GLUCOSE

1. Use

A. Diagnosis/Screening

Recommendation:
Glucose should be measured in plasma in an accredited laboratory to establish the diagnosis of diabetes.

Level of evidence: A

Glucose should be measured in plasma in an accredited laboratory for screening of high-risk individuals.

Level of evidence: E

Analysis in an accredited laboratory is not necessary for routine monitoring

Level of evidence: E

The diagnosis of diabetes is established exclusively by the documentation of hyperglycemia (increased glucose concentrations in the plasma). In 1997, the diagnostic criteria(8) were modified (1) to better identify subjects at risk of retinopathy and nephropathy. The revised (current) criteria include: (a) symptoms of diabetes and casual (i.e., regardless of the time of the preceding meal) plasma glucose ≥ 11.1 mmol/L (200 mg/dL), (b) fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL) or (c) 2-h postload glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT) (1). If any one of these three criteria is met, confirmation by repeat testing on a subsequent day is necessary to establish the diagnosis. (Note that repeat testing is not necessary in patients who have unequivocal hyperglycemia with acute metabolic decompensation.) Although included as a criterion, the OGTT wasn't recommended for routine clinical use in non-pregnant individuals (see below).

Population screening for type 2 diabetes, previously controversial, is now recommended for those at risk of developing the disease (1, 9). The ADA proposes that FPG should be measured in all asymptomatic people aged 45 years or more. If results are < 6.1 mmol/L (110 mg/dL), testing should be repeated at 3-year intervals. Screening should be considered at a younger age or be carried out more frequently in individuals at increased risk of diabetes (see Ref (1) for conditions associated with increased risk). Because of the increasing prevalence of type 2 diabetes in children, screening of children has been suggested recently (10). Starting at age 10 years, testing should be performed every 2 years in overweight individuals who have two other risk factors, namely family history, race/ethnicity and signs of insulin resistance (10). Despite these recommendations, there is no published evidence that treatment based on screening has value. The cost-effectiveness of screening for type 2 diabetes has been estimated. The incremental cost of screening all persons aged 25 years or older was estimated to be $236,449 per life-year gained and $56,649 per quality-adjusted life-year gained (11). Interestingly, screening was more cost-effective at ages younger than the 45 years currently recommended.

A. Monitoring/Prognosis

Recommendation: Although there is evidence linking high plasma glucose concentrations to adverse outcome, substantially more data are available that directly correlate increased glycated hemoglobin with complications of diabetes. Routine measurement of plasma glucose concentrations in an accredited laboratory is not recommended as the primary means of monitoring or evaluating therapy in individuals with diabetes.

Level of evidence: E

There is a direct relationship between the degree of plasma glucose control and the risk of late renal, retinal and neurological complications. This correlation has been demonstrated for type 1 (12) and more recently for type 2 (13) diabetes.

Persons with type 1 diabetes who maintained lower average plasma glucose concentrations exhibited a significantly lower incidence of microvascular complications, namely diabetic retinopathy, nephropathy and neuropathy (12). Although intensive insulin therapy reduced hypercholesterolemia by 34%, the risk of macrovascular disease was not significantly decreased. Similar results were obtained in patients with type 2 diabetes (13). Intensive plasma glucose control in patients with type 2 diabetes significantly reduced microvascular complications, but no significant difference was detected for macrovascular disease (myocardial infarction or stroke) (13). In both studies, patients in the intensive group maintained lower median plasma glucose concentrations. Analyses of the outcomes were linked to glycated hemoglobin (GHb), which was used to evaluate glycemic control, rather than glucose concentration. Moreover, most clinicians use the ADA recommendations which define a target GHb concentration as the goal for optimum glycemic control (14).

There is some evidence directly linking higher glucose concentrations to a poor prognosis. For example, the 10 year survival of 6681 people in a Japanese town was reduced if FPG was > 7.8 mmol/L (140 mg/dL) (15). Similar findings were obtained in 1939 patients with type 2 diabetes followed for a mean of 15 years where multiple logistic regression revealed that the risk of death was significantly increased for patients with FPG ≥ 7.8 mmol/L (140 mg/dL) (16). Subjects with type 2 diabetes with FPG > 7.8 mmol/L (140 mg/dL) had increased cardiovascular mortality (17). Furthermore, comparison of 300 patients with a first myocardial infarction and 300 matched controls revealed that a moderately increased FPG was a risk factor for infarction (18). Notwithstanding these observations, neither random nor fasting glucose concentrations should be measured in an accredited laboratory as the primary means of routine monitoring of patients with diabetes. Laboratory plasma glucose testing can be used to supplement information from other testing, to test the accuracy of self-monitoring (see below) or when adjusting the dose of oral hypoglycemic agents (9). In addition, individuals with well-controlled type 2 diabetes who are not on insulin therapy can be monitored with periodic measurement of FPG, although analysis need not be done in an accredited laboratory (19, 20).

2. Rationale

A. Diagnosis

The disordered carbohydrate metabolism that underlies diabetes manifests as hyperglycemia. Therefore, measurement of plasma glucose is the sole diagnostic criterion. This strategy is indirect as hyperglycemia reflects the consequence of the metabolic derangement, not the cause. However, until the underlying molecular pathophysiology of the disease is identified, plasma glucose concentrations are likely to remain an essential diagnostic modality.

B. Screening

Screening is recommended for several reasons. The onset of type 2 diabetes is estimated to occur ~4-7 years before clinical diagnosis (21) and epidemiological evidence indicates that complications may begin several years before clinical diagnosis. Furthermore, at least 30% of people in the U.S. with type 2 diabetes are undiagnosed (22). Notwithstanding this recommendation, there is no evidence that population screening of plasma glucose concentrations provides any benefit. Outcome studies should be performed to justify screening.

3. Analytical Considerations

A. Preanalytical

Recommendation: Blood for fasting plasma glucose analysis should be drawn after the subject has fasted overnight (at least 8 h). Plasma should be separated from the cells within 60 min; if this is not possible, a tube containing a glycolytic inhibitor such as sodium fluoride should be used for collecting the sample.

Level of evidence: B

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 ad lib (1). Recent evidence reveals a diurnal variation in FPG, with mean FPG higher in the morning than in the afternoon, indicating that many cases of undiagnosed diabetes would be missed in patients seen in the afternoon (23). Glucose concentrations decrease ex vivo with time in whole blood due to glycolysis. The rate of glycolysis—reported to average 5-7% (~ 0.6 mmol/L; 10 mg/dL) per hour (24)—varies with the glucose concentration, temperature, white blood cell count and other factors (25). Glycolysis can be attenuated by inhibition of enolase with sodium fluoride (2.5 mg fluoride/mL of blood) or, less commonly, lithium iodoacetate (0.5 mg/mL of blood). These reagents can be used alone or, more commonly, with anticoagulants such as potassium oxalate, EDTA, citrate or lithium heparin. Although fluoride maintains 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 (24). (Note that leukocytosis will increase glycolysis even in the presence of fluoride if the white cell count is very high.) After 4 h, the glucose concentration is stable in whole blood for 72 h at room temperature in the presence of fluoride (24). In separated, nonhemolyzed, sterile serum without fluoride the glucose concentration is stable for 8 h at 25 °C and 72 h at 4 °C (26).

Glucose can be measured in whole blood, serum or plasma, but plasma is recommended for diagnosis. The molality of glucose (i.e., amount of glucose per unit water mass) in whole blood and plasma is identical. Although red blood cells 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 whole blood if the hematocrit is normal. Glucose concentrations in heparinized plasma are reported to be 5% lower than in serum (27). The reasons for the latter difference are not apparent but may be due to the shift in fluid from erythrocytes to plasma caused by anticoagulants. The glucose concentrations during an OGTT in capillary blood are significantly higher than those in venous blood [mean of 1.7 mmol/L (30 mg/dL), equivalent to 20-25% (28)], but the mean difference in fasting samples is only 0.1 mmol/L (2 mg/dL) (28, 29).

Reference values: Glucose concentrations in healthy individuals vary with age. Reference intervals in children are 3.3 – 5.6 mmol/L (60-100 mg/dL), similar to the adult range of 4.1 – 5.9 mmol/L (74-106 mg/dL) (26). Note that the ADA criteria (1), not the reference values, are used for the diagnosis of diabetes. Moreover, the threshold for diagnosis of hypoglycemia is variable. The reference values are not useful to diagnose these conditions. In adults, mean fasting plasma glucose increases with increasing age from the third to the sixth decade (30), but does not increase significantly after age 60 (31, 32). By contrast, glucose concentrations after a glucose challenge are substantially higher in older individuals (31, 32). Evidence of an association of increasing insulin resistance with age is inconsistent (33).

B. Analytical

> **Recommendation:** Enzymatic methods for glucose analysis are relatively well standardized. Despite the low imprecision at the diagnostic decision limits of 7.0 mmol/L (126 mg/dL) and 11.1 mmol/L (200 mg/dL), classification errors may occur. Because of the relatively large intraindividual biological variability (CVs of ~ 5-7%), FPG values of 5.8 – 6.9 mmol/L (105-125 mg/dL) should be repeated and individuals with FPG of 5.3 – 5.7 mmol/L (96-104 mg/dL) should be considered for follow-up at intervals shorter than the current ADA recommendation of every 3 years.
>
> Level of evidence: E

Glucose is measured almost exclusively by enzymatic methods. Analysis of proficiency surveys conducted by the College of American Pathologists (CAP) reveals that hexokinase or glucose oxidase is used in virtually all the analyses performed in the U.S. (26). A few laboratories (~1%) use glucose dehydrogenase. At a plasma glucose concentration of ~8.2 mmol/L (147 mg/dL), imprecision among laboratories using the same method had a CV <4% (excluding glucose dehydrogenase) (26). Similar findings have been reported for glucose analysis in samples from patients. For example, comparison of plasma samples from 240 subjects revealed a 5% difference in mean glucose concentrations measured by the hexokinase and glucose oxidase methods (34).

No consensus has been achieved on the goals for glucose analysis. Numerous criteria have been proposed to establish analytic goals. These include expert opinion (consensus conferences), opinion of clinicians, regulation, state of the art and biological variation (35). A rational and realistic recommendation that has received some support is to use biological criteria as the basis for analytic goals. It has been suggested that imprecision should not exceed one half of the within-subject biological CV (36, 37). For plasma glucose, a CV < 2.2% has been suggested as a target for imprecision, with 0% bias (37). Although this recommendation was proposed for within-laboratory error, it would be desirable to achieve this goal for inter-laboratory imprecision to minimize differences among laboratories in the diagnosis of diabetes in individuals whose glucose concentrations are close to the threshold value. Therefore, the goal for glucose analysis should be to minimize total analytical error and methods should be without measureable bias. A national program using samples (e.g., fresh frozen plasma) that eliminate matrix effects should be developed to assist in the achievement of this objective.

4. Interpretation

Knowledge of intraindividual variability of FPG concentrations is essential for meaningful interpretation of patient values. An early study, which repeated the OGTT in 31 nondiabetic adults at 48 h intervals, revealed that FPG in 22 subjects (77%) varied by <10% and in 30 subjects (97%) varied by <20% (38). Biological variation includes within-subject and between-subject variation. Careful evaluation over several consecutive days revealed that intraindividual variation of FPG in healthy subjects [mean glucose of 4.9 mmol/L (88 mg/dL)] exhibited within- and between-subject CVs of 4.8-6.1% and 7.5-7.8%, respectively (39, 40). Larger studies have revealed 6.4-6.9% CVs for FPG in 246 normal (41) and 193 newly diagnosed untreated patients with type 2 diabetes (42). The latter study, which measured FPG by glucose oxidase (intra- and interassay CVs <2%) on two consecutive days, obtained 95% confidence intervals (CI) of ± 14.8% for total variability and ±13.7% for biological variability. If a CV (biological) of 6.9% is applied to a true glucose concentration of 7.0 mmol/L (126 mg/dL), the 95% CI would encompass glucose concentrations of 6.1-7.9 mmol/L (109-143 mg/dL). If the CV of the glucose assay (~4%) is included, the 95% CI is ~ ±18%. Thus, the 95% CI for a fasting glucose concentration of 7.0 mmol/L (126 mg/dL) would be 7.0 ± 18% (126 ± 18%), namely 5.7-8.3 mmol/L (103-149 mg/dL). Using assay imprecision of 4% (CV) only (excluding biological variability), would yield 95% CI of 6.4 – 7.6 mmol/L (116-136 mg/dL) among laboratories for a true glucose concentration of 7.0 mmol/L (126 mg/dL). One should bear in mind that these ranges include 95% of subjects and other individuals will be outside this range. The biological variability is substantially greater than analytic variability. Using biological variation as the basis for deriving analytical performance characteristics (35), the following desirable specifications for glucose have been proposed (43): analytical imprecision ≤ 3.3%, bias ≤ 2.5% and total error ≤ 7.9%.

A short turnaround time for glucose analysis is not usually necessary for the diagnosis of diabetes. In some clinical situations, such as acute hyper- or hypoglycemic episodes in the Emergency Department or treatment of diabetic ketoacidosis (DKA), rapid analysis is desirable. A turnaround time of 30 min has been proposed (44). However, this value is based on requirements by clinicians and no outcome data have been published that validate this figure. Inpatient management of diabetic patients may on occasion require a rapid turnaround time (minutes, not hours). Bedside monitoring with glucose meters has been adopted by many as a practical solution (45).

Frequency of measurement

The frequency of measurement of plasma glucose is dictated by the clinical situation. The ADA recommends that an increased FPG or abnormal OGTT must be confirmed to establish the diagnosis of diabetes (1). Screening by FPG is recommended every 3 years if <6.1 mmol/L (<110 mg/dL), 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 and by assessment of GHb in an accredited laboratory. Appropriate intervals between measurements of glucose in acute clinical situations (e.g., patients in hospital, patients with DKA, neonatal hypoglycemia, etc.) are highly variable and may range from 30 min to 24 hours or more.

5. Emerging considerations

Non- or minimally-invasive analysis of glucose is addressed on page 21.

METERS

Portable meters for measurement of blood glucose concentrations are used in three major settings: i) in acute and chronic care facilities (at the patient's bedside and in clinics, at hospitals); ii) in physicians' offices and iii) by patients at home, work and school. The last, self-monitoring of blood glucose (SMBG), is performed at least once a day by 40% and 26% of individuals with type 1 and 2 diabetes, respectively, in the United States (46). The worldwide market for SMBG is $2.7 billion-per-year, with annual growth estimated at 10-12% (47). The ADA lists the following indications for SMBG: i) achievement and maintenance of glycemic control; ii) prevention and detection of hypoglycemia; iii) avoidance of severe hyperglycemia; iv) adjusting to changes in life-style and v) determining the need for initiating insulin therapy in gestational diabetes mellitus (GDM) (48). It is recommended that most individuals with diabetes attempt to achieve and maintain blood glucose concentrations as close to those found in non-diabetic individuals as is safely possible (14).

1. Use

A. Diagnosis/Screening

> **Recommendation:** There is no published data to support a role for portable meters in the diagnosis of diabetes or for population screening. The imprecision of the meters, coupled with the substantial differences among meters, precludes their use in the diagnosis of diabetes and limits their usefulness in screening for diabetes.
>
> Level of evidence: E

The criteria for the diagnosis of diabetes are based upon outcome data (the risk of micro- and macrovascular disease) correlated with plasma glucose concentrations—both fasting and 2 h after a glucose load—assayed in an accredited laboratory (1). Whole blood is used in portable meters. Although many portable meters have been programmed to report a plasma glucose concentration, the imprecision of the current meters (see below) precludes their use in the diagnosis of diabetes. Similarly, screening by portable meters, although attractive because of convenience, ease and accessibility, would generate many false positives and false negatives.

B. Monitoring/Prognosis

> **Recommendation:** SMBG is recommended for all insulin-treated patients with diabetes. For type 1 patients, SMBG is recommended three or more times a day. SMBG may be desirable in patients treated with sulfonylureas or other insulin secretagogues and in all patients not achieving goals.
>
> Level of evidence: B
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> In patients with type 2 diabetes, SMBG may help achieve better control, particularly when therapy is initiated or changed. However, there are no data to support this concept. The role of SMBG in patients with stable type 2 diabetes controlled by diet alone is not known.
>
> Level of evidence: C

SMBG is recommended for all patients with diabetes who are receiving insulin. Tight glycemic control can decrease microvascular complications in individuals with type 1 (12) or type 2 (13) diabetes. Intensive plasma glucose control in patients with type 1 diabetes was achieved in the Diabetes Control and Complications Trial (DCCT) by participants performing SMBG at least four times per day (12). Therapy in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) (13) was adjusted according to FPG concentrations – SMBG was not evaluated.

Faas et al. (49) reviewed eleven studies, published between 1976 and 1996, that evaluated SMBG in patients with type 2 diabetes. Only one of the published studies reported that SMBG produced a significantly positive improvement, namely lower GHb. The authors of the review concluded that the efficacy of SMBG in type 2 diabetes is questionable (49). Similar conclusions were drawn in a recent meta-analysis (50) and in a sample of patients with type 2 diabetes in the National Health and Nutrition Examination Survey (NHANES) (51). Although SMBG may be useful in initiating or changing therapy in patients with type 2 diabetes, clinical studies are needed to define its role in outcome in patients with type 2 diabetes.

2. Rationale

SMBG allows patients with diabetes to achieve and maintain specific glycemic goals. Knowledge of plasma or blood glucose concentrations is necessary for insulin-requiring patients, particularly those with type 1 diabetes, to determine appropriate insulin doses at different times of the day (48). Patients adjust the amount of insulin according to their plasma or blood glucose concentration. Frequent SMBG is particularly important for tight glycemic control in type 1 diabetes.

Hypoglycemia is a major, potentially life-threatening complication of the treatment of diabetes. The risk of hypoglycemia increases significantly with pharmacologic therapy directed towards maintaining the glycemic range as close to those found in non-diabetic individuals as possible (12, 13). The incidence of major hypoglycemic episodes—requiring third-party help or medical intervention—was 2- to 3-fold higher in the intensive group than in the conventional group in clinical trials of patients with type 1 and type 2 diabetes (12, 13). Furthermore, many diabetic patients, particularly those with type 1 diabetes, lose the autonomic warning symptoms that normally precede neuroglycopenia ("hypoglycemic unawareness") (52), increasing the risk of hypoglycemia. SMBG can be useful for detecting asymptomatic hypoglycemia and allowing patients to avoid major hypoglycemic episodes.

3. Analytical Considerations

A. Preanalytical

> **Recommendation:** Patients should be instructed in the correct use of glucose meters, including quality control. Comparison between SMBG and concurrent laboratory glucose analysis should be performed at regular intervals to evaluate the accuracy of patient results.
>
> Level of evidence: B

Multiple factors can interfere with glucose analysis with portable meters. Several of these, such as improper application, timing and removal of excess blood (26), have been eliminated by advances in technology. Important variables that may influence the results of bedside glucose monitoring include changes in hematocrit (53), altitude, environmental temperature or humidity, hypotension, hypoxia and high triglyceride concentrations (54). Furthermore, most meters are inaccurate at very high or very low glucose concentrations. Another important factor is variability of results among different glucose meters. Different assay methods and architecture result in lack of correlation among meters, even from a single manufacturer. In fact, two meters of the same brand have been observed to differ substantially in accuracy (55, 56). Patient factors are also important, particularly adequate training. Recurrent education at clinic visits and comparison of SMBG with concurrent laboratory glucose analysis improved the accuracy of patients' blood glucose readings (57). In addition, it is important to evaluate the patient's technique at regular intervals (9).

B. Analytical

Recommendation: Multiple performance goals for portable glucose meters have been proposed. These targets vary widely and are highly controversial. No published study has achieved the goals proposed by the ADA. Manufacturers should work to improve the imprecision of current meters.

Level of evidence: E

We recommend meters that measure and report plasma glucose concentrations to facilitate comparison with assays performed in accredited laboratories.

Level of evidence: E

At least 25 different meters are commercially available and are reviewed annually in the American Diabetes Association's Buyer's Guide to Diabetes Products (58). Virtually all the meters use strips that contain glucose oxidase or hexokinase. A drop of whole blood is applied to a strip that contains all the reagents necessary for the assay. Some meters have a porous membrane that separates erythrocytes and analysis is performed on the resultant plasma. Meters can be calibrated to report plasma glucose values, even when glucose is measured in whole blood. An IFCC working group recently recommended that glucose meters be harmonized to the concentration of glucose in plasma, irrespective of the sample type or technology (59). The meters use reflectance photometry or electrochemistry to measure the rate of the reaction or the final concentration of the products. The meter provides a digital readout of glucose concentration. Most meters claim a reportable range of 1.7-33.3 mmol/L (30-600 mg/dL).

Several important technological advances that decrease operator error have been made in the last few years. These include "no wipe" strips, automatic commencement of timing when both the sample and the strip are in the meter, smaller sample volume requirements, an error signal if sample volume is inadequate, "lock out" if controls are not assayed, bar code readers and the ability to store up to several hundred results that can subsequently be downloaded for analysis. Together these improvements have resulted in superior performance by new meters (60).

Multiple analytical goals have been proposed for the performance of glucose meters. The rationale for these is not always clear. In 1987 the ADA recommended a goal of total error (user plus analytical) of < 10% at glucose concentrations of 1.7-22.2 mmol/L (30-400 mg/dL) 100% of the time (61). In addition, it was proposed that values should differ by < 15% from those obtained by a laboratory reference method. The recommendation was modified in response to the significant reduction in complications by tight glucose control in the DCCT. The revised performance goal, published in 1996 (48), is for analytic error < 5%. To our knowledge, there are no published studies of glucose meters that have achieved the ADA goal of analytic error of <5%.

The CLIA 88 goal is less stringent than that of the ADA; results with meters should be within 10% of target values or ± 0.3 mmol/L (6 mg/dL), whichever is larger. NCCLS recommendations (62) are ± 20% of laboratory glucose at >5.5 mmol/L (100 mg/dL) and ± 0.83 mmol/L (15 mg/dL) of laboratory glucose if the glucose concentration is < 5.5 mmol/L (100 mg/dL). These are undergoing revisions. New NCCLS guidelines, anticipated to be published late in 2002, propose that for test readings >4.2 mmol/L (75 mg/dL), the discrepancy between meters and central laboratory should be <20%; for a glucose concentration ≤ 4.2 mmol/L (75 mg/dL), the discrepancy should not exceed 0.83 mmol/L (15 mg/dL) (NCCLS, in preparation).

A different approach was proposed by Clarke (63) who developed an Error Grid that attempts to define clinically important errors by identifying fairly broad target ranges. In addition, two novel approaches were suggested very recently. In the first, 201 patients with longstanding type 1 diabetes were questioned to estimate quality expectations for glucose meters (64). Based on patients' perceptions of their needs and of their reported actions in response to changes in meas-

ured glucose concentrations, a goal for analytical quality at hypoglycemic concentrations was a CV of 3.1%. Excluding hypoglycemia, the analytical CV to meet the expectations of 75% of the patients was 6.4-9.7%. The authors recommended an analytical CV of 5%, with a bias ≤ 5% (64). The second method used simulation modeling of errors in insulin dose (65). The results revealed that meters that achieve both a CV and a bias <5% rarely lead to major errors in insulin dose. However, to provide the intended insulin dosage 95% of the time, the bias and CV needed to be <1-2%, depending upon the dosing schedule for insulin and the ranges of glucose concentrations for the individual patient (65). No meters have been shown to achieve CVs of 1-2% in routine use. Given the bias and imprecision of meters, no studies have evaluated this target which is based on simulation modeling. The lack of consensus on quality goals for glucose meters reflects the absence of agreed objective criteria. Using the same biological variation criteria described above for glucose analysis in accredited laboratories, (Section 4, Interpretation), we suggest a goal for total error (including both bias and imprecision) of ≤ 7.9%. However, additional studies are necessary to accurately define this goal.

There is a very large variability in the performance of different meters. Although current meters, as predicted, exhibit performance superior to prior generations of meters (60), imprecision remains high. For example, a study conducted under carefully controlled conditions where all assays were performed by a single medical technologist resulted in only ~ 50% of analyses meeting the ADA criterion of < 5% deviation from reference values (60). Performance of older meters was substantially worse: 2 of the 4 meters produced results within 5% of reference values for only 33% of analyses. Another recent study that evaluated meter performance in 226 hospitals by split-samples analyzed simultaneously on meters and laboratory glucose analyzers revealed that 45.6%, 25% and 14% differed from each other by > 10%, > 15% and > 20%, respectively (66). Recent analysis of the clinical and analytical accuracy of portable glucose meters (all measurements done by one person) demonstrated that none of the meters met the ADA criterion and only 2 meters had 100% of the estimations in the clinically acceptable zones by Error Grid analysis (67).

Recommendation: Clinical studies are needed to determine the analytic goals for glucose meters. At a minimum, the end-points should be glycated hemoglobin and frequency of hypoglycemic episodes. Ideally, outcomes (e.g., long-term complications and hypoglycemia) should also be examined.

Level of evidence: E

Frequency of measurement

SMBG should be performed at least four times per day in patients with type 1 diabetes. Monitoring less frequently than four times a day results in a deterioration of glycemic control (48, 68, 69). Published studies reveal that self-monitoring is performed by patients much less frequently than recommended. Data from NHANES III collected between 1988 and 1994 reveal that SMBG was performed at least once a day by 39% of patients taking insulin and 5-6% of those treated with oral agents or diet alone (51). Moreover, 29% and 65% of patients treated with insulin and oral agents, respectively, monitored their blood glucose less than once per month. However, no evaluation has been performed to verify that four times a day is ideal or whether some other frequency or timing (e.g., post-prandial testing) would improve glycemic control. For example, adjustment of insulin therapy in women with GDM according to the results of post-prandial, rather than pre-prandial, plasma glucose concentrations improved glycemic control and reduced the risk of neonatal complications (70). The optimal frequency of SMBG for patients with type 2 diabetes is unknown.

Current ADA recommendations suggest daily SMBG for patients treated with insulin or sulfonylureas (14) to detect hypoglycemia. However, published evidence shows no correlation between the frequency of SMBG in type 2 diabetes and glycemic control (49-51). There is no known role for SMBG in patients with type 2 diabetes who are treated with diet alone.

ORAL GLUCOSE TOLERANCE TEST (OGTT)

Recommendation: The oral glucose tolerance test is not recommended for the routine diagnosis of type 1 or type 2 diabetes mellitus. It is recommended for establishing the diagnosis of gestational diabetes mellitus.

Level of evidence: B

1. Use

The OGTT, once the gold standard for diagnosing diabetes mellitus, is now not recommended by the ADA for diagnosing either type 1 or type 2 diabetes, but continues to be recommended in a limited fashion by the World Health Organization (WHO) (71, 72). The oral glucose challenge (or glucose tolerance test) continues to be recommended by both the ADA and the WHO for establishing the diagnosis of gestational diabetes mellitus (GDM). Neither group recommends use of the extended 3-5 h glucose tolerance test in routine practice.

2. Rationale

Inability to respond appropriately to a glucose challenge, i.e., glucose intolerance, represents the fundamental pathological defect in diabetes mellitus. The rationale for the ADA not recommending that the glucose tolerance test be used routinely to diagnose type 1 and 2 diabetes is that appropriate use of FPG could identify approximately the same prevalence of abnormal glucose metabolism in the population as the OGTT. Furthermore, the OGTT is impractical in ordinary practice. The consensus was that a 2 h plasma glucose cutoff of ≥ 11.1 mmol/L (200 mg/dL) hould be used as it was predictive of the occurrence of microangiopathy (72). However, approximately only one-fourth of the individuals with 2 h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) have a FPG ≥ 7.8 mmol/L (140 mg/dL), which was the FPG previously recommended to diagnose diabetes mellitus. The currently recommended FPG value of 7.0 mmol/L (126 mg/dL) corresponds better to a 2-h value in the OGTT of >11.1 mmol/L (200 mg/dL), and thus with development of complications.

Use of the OGTT to classify individuals with impaired glucose tolerance (IGT) and diabetes remains controversial. Recent studies (73-76) indicate that individuals classified with IGT by the OGTT (WHO criteria) have increased risk of cardiovascular disease, but many of these individuals do not have impaired fasting glucose (IFG) by the new ADA criteria. Furthermore, the OGTT (WHO criteria) identifies diabetes in approximately 2% more individuals than the FPG (ADA criteria) (77). Finally, diabetic patients with both abnormal FPG and 2 h OGTT have a higher risk of premature death than those with only an increased FPG concentration (78).

The 2 h glucose tolerance test continues to be recommended for the diagnosis of GDM by both the ADA and WHO (71, 72). Deterioration of glucose tolerance occurs normally in pregnancy especially in the third trimester. Diagnosing and treating GDM is essential to prevent associated perinatal morbidity and mortality.

3. Analytical Considerations

The reproducibility of the OGTT has received considerable attention. In numerous studies, the reproducibility of the OGTT in classifying patients ranges from 50-66% (79). Possible factors contributing to the lack of reproducibility include biologic variation of plasma glucose concentrations, the variable effects of administration of a hyperosmolar glucose solution on gastric emptying and effects of ambient temperature (41, 79-81). The accuracy and reproducibility of glucose assays is not a limiting factor in this regard.

4. Interpretation

A. Diagnosing type 1 and 2 diabetes. The ADA and WHO have different recommendations:

1. ADA: Not recommended for routine clinical use except in pregnant women (72).

2. WHO: When the FPG concentration is in the IFG range [6.1 mmol/L (110 mg/dL)-7.0 mmol/L (126 mg/dL)] an OGTT is recommended (71). After three days of unrestricted diet and an overnight fast (8-14 h), FPG is measured, followed by the oral ingestion of 75 g anhydrous glucose (or partial hydrolysates of starch of the equivalent carbohydrate content) in 250-300 ml of water over 5 min. For children, the dose is 1.75 g glucose/kg up to 75 g glucose. Blood samples are collected 2 h after the load, and plasma glucose analyzed. Results are interpreted as detailed in Table 3.

Table 3: WHO Criteria for Interpreting 2 h OGTT*

	0 h	2 h
Impaired Fasting Glucose	≥ 6.1 mmol/L (110 mg/dL) < 7.0 (126)	< 7.8 (140)
Impaired Glucose tolerance	< 7.0 (126)	≥ 7.8 (140) - < 11.1 (200)
Diabetes	≥ 7.0 (126)	≥ 11.1 (200)

*Any single abnormal value should be repeated on a separate day.

B. Gestational Diabetes Mellitus (GDM)

ADA: The ADA modified their recommendations for laboratory diagnosis of GDM in 2000 (82). Their guidelines follow:

1. Low risk patients require no testing.
   Low risk status is limited to women meeting all of the following:
   • Age < 25 years
   • Weight normal before pregnancy
   • Member of an ethnic group with a low prevalence of GDM
   • No known diabetes in first-degree relatives
   • No history of abnormal glucose tolerance
   • No history of poor obstetric outcome

2. Average risk patients (all patients who fall between low and high risk) should be tested at 24-28 weeks of gestation (see below for testing strategy).

3. High risk patients should undergo immediate testing. They are defined as having any of the following:
   • Marked obesity
   • Personal history of gestational diabetes mellitus
   • Glycosuria
   • Strong family history of diabetes

The first step in laboratory testing is identical to that for diagnosing type 1 or 2 diabetes. That is a FPG ≥ 7.0 mmol/L (126 mg/dL) or a casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL) confirmed on a subsequent day.

However, if the above tests are normal, the ADA recommends that average and high risk patients receive a glucose challenge test following one of two methods:

1. One-step: Perform either a 100 g or 75 g OGTT. This one-step approach may be cost-effective in high-risk patients or populations (e.g., some Native-American groups).
   - The 100 g OGTT is the most commonly used, standard test supported by outcome data. Two or more of the venous plasma glucose concentrations indicated in Table 4 must be met or exceeded for a positive diagnosis.
   - Alternatively, a 75 g OGTT can be performed, but it is not as well validated as the 100 g test. In the 75 g test, diagnostic criteria for plasma glucose values are the same as for the 100 g test, except that there is no 3 h measurement. Two or more of the venous plasma glucose values must equal or exceed the cut-offs to diagnose GDM.
2. Two-step: The first step is a 50 g oral glucose load (the patient does not need to be fasting), followed by a plasma glucose determination at 1 h. A plasma glucose value ≥ 7.8 mmol/L (140 mg/dL) indicates the need for definitive testing. A value of ≥ 7.2 mmol/L (130 mg/dL) may be used as it will detect approximately 10% more diabetic patients. The second and definitive test is one of the two OGTTs described above.

Table 4: Criteria for interpreting 100-g Oral Glucose Tolerance Test

	mmol/L	mg/dL
Fasting	5.3	95
1 h	10.0	180
2 h	8.6	155
3 h	7.8	140

The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥ 150 g carbohydrate per day) and unlimited physical activity. The subject should be seated and should not smoke throughout the test.

5. Emerging considerations

The main issues of controversy are: 1) the lower sensitivity of FPG compared to the OGTT in diagnosing diabetes mellitus (2% of cases missed with FPG), 2) the value of classifying individuals as having IGT (recommended by WHO, but not the ADA) and 3) The appropriate use in GDM.

The lower sensitivity of the FPG compared to the OGTT in diagnosing diabetes mellitus is closely linked to epidemiological evidence that the OGTT better identifies patients at risk for developing complications of diabetes. This includes assessment of the risk of developing cardiovascular disease (83), macrosomia (84) and of predicting increased risk of death (85). The continuing use of the OGTT to diagnose diabetes mellitus has been supported by Australian and New Zealand diabetes professional organizations (86).

The appropriate use of the OGTT for diagnosing GDM is particularly controversial. The recommendation at the Fourth International Workshop - Conference on Gestational Diabetes Mellitus (87), that 5-10% lower glucose values be adopted for diagnosing gestational diabetes, is now adopted by the ADA.

There remains a lack of consensus regarding the use of the 100 g vs. 75 g OGTT for the definitive diagnosis of GDM. It would seem practical and probably diagnostically acceptable to use primarily the 75 g OGTT. However, appropriate diagnostic thresholds continue to be in dispute (86, 88). These discrepancies in recommendations reflect the state of knowledge about GDM, which continues to evolve with enhanced and expanded clinical research.

URINE GLUCOSE

Recommendation: Semi-quantitative urine glucose testing is not recommended for routine care of patients with diabetes mellitus.

Level of evidence: C

1. Use

Semiquantitative urine glucose testing, once the hallmark of diabetes care in the home setting, has now been replaced by SMBG (see above). Semiquantitative urine glucose monitoring should be considered only for patients who are unable to or refuse to perform SMBG, since urine glucose concentration does not accurately reflect plasma glucose concentration (89, 90).

2. Rationale

Although urine glucose is detectable in patients with grossly increased blood glucose concentrations, it provides no information about blood glucose concentrations below the variable renal glucose threshold [~ 10 mmol/L (180 mg/dL)]. This alone limits its usefulness for monitoring diabetes under modern care recommendations. Furthermore, the concentration of the urine affects urine glucose concentrations and only average glucose values between voidings are reflected, further minimizing the value of urine glucose determinations.

3. Analytical Considerations

Semiquantitative test-strip methods utilizing specific reactions for glucose are recommended. Most commercially available strips utilize the glucose oxidase reaction (26). Test methods that detect reducing substances are not recommended as they are subject to numerous interferences, including numerous drugs, and non-glucose sugars. When used, single voided urine samples are recommended (90).

4. Interpretation

Because of the limited use of urine glucose determinations, semiquantitative specific reaction-based test strip methods are adequate.

NON- OR MINIMALLY-INVASIVE GLUCOSE ANALYSES

Recommendation: Non-invasive glucose analyses cannot be recommended as replacements for SMBG or glucose measurements by an accredited laboratory. Ongoing developments in the field, such as use of the new Gluco Watch Biographer, may influence this recommendation.

Level of evidence: E

1. Use

The need for a device for "continuous" in vivo monitoring of glucose concentrations in blood is a very high priority as patients are required to control their plasma glucose more closely (12, 72, 90). Currently, there are only two devices that have been approved by the FDA for non- or minimally-invasive glucose sensing, the "Gluco Watch Biographer" (Cygnus), and the "Continuous Glucose Monitoring System" (MiniMed). Although promising, routine use of these devices cannot be recommended at this time because clinical studies remain limited. Both devices require calibration and confirmation of accuracy with conventional SMBG.

2. Rationale

The first goal for developing a reliable in vivo glucose sensor is to detect unsuspected hypoglycemia. The importance of this goal has been increasingly appreciated with the recognition that strict glucose control is accompanied by a marked increase in the risk of hypoglycemia (12, 90). Therefore, a sensor designed to detect severe hypoglycemia alone would be of value. In contrast, a full-range, reliable in vivo glucose monitor is a prerequisite for the development of an artificial pancreas that measures blood glucose concentrations and automatically adjusts insulin administration.

3. Analytical Considerations

The goal here is not to comprehensively review the status of research in this important area, but to make recommendations for current use. There have been a number of recent reviews on this topic (91, 92), and it has been the subject of national conferences. For example, non-invasive testing technology was the subject of the Oak Ridge Conference of AACC in 1999, with considerable attention focused on glucose-sensing technology (93), and a symposium at the 1999 ADA meeting concentrated on non-invasive glucose sensing (94).

Key technological advances in minimally or non-invasive glucose monitoring can be summarized as shown in Table 5 on the next page.

Table 5: Minimally and Non-invasive Methodology for in Vivo Glucose Monitoring*

1. Transcutaneous needle-type enzyme electrodes

2. Totally implanted sensors
- Enzyme electrodes
- Near infrared fluorescence-based

3. Sampling technologies
- Microdialysis
- Reverse iontophoresis

4. Non-invasive technologies
- Near infrared spectroscopy
- Light scattering
- Photoacoustic spectroscopy

*From Pickup et al. (91)

The transcutaneous sensors and implanted sensors employ multiple detection systems including enzyme- (usually glucose oxidase), electrode- and fluorescence-based techniques. Alternatives to enzymes as glucose recognition molecules are being developed, including artificial glucose "receptors" (95, 96). Fluorescence technologies include use of engineered molecules, which exhibit altered fluorescence intensity or spectral characteristics upon binding glucose, or use of competitive binding assays that employ two fluorescent molecules in the fluorescent resonance energy transfer (FRET) technique (97-101).

Methods to sample tissue, often referred to as "non-invasive" but are in fact "minimally invasive", vary among test systems. The underlying fundamental concept is that the concentration of glucose in the interstitial fluid correlates with blood glucose. Most microdialysis systems are inserted subcutaneously (102-105). In contrast, "reverse iontophoresis", which is the basis of the FDA approved "Gluco Watch" (Cygnus), employs a low-level electrical current on the skin, which by convective transport (electro-osmosis) moves glucose across the skin. Then the concentration of glucose is measured by a glucose oxidase electrode detector (106, 107).

Finally, considerable research has been focused on developing totally non-invasive technology for glucose sensing. Of these, near infrared spectroscopy has been most intensively investigated, but unpredictable spectral variations continue to hinder progress (108-112). Similar problems have impaired the successful use of light scattering (113, 114). Finally, photoacoustic spectroscopy, although less studied, has yielded some encouraging preclinical results. In this technique, pulsed infrared light, when absorbed by molecules, produces detectable ultrasound waves, the intensity and patterns of which can theoretically be tuned to detect glucose (115-117).

4. Interpretation

Only the Gluco Watch Biographer (Cygnus) and the Continuous Monitoring System (CMS) (MiniMed) have received FDA approval at the time of writing. Therefore, only they will be considered here. The two devices have vastly differing applications. The Gluco Watch is designed to analyze "glucose" approximately three times per hour for up to 12 h, and appears best suited for detecting unsuspected hypoglycemia. In contrast, the Continuous Monitoring System

is intended for one-time or occasional use, rather than ongoing daily use. The information derived by these devices is intended to assist physicians to guide patients to improve their diabetes control, the values being downloaded into a computer in the physicians' offices.

The Continuous Monitoring System consists of a subcutaneous glucose sensor, which is connected to a monitor worn externally. Glucose is monitored every 5 min for up to 72 h and at the end of that period the data are transferred to another computer for analyses. Values are not displayed on the externally worn monitor.

The Gluco Watch provides frequent measurements for up to 12 h after a single calibration. Calibration with reference plasma glucose values is required, and sampling time limits the frequency of measurements to approximately three per hour. In limited, but promising, clinical trials, the Gluco Watch provided reasonable correlation with SMBG (106, 107). For example, in 28 patients with type 1 diabetes tested in a clinic setting, the Gluco Watch values had a correlation of 0.90 (n = 1 554 pairs of data) with capillary blood glucose. In 12 patients in the home setting, the correlation of Gluco Watch values with SMBG values was r = 0.85 (205 paired data points). The correlation between two Gluco Watches worn simultaneously was r = 0.94 (107). Despite the recent approval of the Gluco Watch by the FDA, its use has not been rigorously tested in a clinically relevant home setting, nor has it been tested in children. However, if it proves to reliably detect unsuspected hypoglycemic episodes in such settings, we should see widespread use of the Gluco Watch and continued improvement of the technology.

Currently, there are no analytical standards for non- and minimally-invasive glucose analyses. Such standards will clearly need to be different for different proposed uses. For example, the reliability, precision and accuracy requirements for a glucose sensor that is linked to a system that automatically adjusts insulin doses will be vastly different from a sensor in a system designed to sound an alarm in cases of apparent extreme hyper/hypoglycemia. It seems intuitively obvious that a larger imprecision can be tolerated in instruments that make frequent readings during each hour than in an instrument used only 2 or 3 times per day to adjust a major portion of a person's daily insulin dose.

5. Emerging considerations

With the first approvals of self-monitoring, non-invasive glucose sensors by the FDA, it is anticipated that there will be renewed efforts to bring other technologies forward into clinical studies. Ultimately, we shall see improved methods for non-invasive or minimally-invasive glucose measurements that will complement current self glucose monitoring techniques.