Glucose (Blood, serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Glucose (plasma; also blood, serum)

1.2 Alternative names
None, though when used therapeutically, glucose is often referred to as 'dextrose'.

1.3 NMLC code

1.4 Description of analyte
Glucose is a monosaccharide hexose sugar.

1.5 Function of analyte
Glucose is an obligate metabolic fuel for some tissues (e.g. erythrocytes) and preferred fuel (particularly in the short term) for many others (e.g. central nervous system). In the body, there are three sources: dietary carbohydrate; gluconeogenesis (e.g. from lactate) and hepatic glycogenolysis. Glycogen is a glucose polymer and the principal storage form. Glycogen is also stored in skeletal muscle but the glucose derived from it is not released into the circulation.
Glucose concentrations in the blood are maintained within a narrow range by the action of various hormones, the principal of which are insulin (which has hypoglycaemic actions) and glucagon (hyperglycaemic).

2 Sample requirements and precautions

2.1 Medium in which measured
1. Glucose can be measured in blood, serum or plasma: this article refers only to measurements in these fluids made in laboratories. Point-of-care testing (using capillary blood) is well established. Interstitial fluid [glucose] measurement and non-invasive (extracorporeal) measurements are not considered here.
2. Glucose can also be measured in cerebrospinal fluid as an adjunct to the diagnosis of meningitis. It was formerly proposed that its measurement in e.g. pleural fluid could contribute to distinguishing between an aspirate and an exudate, but it is of no value in this context.
3. Measurement of glucose in urine is the subject of a separate entry.

2.2 Precautions re sampling, handling etc.
Glucose is the obligate source of energy for erythrocytes; because of this, [glucose] falls in whole blood *in vitro* (at a rate of 0.4 mmol/L/h at room temperature, lower if refrigerated) unless an inhibitor of glycolysis is present. For this reason, blood for glucose measurement is usually collected into tubes containing fluoride (as an inhibitor of glycolysis) and citrate, EDTA or oxalate (as anticoagulants). [Glucose] is stable in plasma or serum only after the fluid has been separated and removed from the

cellular elements, although for practical purposes is suitable for use provided that no more than 90 minutes has elapsed before separation and there is no bacterial contamination or leucocytosis. Note that blood [glucose] tends to be up to 10-15% lower than serum or plasma [glucose] because of its lower intracellular concentration, although the exact percentage depends on haematocrit and the rate of any change in [glucose].
Note that because of the high risk of artefact, there should be a low threshold for repeating measurements of [glucose] when an unexpectedly abnormal result is found.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

1. Diagnosis and monitoring of the treatment of diabetes mellitus and other hyperglycaemic conditions and monitor patients at risk of developing these conditions.
2. Diagnosis and monitoring the treatment of hypoglycaemia and monitoring patients at risk of developing hypoglycaemia
3. Monitoring patients receiving glucose-containing intravenous fluids.

3.2 Limitations

Measurements of glucose cannot provide information as to the cause of either hyper- or hypoglycaemia.
Note that diagnostic values for [glucose] in this article refer to measurements in venous plasma unless where stated otherwise.

4 Analytical considerations

4.1 Analytical methods

Glucose is measured using enzymatic methods. Formerly used non-enzymic colorimetic methods are obsolete. Any of three enzymes may be used: hexokinase, glucose dehydrogenase and glucose oxidase in reactions either coupled to a chromophore or involving the generation of an electric current. The assays that generate electric current are particularly suitable for use in point of care instruments.

1. Hexokinase (E.C.2.7.1.1) coupled with glucose 6-phosphate dehydrogenase (βD-glucose 6-phosphate: $NAD(P)^+$ 1-oxidoreductase, EC 1.1.1.49) (GD). The reactions are:

   Glucose + MgATP → (HK) → glucose 6-phosphate (G6P) + MgADP
   G6P + $NAD(P)^+$ → (GD) → 6-phosphogluconolactone + NAD(P)H + H^+

   The formation of NAD(P)H is measured spectrophotometrically at 340 nm. This method, using a specimen blank, is the most widely used. Hexokinase methods can also be used in methods with chromogens to produce a coloured product.
2. Glucose dehydrogenase (βD-glucose: $NAD(P)^+$ 1-oxidoreductase EC 1.1.1.47). The reaction is:

   Glucose + NAD^+ → (G6P dehydrogenase) → 6-phosphogluconolactone + NADH

The formation of NADH is measured spectrophotometrically at 340 nm.

3 Glucose oxidase (βD-glucose: oxygen 1-oxidoreductase, EC 1.1.3.4)

3.1 With generation of a colour chromogen using peroxidase (Mn(II) hydrogen peroxide oxidoreductase, EC 1.11.1.7)

Glucose + O_2 → (glucose oxidase) → gluconolactone + H_2O_2
H_2O_2 + chromogenic oxygen acceptor (e.g. *o*-diansidine) → (peroxidase) → colour chromogen + H_2O

3.2 Using polarography

In this variant, the consumption of oxygen is measured directly. Glucose oxidase is specific for β-D-glucose, whereas in solution, glucose is approximately 2/3 in the α form and 1/3 in the β. Kits incorporate mutarotase to convert the α form to the β.

The major routine methods are based on hexokinase or glucose oxidase. The glucose oxidase method is suitable for use in dry slide techniques.

4.2 Reference method

A version of the hexokinase enzymatic method (see 4.1) in which serum or plasma is first deproteinated.

4.3 Reference material

D-glucose (Standard Reference Material (SRM) 917, National Bureau of Standards, Washington DC, USA).

4.4 Interfering substances

1. Hexokinase method: haemolysis (Hb >0.5 g/dL) causes negative, and bilirubin and triglycerides (> 55 mmol/L), positive, interference.
2. Glucose oxidase method: peroxidase is inhibited by various substances including bilirubin and haemoglobin, leading to low results.

4.5 Sources of error

The glucose oxidase-polarography method is not suitable for whole blood because red cells consume oxygen.

5 Reference intervals and variance

5.1.1 Reference intervals

Blood [glucose] varies in relation to food intake. Cut-off values for diagnosis of conditions of impaired glucose tolerance are discussed in section 9.

Lower reference limits are defined for fasting specimens: the value at which symptoms of hypoglycaemia become apparent is highly variable between individuals. A value of <2.8 mmol/L (venous plasma) is commonly used, but decreased endogenous insulin secretion may be detectable at <4.0 mmol/L.

Upper reference limits are defined for fasting and post standardised glucose intake specimens. Two values are recommended for the upper reference limit (fasting): 5.6 mmol/L (American Diabetic Association, ADA) and 6.1 mmol/L (World Health Organisation, WHO).

For non-fasting values, see (6.1).

5.1.2 The same reference limits apply across the entire age-range, and do not differ
between males and females.
5.1.3 Extent of variation
5.1.3.1 Interindividual CV: 12.5%
5.1.3.2 Intraindividual CV: 8.3%
5.1.3.3 Index of individuality: 0.66
5.1.3.4 CV of method: typically <2%
5.1.3.5 Critical difference: 24%
5.1.4 The variation in [glucose] is due to the time since (and the nature of) the last meal and factors that the removal of glucose from the blood, particularly the hormonal milieu and requirements for energy consumption.

6 Clinical uses of measurements and interpretation of results

6.1 Uses and interpretation

1. Diagnosis of diabetes mellitus

Diabetes may be suspected on clinical grounds or screened for in individuals at risk, e.g patients with pancreatic insufficiency, endocrinopathies known to cause hyperglycaemia etc.

Diabetes mellitus is diagnosed if venous plasma glucose is ≥7.0 mmol/L (fasting) or 11.1 mmol/L (2 h after ingestion of 75 g anhydrous glucose or equivalent (i.e. the oral glucose tolerance test) in a symptomatic patient; in an asymptomatic patient, a second such value must be demonstrated on a different day.

2. Diagnosis of impaired glucose tolerance and impaired fasting glycaemia

Impaired glucose tolerance is diagnosed if fasting glucose is <7.0 mmol/L and 2 h post-glucose ingestion glucose is ≥7.8 mmol/L but <11.1 mmol/L; Impaired fasting glycaemia is diagnosed on WHO criteria if fasting glucose is ≥6.1 mmol/L and <7.0 mmol/L (ADA criteria, >5.6 mmol/L and <7.0 mmol/L, respectively).

3. Monitoring treatment of established diabetes

Blood glucose measurements, often by patients, can provide important information to guide treatment, especially when intensive insulin regimens are used. Measurements of glycated haemoglobin (HbA1c) are preferred for assessment of the adequacy of treatment over the longer term. Measurements of glucose are also required to confirm a clinical diagnosis of hypoglycaemia (see (7)).

4. Monitoring treatment of hyperglycaemia

Glucose measurements are essential to inform the management of diabetic ketoacidosis and hyperosmolar non-ketotic hyperglycaemia.

5. Monitoring treatment of diabetes during surgery etc.

Trauma, surgery, intercurrent illness etc, all increase insulin requirements and have the potential to cause a deterioration in glycaemic control: regular monitoring of [glucose] is essential under such circumstances.

6. Monitoring treatment involving intravenous glucose infusion

Regular measurements of glucose are essential to the prevention of hyperglycaemia during intravenous glucose infusion, e.g. as part of parenteral nutrition.

7. Diagnosis and monitoring the treatment of hypoglycaemia.

A laboratory glucose measurement is essential for the diagnosis of hypoglycaemia of any cause (although treatment should not be delayed pending the receipt of a result when the condition has been diagnosed clinically) and in the monitoring of treatment, both to ensure its adequacy and to avoid hyperglycaemia.

6.2 Confounding factors
None.

7 Causes of abnormal results

7.1 High concentrations (assuming patient is not receiving glucose orally or parenterally).

7.1.1 Causes:

- diabetes mellitus (type 1, type 2 or secondary)
- impaired glucose tolerance
- impaired fasting glycaemia.

7.1.2 Investigation
See 6.1. Formal glucose tolerance testing is only indicated in individuals in whom a diagnosis of diabetes is being considered and in whom fasting or post-prandial glucose concentrations alone is/are not diagnostic. Note that even in a patient with clinical features suggestive of diabetes, the diagnosis is unlikely if random glucose is <5.5 mmol/L.

7.2 Low concentrations

7.2.1 Causes of hypoglycaemia include:

- treatment with insulin or some oral hypoglycaemic drugs
- hyperinsulinism (e.g insulinoma)
- other tumours
- alcohol and other drugs
- endocrinopathies, e,g, adrenal or pituitary failure
- chronic liver or kidney disease
- sepsis
- gastric surgery leading to rapid transit
- inherited metabolic diseases
- etc.

7.2.2 Investigation
Once hypoglycaemia has been confirmed by laboratory measurement and clinical features shown to resolve on restoration of normoglycaemia, the following should be measured *when the patient is hypoglycaemic*: insulin, C-peptide, (proinsulin).

- high [insulin] and [C-peptide]: endogenous hyperinsulinism
- high [insulin], low [C-peptide]: exogenous hyperinsulinism
- low [insulin], low [c-peptide]: endocrinopathies; liver, kidney disease; inherited metabolic diseases.

Measurement of serum 3-OHbutyrate may also be informative. Insulin suppresses the production of this metabolite. A concentration >600 μmol/L in a patient with suppressed insulin secretion suggests an endocrine cause for the hypoglycaemia.

7.3 Notes

1. Severe, symptomatic hyperglycaemia and hyperglycaemia of any degree with ketosis are medical emergencies. Patients are likely to require hospital admission and management according to standard protocols, including intravenous fluids and insulin.
2. Symptomatic hypoglycaemia is a medical emergency. Patients require the immediate administration of glucose (orally or parenterally) or intramuscular glucagon to raise their blood glucose concentration; glucose administration may need to be continued or repeated until the underlying cause is diagnosed and treated.
3. Because of the profound clinical consequences of hypo- and hyperglycaemia if untreated, laboratories should establish and document 'telephone alert values' and have a documented policy for informing an appropriate medical officer should such a result be found.
4. Formal glucose tolerance testing is only required in suspected diabetes if preliminary results are equivocal.
5. Point of care instruments are satisfactory for monitoring [glucose] but should not be used to diagnose diabetes. In suspected hypoglycaemia, a point-of-care result must be confirmed by a laboratory measurement, though this should not hinder initiation of treatment.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

1. Diabetes mellitus and other hyperglycaemic states are diagnosed on the basis of glucose measurements (See 9.2.1). Sensitivity and specificity are thus 100%.
2. Hypoglycaemia is diagnosed on the basis of measurements of glucose, characteristic clinical features (of increased sympathetic activity and neuroglycopaenia) and the resolution of these features when euglycaemia is restored. There is, however, variation within and between individuals as to the [glucose] at which clinical features become apparent.
Physiological disturbances can typically be detected at higher [glucose] than cause symptoms.

9 Systematic reviews and guidelines

9.1 Systematic reviews

Numerous reviews have been published. They fall into two categories: those examining the evidence that hyperglycaemia is a risk factor e.g. for cardiovascular disease, and those examining the evidence of benefit from monitoring blood glucose. For example:
1. Kelly TN, Bazzano LA, Fonseca VA *et al*. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Int Med 2009; 191:394-403. *The authors conclude that intensive glucose control decreases the risk of non-fatal myocardial infarction but not cardiovascular death or all cause mortality, and is associated with a significant increase in the risk of hypoglycaemia*.
2. Coster S, Gulliford MC, Seed PT *et al*. Monitoring blood glucose control in diabetes mellitus: a systematic review. Health Technology Assessment 2000;4(12). *The authors concluded that despite the wide usage of glucose self-monitoring, its optimal use had not been determined..*
3. Polsup N, Suksomboon N, Jiamsathit W. Systematic review of the benefits of self-monitoring of blood glucose on glycemic control in type 2

diabetes patients. Diabetes Technology and Therapeutics 2008; 10(Supplement 1): S51-S66. *The authors concluded that self-monitoring of blood glucose used to adjust treatment regimens led to improved glycaemic control in patients with type 2 diabetes not treated with insulin.* See also: http://www2.cochrane.org/reviews/en/ab005060.html (accessed 26.iv.2012)

9.2 Guidelines

1. NICE and Diabetes: a summary of relevant guidelines. www2.cochrane.org/reviews/en/ab005060.html (accessed 26.iv.2012) *This summary refers to both diagnosis and management. Diagnostic cut offs for venous plasma glucose are:*
normal: <6.1 mmol/L (fasting)
impaired fasting glycaemia ≥6.1 mmol/L, <7.0 mmol/L (fasting)
impaired glucose tolerance <7.0 mmol/L (fasting) *and* ≥7.8 mmol/L, <11.1 mmol/L (2 h post glucose).
Diabetes ≥7.0* mmol/L (fasting) *or* >11.1* mmol/L (2 h post glucose). (2 h post glucose = 2 h following ingestion of 75 g anhydrous glucose.)
*In asymptomatic individuals, two results on separate days in the diabetic range are required for diagnosis.
2. Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. NICE Clinical Guideline 15, July 2004 updated March 2010 with additional changes April 2010.
3. Type 2 diabetes: national clinical guideline for management in primary and secondary care. National Collaborating Centre for Chronic conditions. NICE Clinical Guideline 66 May 2009 (update CG87, June 2009 refers to newer agents for treatment).

9.2 Recommendations

http://www.patient.co.uk/doctor/Self-Monitoring-Blood-Glucose-(SMBG)-in-Diabetes-Mellitus.htm (accessed 26.iv.2012) *Detailed recommendations on the role and frequency of self monitoring of blood glucose in diabetes based on SIGN and NICE guidelines and other sources.*

10 Links

10.1 Related analytes

None

10.2 Related tests

1. Semi-quantitative detection of urine glucose was formerly widely used to monitor patients with diabetes, but is now only appropriate for patients not treated with insulin who are unable or unwilling to perform blood glucose measurements. Detection of urine glucose has no role in the diagnosis of diabetes.
2. Glycated haemoglobin (HbA1c) is recommended for monitoring established diabetes; consideration is currently being given to allowing diabetes to be diagnosed on the basis of HbA1c values.
3. A dipstick test for urinary ketones is sufficient to indicate ketosis in suspected diabetic ketoacidosis or patients at risk therof. Measurement of blood ketones is available but seldom required.

4. Measurement of albumin:creatinine ratio is used to detect incipient diabetic nephropathy.

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