

# The patient with hyperglycaemia

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## Introduction

Diabetes mellitus and hyperglycaemia are complex and common clinical problems that have serious adverse consequences for patient morbidity and mortality. In the past year, a body of revised guidelines and opinions has emerged from the South African, British, American and European diabetes authorities. An overview of these guidelines and position statements on diabetes mellitus in general, and perioperative hyperglycaemia, in particular, is offered. Perioperative hyperglycaemia is a very common problem, both because the actual incidence may be increasing worldwide,<sup>2</sup> and also because it describes a much wider problem than just diabetes mellitus.

## Definition

Perioperative hyperglycaemia includes patients from the four classical diabetes mellitus classes, as well as a further two groups. These two groups are firstly, the patient group with an increased risk of diabetes (pre-diabetics), and secondly, the group with stress-induced hyperglycaemia.

Patients with an increased risk of acquiring diabetes (pre-diabetics) have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) levels following the oral glucose tolerance test (OGTT).<sup>1,3,5</sup> While these patients' glucose levels do not meet the criteria for diabetes, they are too high to be classified as normal. The American Diabetes Association (ADA) defines patients as having IFG if they have a fasting plasma glucose (FPG) between 100-125 mg/dl (5.6- 6.9 mmol/l), and having IGT if they have a two-hour plasma glucose in the 75-g OGTT of 140-199 mg/dl (7.8-11.0 mmol/l). The ADA also recognises patients with a glycosylated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level between 5.7% and 6.4% as being pre-diabetic.<sup>5</sup>

The World Health Organization (WHO) and the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) both discourage the use of the term "pre-diabetes" to describe IGT and IFG. They endorse the use of the term "intermediate hyperglycaemia" instead.<sup>1</sup>

Patients with stress-induced hyperglycaemia present with in-patient hyperglycaemia which normalises when the admission-related stressor abates. Hyperglycaemia occurs in the face of a normal HbA<sub>1c</sub> in these patients and can

have a worse outcome than hyperglycaemia in patients with diabetes.<sup>3,6</sup> This suggests a different pathophysiology to that of diabetes mellitus.<sup>3,6</sup> Nyika et al found that stress-induced hyperglycaemia occurred in healthy bungee jumpers who did not have diabetes. This was because of decreased pancreatic beta-cell function and insulin resistance, as a result of the stress experienced when they performed a bungee jump.<sup>7</sup>

## Incidence

In 2011, figures for the incidence of diabetes mellitus in the USA were found to be approximately 8.3%,<sup>12</sup> and between 4% and 5% in the UK.<sup>14</sup> The International Diabetes Federation (IDF) estimated the 2011 prevalence in South Africa to have been approximately 6.4%.<sup>1</sup> However, the World Diabetes Foundation and the IDF believe that anywhere between 50% and 85% of patients with diabetes are undiagnosed in South Africa.<sup>1</sup> In 2008, Biccard found the incidence of diabetes among South African patients with peripheral artery disease to be roughly 36%.<sup>2</sup> This is an increase from figures published in 1999, by Robbs, of approximately 10% for the same type of South African patient.

## Classification and diagnosis

The ADA and SEMDSA classify diabetes mellitus according to four clinical classes:<sup>1,5</sup>

- *Type 1 diabetes:* Type 1 diabetes results from pancreas beta-cell destruction, usually leading to absolute insulin deficiency. It is responsible for approximately 5% of clinical cases and insulin therapy is required.
- *Type 2 diabetes:* Type 2 diabetes results from a progressive insulin secretory defect on the background of insulin resistance and is responsible for approximately 90% of clinical cases. A step-wise therapy regime is required, beginning with the oral agents, but insulin may also be needed.
- *Other specific types of diabetes due to other causes:* Other specific types of diabetes due to other causes include 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 causes, e.g. treating human

**Table 1:** Society for Endocrinology, Metabolism and Diabetes of South Africa criteria for the diagnosis of diabetes mellitus<sup>1</sup>

Diagnostic test	IFG	IGT	Diabetes
FPG*	6.1-6.9 mmol/l	< 7 mmol/l (if measured)	≥ 7 mmol/l, or
2-hour PG (2-hour PG during OGTT)**	< 7.8 mmol/l (if measured)	7.8-11 mmol/l	≥ 11.1 mmol/l, or
Glycated HbA <sub>1c</sub> ***			≥ 6.5%, or
(RPG)****			≥ 11.1 mmol/l if classic symptoms of diabetes or hyperglycaemic crisis are present

FPG: fasting plasma glucose, HbA<sub>1c</sub>: haemoglobin A<sub>1c</sub>, IGT: impaired glucose tolerance, IFG: impaired fasting glucose, OGTT: oral glucose tolerance test, PG: plasma glucose, RPG: random plasma glucose

\*: Fasting is defined as no caloric intake for at least eight hours.

\*\* : The test should be performed as described by the World Health Organization using a glucose load that contains the equivalent of 75 g anhydrous glucose dissolved in 250 ml water, ingested over five minutes.

\*\*\*: This is provided that the test method meets stringent quality assurance criteria, that the assay is standardised according to criteria aligned with the international reference values [National Glycohemoglobin Standardization Program (NGSP)-certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay], and that no conditions are present which preclude its accurate measurement.

\*\*\*\*: "Random" (casual) is defined as any time of day, without regard to the time of the last meal. The classic symptoms of hyperglycaemia include polyuria, polydipsia and weight loss. "Hyperglycaemic crisis" refers to diabetic ketoacidosis or hyperosmolar nonketotic hyperglycaemia.

immunodeficiency virus/acquired immune deficiency syndrome, or following organ transplantation.

- *Gestational diabetes mellitus*: Gestational diabetes mellitus is diagnosed in pregnancy, and is not clearly overt diabetes.

Since 2009, the ADA criteria for the diagnosis of diabetes has included a HbA<sub>1c</sub> ≥ 6.5%.<sup>5</sup> The 2012 SEMDSA guideline for the management of type 2 diabetes (revised) also includes the HbA<sub>1c</sub> under the criteria for diagnosis, with provisos.<sup>1</sup>

Several factors may influence HbA<sub>1c</sub> measurement and must be taken into account when analysing an HbA<sub>1c</sub> result, namely:<sup>1</sup>

- Erythropoiesis that is elevated or decreased by factors such as iron deficiency or chronic liver disease.
- Altered haemoglobin, for example in haemoglobinopathies or methaemoglobinaemia.
- Glycation of the haemoglobin by drugs.
- Erythrocyte destruction, that causes abnormal haemoglobin levels.
- Technical errors that result in false low or high readings.

Furthermore, the HbA<sub>1c</sub> result is skewed toward the haemoglobin produced in the past 30 days and does not give an accurate account of the full 180-day prior period.<sup>1</sup>

The 75-g OGTT is indicated:

- In asymptomatic, high-risk individuals.
- If the FPG is 5.6-6.9 mmol in detection and screening programmes.
- If random plasma glucose is 5.6-11 on screening. Alternatively a FPG is indicated in this group.
- HbA<sub>1c</sub> of 6-6.4% (possibly; no available data).

## Screening

Any patient with a random glucose ≥ 180 mg/dl (10 mmol/l),<sup>3</sup> and/or patients who are identified by the SEMDSA criteria for screening for type 2 diabetes in asymptomatic adults should be investigated for undiagnosed diabetes preoperatively.<sup>1</sup>

## Society for Endocrinology, Metabolism and Diabetes of South Africa criteria for screening for diabetes in asymptomatic adult individuals<sup>1</sup>

Testing should be considered in all adults who are overweight (with a body mass index > 25 kg/m<sup>2</sup>), and who have one or more additional risk factors:

- Physical inactivity.
- Hypertension (blood pressure > 140/90 mmHg, or on treatment for hypertension).
- A first-degree relative with diabetes.
- Dyslipidaemia.
- Women with polycystic ovary syndrome.
- A high-risk ethnic group, e.g. of South African descent.
- A history of cardiovascular disease.
- Women who delivered a baby > 4 kg, or who were diagnosed with gestational diabetes.
- IGT or IFG on previous testing.
- Other clinical conditions associated with insulin resistance, e.g. severe obesity and acanthosis nigricans.

In the absence of the above criteria, testing for diabetes should begin at 45 years of age.

If results are normal, testing should be repeated at three-year intervals. Consideration should be given to more frequent testing depending on initial results (e.g. those with IFG or IGT should be tested yearly), and risk status.

OGTT is the preferred test. FPG and HbA<sub>1c</sub> are also acceptable.

## 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 increases morbidity by 3-4 times that of a nondiabetic population because of vascular and neuropathic complications.<sup>1,8</sup>

Complications of poorly controlled hyperglycaemia include the acute manifestation of dehydration and metabolic dysfunction of ketoacidosis (DKA), hyperosmolar nonketotic 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.<sup>4</sup>

Chronic uncontrolled hyperglycaemia leads to micro- and macrovascular complications. Microvascular complications include retinopathy, nephropathy and neuropathy. Macrovascular complications are coronary artery disease and cerebrovascular disease.

The United Kingdom Prospective Diabetes Study (UKPDS) clearly showed a decreased rate of microvascular complications if patients' HbA<sub>1c</sub> was kept  $\leq 7\%$ . Unfortunately, the same benefit could not be shown for macrovascular complications.<sup>15</sup>

In South Africa, the mortality that is secondary to diabetes and diabetic complications is higher than that of international standards. Generally, the reasons for this include poor glycaemic control, poor monitoring of associated complications and inadequate management of hypertension and hypercholesterolaemia.<sup>2,9</sup>

The 2012 SEMDSA guidelines also include therapy goals for diabetic patients' lipid profile and hypertension management.<sup>1</sup>

Even moderate control of hypertension is more important than an emphasis on glycaemic control alone for a better outcome in patients with chronic diabetes and recently diagnosed hypertension.<sup>4</sup> Treatment of hypertension in patients with diabetes shows a consistent reduction in the incidence of macrovascular complications.<sup>1</sup>

There should be a high index of suspicion for associated cardiovascular disease in known patients with diabetes. Any patient with autonomic neuropathy, or any other two myocardial ischaemia risk factors (smoking, a 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.<sup>4</sup>

### Control of hyperglycaemia (chronic, outpatient setting)

SEMDSA and the ADA/European Association for the Study of Diabetes provide clear guidelines and algorithms for the chronic control of hyperglycaemia.<sup>1,13,15</sup>

The emphasis is now on a patient-centered approach in which clinicians and patients act as partners in order to reach a consensus on the therapeutic course of action. This is mainly because patients self-experiment, and have the best long-term experience in managing their own specific situation.

The first-line oral agent of choice for noninsulin diabetics is metformin. It is cheap, highly efficacious and has a low risk of causing hypoglycaemia or weight gain.<sup>17</sup> The main initial side-effects are gastrointestinal disturbances and lactic acidosis in renal failure patients, or those with lactic acidosis that has been caused by something else.

Should patients require second- or third-line additional oral agents, the guidelines become less clear. The newer dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonist agents are popular because they have a low risk of causing hypoglycaemia and weight gain. The main drawback is that they are expensive.<sup>1,17</sup>

### Control of perioperative hyperglycaemia

Diabetes UK, in its position statement and care recommendations, issued the *National Health Service diabetes guideline for the perioperative management of the adult patient with diabetes*.<sup>14</sup>

These recommendations include the following:

- Always try to keep the patient on his or her usual medication as far as possible. As much as possible, avoid using a variable-rate insulin infusion.
- Poor preoperative glycaemic control will lead to poor postoperative outcomes. Where appropriate and feasible, patients should be optimised preoperatively if their HbA<sub>1c</sub>  $\geq 8.5\%$ .
- Always keep the patient's starvation time to a minimum by prioritising patients on the list, and not scheduling patients with diabetes for afternoon or evening lists. (Starvation causes glucagon release which promotes hepatic glucose production and lipolysis, resulting in hyperglycaemia and ketosis).
- Surgery causes a metabolic stress response. Initially, this leads to inhibition of insulin secretion, followed by a period of insulin resistance postoperatively, i.e. even nondiabetic patients may exhibit transient hyperglycaemia following major surgery.
- Facilitate as early a return to the patient's usual diet and diabetes regime as possible.
- Patients who will only be missing one meal should be kept on their usual medication. The use of a variable-rate insulin infusion should be avoided.
- A variable rate insulin infusion will be necessary in patients who will be missing more than one meal.
- Measure the blood glucose once before induction and then hourly, intra-, and postoperatively. The target should be blood glucose levels of 6-10 mmol/l. However, levels of 4-12 are acceptable. (Measure more frequently if levels are outside the target range).
- Patients with hyperglycaemia have increased perioperative morbidity, and a mortality of up to 50% higher than that of nonhyperglycaemic patients.
- Errors in insulin use are so common that insulin is listed in the top five of high-risk, in-patient medications. One third of all lethal in-patient drug errors are due to insulin.

As far as possible, try to avoid placing a non-insulin dependent diabetic on insulin. If a variable-rate insulin infusion must be used, ensure that clear and explicit guidelines are documented on the patient chart.

- Patients who are usually controlled on long-acting insulin analogue agents should continue these alongside the variable-rate insulin infusion if one is used. This will allow the patient to return quickly to his or her normal baseline once the variable rate insulin infusion is stopped.
- *Patients on metformin:* Metformin is renally excreted. Patients with renal failure may develop high metformin levels which can lead to an increased risk of the development of lactic acidosis. Metformin should be stopped for the duration of the fasting period in renally impaired patients.

If the patient is going to miss one meal only, he or she should continue taking metformin as usual, unless on a three-times-per-day regimen, in which case the midday dose should be omitted.

If metformin is co-administered with a nephrotoxic agent, like intravenous radiocontrast, to a patient with impaired renal function, the patient could develop lactic acidosis. (According to the Royal College of Radiologists, it is safe to continue with metformin following intravenous radiocontrast administration, provided the patient has a normal serum creatinine level and/or estimated glomerular filtration rate > 50 ml/minute/1.73 m<sup>2</sup>.)

The Society for Ambulatory Anesthesia, in its consensus statement on perioperative blood glucose management of 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 as these patients have an altered counter-regulatory response which may result in hypoglycaemic symptoms developing at normal blood glucose levels.<sup>10</sup> These patients' intraoperative glucose requirements may also be higher than their postoperative requirements, further emphasising the need 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 tightly controlled regimen.<sup>11</sup>

### Surgery for diabetes

Bariatric surgery and pancreas or islet transplants have shown excellent results in suitable patients.

### The future

Diabetes and hyperglycaemia will continue to be an area of intense and explosive research.

The search for evidence-based support for specific two- and three-drug combinations for type 2

diabetes control is an area of clinical concern that is under scrutiny.<sup>1</sup>

Animal experimentation on the sirtuin 1 (SIRT 1) receptor, or the "skinny gene", which is downregulated in type 2 diabetes mellitus. It can be upregulated by resveratrol, a chemical extracted from red wine. It is also implicated in ageing and inflammation.<sup>16</sup>

### Last word

DKA should always be considered and surgery postponed until this is under control.

Glucose must be monitored hourly on the day of surgery unless hypo- or hyperglycaemia occurs, in which case, monitoring needs to be more frequent until the target range is reached.

It is necessary to be vigilant in order to avoid hypoglycaemia.

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