably attributable to the arteriovenous difference. The interindividual VP/CB ratio was related to the nutritional state, confirming an earlier report by Larsson-Cohn (26). The mean ratio from the entire GTT was 1.09-fold higher in diabetics than in healthy individuals (Table 1). A higher VP/CP ratio has also been observed in gestational diabetes (27) and was explained by a decrease in the arteriovenous difference. Lind et al. (21) found that the differences between these two sample systems in the fasting state were too trivial to be worth correcting for healthy and pregnant women. However, in diabetics, the VP/CB ratio cannot be neglected.

In conclusion, conversion of glucose concentrations determined in different sample systems by use of factors is an oversimplification and probably leads to unpredictable rates of discordant disease classifications. These problems are becoming more relevant with the widespread use of point-of-care testing instruments, including blood gas analyzers with integrated glucose sensors that measure glucose in the plasma water fraction. The only solution for this dilemma is to use only one sample system. The experimental data clearly indicate that the use of plasma should be preferred to diagnose glucose intolerance, including diabetes. The logistic disadvantages are the centrifugation step and the prevention of glycolysis. In the present study, in vitro glycolysis could be neglected. In cases in which samples may need 2–4 h until processing can be started in the laboratory, unpredictable glycolysis will occur, even in the presence of fluoride (28, 29). Chan et al. (30) showed that delays in processing blood specimens in hospital practice may lead to misclassification in up to 7% of GTTs. Stahl et al. (31) proposed storage on ice for not more than 1 h until centrifugation. However, this recommendation may not be acceptable for many hospitals. The use of capillary hemolyzate together with a reduced decision limit thus may be a second choice for the detection of diabetes.

References


β-Trace Protein as a Marker for Cerebrospinal Fluid Rhinorrhea, Erich Arrer,1* Cem Meco,2 Gerhard Oberascher,2 Wolfgang Piotrowski,3 Klaus Albegger,2 and Wolfgang Patsch4 (1 Department of Laboratory Medicine, 2 Ear, Nose, and Throat Department, and 3 Department of Neurosurgery, Landeskliniken Salzburg, Müllner Hauptstrasse 48, A-5020 Salzburg, Austria; * author for correspondence: fax 43-662-4482-885, e-mail e.arrer@lks.at)

Cerebrospinal fluid (CSF) leakage occurs mainly as a complication of head injuries or skull-base surgeries, but may also occur spontaneously or as a result of nontraumatic processes such as inflammatory disorders or tumors (1). Detection and management of CSF leakage is essential to prevent possible life-threatening infections of the central nervous system (2). Radiologic and invasive procedures may be used for the diagnosis of CSF leaks, but these procedures are laborious, expensive, and present potential risk to the patient. Therefore, noninvasive laboratory methods serve as screening procedures before definitive procedures are used to localize the site of the defect.

Laboratory assessment of CSF leakage relies on compositional differences between CSF and other body secretions. The β2-transferrin (β2Tr) +-fraction, or asialotransferrin, is a brain-specific variant of transferrin that lacks neuraminic acid. It therefore can be distinguished from serum transferrin by electrophoretic procedures and used to detect CSF rhinorrhea (3,4). However, β2Tr is present in aqueous humor and in perilymph fluid and can be detected in serum, especially in chronic alcohol abusers and in patients with inborn errors of glycoprotein metabolism or genetic variants of transferrin (5,6).

β-Trace protein (βTP), recently identified as prostaglandin D2 synthase (7), is another brain-specific protein that is produced mainly in the leptomeninges and the choroid plexus and is secreted into the CSF. βTP is the second most abundant protein in CSF after albumin. However, it is also present in other body fluids, including serum, albeit at much lower concentrations than in CSF (8). Immunoelectrophoretic methods for βTP have been applied as a screening procedure for CSF leaks (9,10). Recently, a nephelometric assay for the quantification of βTP was introduced that promised several advantages over current CSF detection methods, including enhanced sensitivity and reduced turnaround time (11). We therefore evaluated this assay with respect to its clinical utility in patients with suspected CSF rhinorrhea.

βTP was measured using the Prospec® nephelometer and the N Latex βTP® test (Dade-Behring) according to the manufacturer’s instructions. For standardization, highly purified βTP from human CSF (N Protein Standard UY®) was used because no international standard is available. Precision was monitored using N/T protein Control LC® (Dade-Behring). Nasal secretions were collected using intranasal pledgets (12) and were centrifuged (2000g for 10 min). Viscous secretions were prediluted 1:100 (1 mL + 99 mL) with N dilution buffer®, and the usual 1:100 predilution step included in the automated procedure was omitted for such samples. The range for reliable measurements in serum, nasal secretions, and CSF was 0.1–19.6 mg/L, and the intraassay and interassay CVs were 1.5–5.7% and 1.4–7.2%, respectively (11). Intradermal assay CVs, determined in nasal secretions with a βTP concentration of 1.27 mg/L, were both <4% as determined in our laboratory. Analysis time was <15 min. β2Tr testing was performed as described previously (12,13). In brief, nasal secretions were subjected to electrophoresis, immunofixation, and silver staining for visual inspection.

The sensitivity of the βTP assay for CSF leakage detection and possible matrix effects in nasal secretions was ascertained in mixtures of nasal secretions and CSF. Various dilutions from a control with βTP concentrations of 15.4 mg/L in the CSF and 0.117 mg/L in the nasal secretions were analyzed in duplicate. Measured and calculated βTP concentrations were nearly identical, sug-