

immediately after blood collection followed by separation of plasma from the cells within 30 min (69, 70). These methods are not always practical and are not widely used.

The use of blood collection tubes containing citrate, sodium fluoride, and EDTA offers a practical solution to the problem of glycolysis. A 2009 study showed that acidification of blood using citrate buffer inhibits *in vitro* glycolysis far more effectively than fluoride (70). The mean glucose concentration in samples at 37 °C decreased by only 0.3% at 2 h and 1.2% at 24 h when blood was drawn into tubes containing citrate buffer (citric acid and sodium citrate), sodium fluoride, and sodium EDTA. Acidification (pH 5.3 to 5.9) immediately blocks the activity of glycolytic enzymes, thereby preventing glycolysis (71). Subsequently, several other studies also demonstrated the effectiveness of tubes containing citrate/fluoride/EDTA (CFE) to inhibit glycolysis (72, 73).

A few studies noted that glucose concentrations were higher in samples collected in tubes containing citrate than in control samples (74, 75). While some suggest the increase is spurious (74, 75), others state that the difference is likely due to glycolysis in the samples without citrate (70, 76). In contrast, other studies observe no difference in glucose concentrations between samples collected in tubes containing citrate compared to those with stringent sample handling to prevent glycolysis (70, 76). Importantly, use of the citrate-containing tubes has implications for diagnosis of diabetes. Widespread adoption of these tubes is likely to increase the detection of diabetes, while cases of artifactual hypoglycemia will probably decrease (77). Importantly, elimination of glycolysis is likely to substantially reduce the variability in glucose measurements that is attributable to the wide variation in sample handling prior to analysis in both routine patient care and multicenter research studies. Although commercially available in several countries, particularly in Europe, at the time of writing tubes containing CFE were not available in the US. We strongly encourage manufacturers of blood collection tubes to make these available worldwide.

Glucose can be measured in whole blood, serum, or plasma, but plasma is recommended for diagnosis. [Note that while both the ADA and WHO recommend venous plasma, the WHO also accepts measurement of glucose in capillary (skin-puncture or “fingerstick”) blood (2, 21).] The molality of glucose (i.e., amount of glucose per unit water mass) in whole blood is identical to that in plasma. Although red blood cells (RBCs) are essentially freely permeable to glucose (glucose is taken up by facilitated transport), the concentration of water (kg/L) in plasma is approximately 11% higher than that of whole blood. Therefore, glucose concentrations in plasma are approximately 11% higher than in whole blood if the hematocrit is normal. Glucose concentrations in

heparinized plasma were reported in 1974 to be 5% lower than in serum (78). The reasons for the difference are not apparent, but have been attributed to the shift in fluid from RBCs to plasma caused by anticoagulants. In contrast, some subsequent studies found that glucose concentrations in plasma are slightly higher than serum. The differences observed were approximately 0.2 mmol/L (3.6 mg/dL) (79), approximately 2% (80), or 0.9% (70). Other studies indicate that glucose values measured in serum and plasma are essentially the same (81, 82). Based on these findings, it is unlikely that there is a substantial difference between glucose values in plasma and serum when assayed on current instruments, and any differences are small compared with the day-to-day biological variation of glucose. Measurement of glucose in serum (rather than plasma) is not recommended by clinical organizations for the diagnosis of diabetes (2, 21). Use of plasma allows samples to be centrifuged promptly to prevent glycolysis without waiting for the blood to clot. The glucose concentrations during an OGTT in capillary (fingerstick) blood are significantly higher than those in venous blood (mean of 1.7 mmol/L or 30 mg/dL, equivalent to 20% to 25% (83, 84), probably due to glucose consumption in the tissues. In contrast, the mean difference in fasting samples is only 0.1 mmol/L (2 mg/dL) (83, 84).

Frequency of measurement. The frequency of measurement of blood glucose is dictated by the clinical situation. The ADA, WHO, and IDF recommend that an increased FPG or abnormal OGTT must be confirmed to establish the diagnosis of diabetes (2, 21). Screening by FPG is recommended by the ADA every 3 years beginning at age 35, more frequently in high-risk individuals; however, frequency of analysis in the latter group is not specified. Monitoring is performed by patients themselves who measure glucose with meters or continuous glucose monitoring (CGM) and by assessment of Hb A_{1c} in an accredited laboratory (see below). Appropriate intervals between measurements of glucose in acute clinical situations (e.g., hospitalization, DKA, neonatal hypoglycemia) are highly variable and may range from 30 min to 24 h or more.

Analytical.

Recommendation: *Based on biological variation, glucose measurement should have analytical imprecision ≤2.4%, bias ≤2.1% and total error ≤6.1%. To avoid misclassification of individuals, the goal for glucose analysis should be to minimize total analytical error and methods should be without measurable bias. B (moderate)*

Glucose is measured almost exclusively by enzymatic methods. Analysis of proficiency surveys conducted in 2019 by the College of American Pathologists (CAP) reveals that hexokinase or glucose oxidase is used in