

namely diabetic retinopathy, nephropathy, and neuropathy (50). Although intensive insulin therapy reduced hypercholesterolemia by 34%, the risk of macrovascular disease was not significantly decreased in the original analysis, probably related to the limited number of events and low power (50). Longer follow-up documented a significant reduction in cardiovascular disease in participants originally randomized to intensive glycemic control (51). The effects of tight glycemic control on microvascular complications in people with type 2 diabetes (52) are similar to those with type 1 diabetes, considering the differences in glycemia achieved between the active intervention and control groups in the various trials. The United Kingdom Prospective Diabetes Study (UKPDS) in people with short-duration type 2 diabetes showed that intensive blood glucose control significantly reduced microvascular complications (52). While meta-analyses suggest that intensive glycemic control in individuals with type 2 diabetes reduces cardiovascular disease (53, 54), clinical trials have not consistently demonstrated a reduction in macrovascular disease (myocardial infarction or stroke) with intensive therapy aimed at lowering glucose concentrations in type 2 diabetes. Long-term (10 year) follow-up of the UKPDS population supported a benefit of intensive therapy on macrovascular disease (55), but 3 other trials failed to demonstrate a significant difference in macrovascular disease outcomes between very intensive treatment strategies achieving Hb A_{1c} concentrations of approximately 6.5% (48 mmol/mol) compared with the control groups who had Hb A_{1c} concentrations 0.8% to 1.1% higher (56–58). One study even observed higher cardiovascular mortality in the intensive treatment arm (56). In both the DCCT (50) and UKPDS (52), participants in the intensive group maintained lower median capillary blood glucose concentrations. However, analyses of the outcomes were linked to Hb A_{1c}, which was used to evaluate glycemic control, rather than glucose concentration. Moreover, most clinicians use the recommendations of the ADA and other organizations which define a target Hb A_{1c} concentration as the goal for optimum glycemic control (25, 59).

Laboratory measurements of random or fasting glucose concentrations should not be performed as the primary means of routine outpatient monitoring of people with diabetes. Laboratory plasma glucose testing can be used to supplement information from other testing or to assess the accuracy of self-monitoring (see below) (60).

ANALYTICAL CONSIDERATIONS

Preanalytical.

Recommendation: Blood for fasting plasma glucose analysis should be drawn in the morning after the subject has fasted overnight (at least 8 h). B (low)

Recommendation: To minimize glycolysis, a tube containing a rapidly effective glycolytic inhibitor such as granulated citrate buffer should be used for collecting the sample. If this cannot be achieved, the sample tube should immediately be placed in an ice-water slurry and subjected to centrifugation to remove the cells within 15 to 30 min. Tubes with only enolase inhibitors such as sodium fluoride should not be relied on to prevent glycolysis. B (moderate)

Blood should be drawn in the morning after an overnight fast (no caloric intake for at least 8 h) during which time the subject may consume water as desired (18). Published evidence reveals a diurnal variation in FPG, with mean FPG higher in the morning than in the afternoon, indicating that many cases of diabetes would be missed in individuals screened with FPG in the afternoon (61).

Decrease in glucose concentration in the sample due to glycolysis is a serious and underappreciated problem (62, 63). Glucose concentrations decrease ex vivo in whole blood due to glucose consumption predominantly by red and white blood cells. The rate of glycolysis—reported to average 5% to 7% (approximately 0.6 mmol/L; 10 mg/dL) per hour (64)—varies with the glucose concentration, temperature, white blood cell count, and other factors (62, 65). Such a decrease of glucose will lead to missed diagnoses of diabetes in the large proportion of the population who have glucose concentrations near the cutpoints for diagnosis of diabetes.

The commonly used inhibitors of glycolysis are unable to prevent short-term glycolysis. Glycolysis can be attenuated by inhibiting enolase with sodium fluoride (2.5 mg fluoride/mL of blood) or, less commonly, lithium iodoacetate (0.5 mg/mL of blood). These inhibitors can be used alone or, more commonly, with anticoagulants such as potassium oxalate, EDTA, citrate, or lithium heparin. Unfortunately, although fluoride helps to maintain long-term glucose stability, the rates of decline of glucose in the first hour after sample collection in tubes with and without fluoride are virtually identical and glycolysis continues for up to 4 h in samples containing only fluoride (64). After 4 h, the glucose concentration is stable in whole blood for 72 h at room temperature in the presence of fluoride (64). Leukocytosis will increase glycolysis even in the presence of fluoride if the white cell count is very high (65).

Few effective and practical methods have been available for prompt stabilization of glucose in whole blood specimens. Reduction in glucose concentration from hemolysis can be minimized in 2 ways. The first is to immediately separate blood cells after blood collection (66) [in separated, nonhemolyzed, sterile serum without fluoride the glucose concentration is stable for 8 h at 25 °C and 72 h at 4 °C (66–68)]. Alternatively, the blood tube should be placed in an ice-water slurry