# Perioperative hyperglycaemia

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## Introduction

Perioperative hyperglycaemia is a complex and common clinical problem, with serious adverse consequences for patient morbidity and mortality. A clinical approach to diagnosis, screening and management is offered.

Perioperative hyperglycaemia is a very common problem, both because the incidence may be increasing worldwide,[1] and because it describes a much wider problem than diabetes mellitus only.

## Incidence

Figures for the incidence of diagnosed diabetes mellitus in the USA range between 10-13%,[2,3] and in the UK between 2-5%.[3,4] The World Diabetes Foundation estimated that in 2010 the global prevalence of diabetes was 6.4%, and that the prevalence of diagnosed diabetics in Africa was 3.8%. However, the World Diabetes Foundation claims that more than 85% of diabetics in South Africa are undiagnosed.[5] In 2008, Biccard found the incidence of diabetes among South African patients with peripheral artery disease to be approximately 36%.[1]

## Classification and diagnosis

The American Diabetes Association (ADA) classifies diabetes into four clinical classes:[6]

1. Type 1 diabetes results from pancreas beta cell destruction, usually leading to an absolute insulin deficiency.
2. Type 2 diabetes results from a progressive insulin secretory defect on the background of insulin resistance.
3. Specific types of diabetes are due to other causes, including genetic defects in beta cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), or after organ transplantation).
4. Gestational diabetes mellitus (GDM). This refers to diabetes diagnosed in pregnancy that is not clearly overt diabetes.

Since 2009, the ADA criteria for the diagnosis of diabetes have included a glycosylated haemoglobin A1c ($HbA_{1c}$) > 6.5%.[6]

The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) does not include the $HbA_{1c}$, but their guidelines are currently being reviewed, and the updated guidelines will be published shortly.[7]

While $HbA_{1c}$ is a useful tool, currently it is not recommended to delay elective surgery until glycaemic correction of elevated $HbA_{1c}$ levels is achieved.[2,4]

**American Diabetes Association criteria for the diagnosis of diabetes[6]**

- The American Diabetes Association criteria for the diagnosis of diabetes is a $HbA_{1c} \geq 6.5\%$. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified, and standardised to the Diabetes Control and Complications Trial assay.*

**OR**

- A fasting plasma glucose (FPG) ≥ 126 mg/dl (7 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.*

**OR**

- A two-hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

**OR**

- In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).*

*In the absence of unequivocal hyperglycaemia, the result should be confirmed by repeat testing.

**The Society for Endocrinology, Metabolism and Diabetes of South Africa criteria for the diagnosis of diabetes mellitus[7]**

**A. Symptoms of diabetes**

The classic symptoms of diabetes, including polyuria, polydipsia and weight loss.

**PLUS**

- Casual or random plasma glucose ≥ 11.1 mmol/l. "Casual" is defined as any time of the day, regardless of the time of last meal.

**OR**

- FPG ≥ 7.0 mmol/l. "Fasting" is defined as no caloric intake for at least 8 hours.

**OR**

- Two-hour plasma glucose ≥ 11.1 mmol/l during OGTT The test should be performed as described by the WHO using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in 250 ml water over five minutes. Note: In the absence of unequivocal hyperglycaemia accompanied by acute metabolic decompensation, a confirmatory laboratory glucose test (a FPG, a casual plasma glucose, or a two-hour plasma glucose in a 75 g OGTT) must be carried out in all cases on a different day. Different criteria are used to diagnose gestational diabetes in pregnant women.

**B. If asymptomatic**

The 75 g OGTT is indicated in the following:

- In asymptomatic high-risk individuals.
- If the FPG is 5.6-7. mmol/l in detection or screening programmes.
- If random plasma glucose is 5.6-11.1 on screening. Alternatively, a FPG is indicated in this group.

The WHO 1998/2006 criteria should be used to diagnose diabetes. This emphasises the importance of not diagnosing diabetes on the basis of a single laboratory measurement in the absence of symptoms.

Diagnosis should be based on laboratory plasma glucose (preferred) or capillary plasma glucose.

Conversion factor: plasma glucose (mmol/l) = 0.102 + 1.066 x capillary blood glucose.

In addition to the above group of patients with diabetes, a further two groups of patients with perioperative hyperglycaemia exist. The first is the group of patients who are not diabetic, but who have an increased risk of diabetes (pre-diabetic), and the second is the patient group with stress-induced hyperglycaemia.[2,6]

Patients with an increased risk of diabetes (prediabetes) are those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) levels to the oral glucose tolerance test.[2,6] While these patients' glucose levels do not meet the criteria for diabetes, they are too high to be classified as normal. The ADA defines patients as having impaired fasting glucose (IFG) if they have a FPG between 100 mg/dl-125 mg/dl (5.6 mmol/l - 6.9 mmol/l), and having IGT if they have a two-hour plasma glucose in the 75 g OGTT of 140 mg/dl-199 mg/dl (7.8 mmol/l-11 mmol/l). The ADA also recognises patients with an $HbA_{1c}$ level between 5.7-6.4% as being pre-diabetic.[6]

Patients with stress-induced hyperglycaemia present with in-patient hyperglycaemia, which normalises when the admission-related stressor abates. Hyperglycaemia in these patients occurs in the face of a normal $HbA_{1c}$, and can have a worse outcome than hyperglycaemia in patients with diabetes.[2,8] This suggests a different pathophysiology to that of diabetes mellitus.[2,8] Nyika et al found that stress-induced hyperglycaemia occurred in healthy bungee jumpers, who did not have diabetes. This was due to decreased pancreatic beta cell function and insulin resistance, as a result of the stress experienced at the time of bungee jumping.[9]

## Screening

Any patient with a random glucose ≥ 180 mg/dl (10 mmol/l)[2] and/or patients who are identified by the ADA "criteria for testing for diabetes in asymptomatic adult individuals"[2,6] should be screened for undiagnosed diabetes preoperatively. This includes the ADA criteria for testing for diabetes in asymptomatic adult individuals.[6]

**ADA criteria for testing for diabetes in asymptomatic adult individuals[6]**

1. Testing should be considered in all adults who are overweight [body mass index (BMI) ≥ 25 kg/m$^2$] and who have one or more additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk ethnic group
- Women who delivered a baby > 4.08 kg, or who were diagnosed with GDM
- Hypertension [blood pressure (BP) > 140/90 mmHg, or on treatment for hypertension]
- High-density lipoprotein (HDL) cholesterol < 35 mg/dl (0.90 mmol/l), and/or a
- triglyceride level > 250 mg/dl (2.82 mmol/l)
- Women with polycystic ovary syndrome
- $HbA_{1c}$ ≥ 5.7%, IGT or IFG on previous testing
- Other clinical conditions associated with insulin resistance, e.g. severe obesity and acanthosis nigricans.

- History of cardiovascular disease

2. In the absence of the above criteria, testing for diabetes should begin at age 45 years.
3. If results are normal, testing should be repeated at three-year intervals, and consideration should be given to more frequent testing depending on initial results (e.g. those with prediabetes should be tested yearly) and risk status.

A corresponding set of criteria for children are also listed on the ADA website.

## Clinical problems

Diabetes and hyperglycaemia present a complex set of clinical problems.

Uncontrolled diabetes reduces afflicted patients' life expectancy by a mean of 15 years, and raises morbidity due to vascular and neuropathic complications by three to four times than that of a non-diabetic population.[10]

Complications of poorly controlled hyperglycaemia include the acute manifestations of dehydration and metabolic dysfunction of ketoacidosis (DKA), hyperosmolar non-ketotic coma and lactic acidosis. These patients also suffer chronic problems of wound infection, delayed wound healing, as well as chronic target organ damage, such as cardiovascular disease, cerebrovascular disease, renal disease, autonomic neuropathy and retinopathy.[3]

In South Africa, the mortality that is secondary to diabetes and diabetic complications is higher than international standards. The reasons for this include generally poor glycaemic control, poor monitoring of associated complications, and inadequate management of hypertension and hypercholesterolaemia.[1,11]

In chronic diabetics with recently diagnosed hypertension, even moderate control of the hypertension is more important for a better outcome than an emphasis on glycaemic control alone.[3]

In known diabetics, there should be a high index of suspicion for associated cardiovascular disease. Any patient with autonomic neuropathy or any other two myocardial ischaemia risk factors (smoking, raised cholesterol, dyslipidaemia, hypertension, a family history of coronary artery disease or males > 40 years of age) should be further evaluated by cardiovascular stress testing for ischaemic heart disease.[3]

## Control of hyperglycaemia

In 2001, Van den Berghe advocated the control of hyperglycaemia with a "tight" glucose control regimen (80-110 mg/dl, 4.4-5.6 mmol/l). This has been modified to a "moderately tight" regime over the latter half of the previous decade.[2,12] The current British National Health Service (NHS) guideline, the *Management of adults with diabetes undergoing surgery and elective procedures*, recommends keeping the glucose level between 6-10 mmol/l, with the acceptable range being 4-12 mmol/l.[2,4]

The problem with tight control was an incidence of dangerous hypoglycemia of 9-17%,[4] with no improved outcome in terms of mortality and morbidity, except for a reduction in wound infection.[12] Also, the original study was carried out in an intensive care (ICU) setting, and then extrapolated to non-ICU patients, resulting in a weak level of evidence for theatre use.

Subsequent studies have revealed that the deleterious effects of hyperglycaemia seem to occur from a glucose level of 9 mmol/l or greater.[4]

Furthermore, the Society for Ambulatory Anesthesia (SAMBA) consensus statement on perioperative blood glucose management in patients with diabetes undergoing ambulatory surgery recommends that patients with poorly controlled diabetes, who have to undergo surgery, are maintained at the higher end of the target blood glucose range, nearer their usual baseline value. This is because these patients have an altered counter-regulatory response which may result in hypoglycaemic symptoms developing at normal blood glucose levels.[13] These patients' intraoperative glucose requirements may also be higher than their postoperative requirements, further strengthening the argument for a "high-normal" intraoperative blood glucose target. A stable glucose level, albeit at the "high-normal" end of the range, ensures a far superior outcome than marked blood glucose fluctuations which may occur in the setting of a more tight control regimen.[14]

A relatively recent advance, incretin therapy, is used in type 2 diabetics to elicit the "incretin effect".

Glucagon-like peptide 1 (GLP-1) is a naturally occurring incretin hormone secreted by the small intestine in response to an oral glucose stimulus. GLP-1 levels rise well before the blood glucose level rises. GLP-1 stimulates insulin secretion by the beta cells of the pancreas, inhibits glucagon secretion by the alpha cells of the pancreas, delays gastric emptying (so reducing postprandial hyperglycaemia), and reduces appetite and food intake.[10,15,16]

GLP-1 is inactivated in the body by the enzyme dipeptidyl-peptidase-4 (DPP-4).

Exogenous incretin therapy is achieved by either the injection of GLP-1 analogues or the oral administration of DPP-4 inhibitors.[10,15,16]

A full discussion of the detailed perioperative management of diabetic medication and fluid prescription, glucose and electrolyte monitoring and control, starvation and theatre list booking guidelines, is beyond the scope of this article, but a full set of detailed protocols may be found in the NHS April 2011 *Management of adults with diabetes undergoing surgery and elective procedures: improving standards* guidelines.[4]

Important aspects covered therein include:[4]

- Consideration should always be given to DKA, and surgery postponed, until this is under control.
- Glucose should be monitored hourly on the day of surgery unless hypoglycaemia occurs, in which case more frequent monitoring is required until normoglycaemia is achieved.
- Vigilance should be exercised to avoid hypoglycaemia.

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