Perioperative management of adult diabetic patients. Review of hyperglycaemia: definitions and pathophysiology

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Guidelines

Perioperative management of adult diabetic patients. Review of hyperglycaemia: definitions and pathophysiology

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ABSTRACT

Diabetes mellitus is defined by chronic elevation of blood glucose linked to insulin resistance and/or insulinopaenia. Its diagnosis is based on a fasting blood-glucose level of $\geq$ 1.26 g/L or, in some countries, a blood glycated haemoglobin (HbA1c) level of $>$ 6.5%. Of the several forms of diabetes, type-2 diabetes (T2D) is the most common and is found in patients with other risk factors. In contrast, type-1 diabetes (T1D) is linked to the autoimmune destruction of β-pancreatic cells, leading to insulinopaenia. Insulin deficiency results in diabetic ketoacidosis within a few hours. 'Pancreatic' diabetes develops from certain pancreatic diseases and may culminate in insulinopaenia. Treatments for T2D include non-insulin based therapies and insulin when other therapies are no longer able to control glycaemic levels. For T1D, treatment depends on long (slow)-acting insulin and ultra-rapid analogues of insulin administered according to a 'basal-bolus' scheme or by continuous subcutaneous delivery of insulin using a pump. For patients presenting with previously undiagnosed dysglycaemia, investigations should determine whether the condition corresponds to pre-existing dysglycaemia or to stress hyperglycaemia. The latter is defined as transient hyperglycaemia in a previously non-diabetic patient that presents with an acute illness or undergoes an invasive procedure. Its severity depends on the type of surgery, the aggressiveness of the procedure and its duration. Stress hyperglycaemia may lead to peripheral insulin resistance and is an independent prognostic factor for morbidity and mortality.

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1. Known diabetes

1.1. Definition of diabetes

Diabetes mellitus is defined by chronic elevation of blood-glucose levels linked to insulin resistance and/or insulinopaenia. A diagnosis of diabetes can be made in three situations:

- fasting blood glucose $\geq$ 1.26 g/L (7.0 mmol/L), on two occasions;
- plasma-blood glucose $\geq$ 2 g/L (11.1 mmol/L) at 2 h after consuming a sweet liquid containing a measured amount of glucose (oral glucose tolerance test, OGTT);
- the presence of clinical symptoms (polyuria, polydipsia, unexplained weight loss) with plasma glucose $\geq$ 2 g/L (11.1 mmol/L), irrespective of the time of blood sampling. Measurement of fasting blood-glucose level is currently recommended as the first-line test for diabetes [1].

An OGTT (with measurement of fasting blood glucose and blood-glucose levels at 2 h after oral consumption of 75 g glucose) can also be conducted and is more sensitive (Appendix). Measurement of blood-glycated haemoglobin (HbA1c) is proposed in many countries as a diagnostic test for diabetes at a cut-off value of 6.5% [2].

1.2. Main types of diabetes

Practical sheet A summarises the main characteristics of diabetes. Type-2 diabetes (T2D) is the most common type and is often discovered as an insidious disease because it is asymptomatic at the time of screening high-risk patients. Thus, T2D may be discovered when in the hospital for surgery, with chronic complications already present. The main risk is a hyperosmolar hyperglycaemic state when polyuria/glycosuria and hyperglycaemia (> 1.80 g/L [10 mmol/L]) are not compensated for by polydipsia or parenteral hydration in an unconscious patient.

Type-1 diabetes (T1D) is linked to the autoimmune destruction of β-pancreatic cells, which synthesise insulin. The two components for the physiological secretion of insulin are then no longer active, namely:

- 'basal' secretion (or 'live insulin', which is continuous over the nycthemeral period), and represents approximately 50% of daily requirements;
- prandial secretion (or 'insulin produced when eating').

Substitution of basal insulin should never be stopped, even in a subject with normoglycaemia, due to the major risk of hyperglycaemia followed by ketosis and diabetic ketoacidosis. In general, patients with T1D are familiar with this rule of survival.

'Pancreatic' diabetes, secondary to pancreatic diseases, is less common. It features severe insulinopaenia, with an increased risk of hypoglycaemia because of a simultaneous decrease in glucagon secretion.

Diabetes that develops during pregnancy is discussed in the text named 'Specific situations'.

1.3. Treatment of diabetes

1.3.1. Type-2 diabetes

Practical sheets E 'Treatment of diabetes: non-insulin drugs' and F 'Treatment of diabetes: insulin' summarise the main characteristics of treatments available for T2D. T2D may require treatment with insulin: this is known as insulin-requiring T2D. Insulin and oral glucose-lowering drugs may be combined [1]. Injectable non-insulin treatments also exist, namely glucagon-like peptide 1 (GLP1) receptor agonists, including some that can be injected weekly. The drugs in this class reduce the speed at which the stomach empties after a meal, which may lead to gastroparesis. Preoperative administration of these treatments is indicated in the text named 'Preoperative period'.

1.3.2. Type-1 diabetes

Patients with T1D are always treated with insulin. The most widely used method is by basal-bolus, depicted in Practical sheet F titled 'Treatment of diabetes: insulin'. Basal secretion of insulin is substituted by one or two injections of slow- or intermediate-acting insulin. Basal insulin should be supplied constantly, although the dose may have to be decreased if there is hypoglycaemia. Substitution of prandial insulin is done by injecting an ultra-rapid analogue of insulin, with a larger amount injected after a meal rich in carbohydrates. Insulin is generally injected before the meal, although it may be sometimes administered just after a meal if the amount of carbohydrates consumed is precisely known. Rapid (or normal) insulin is no longer used because it has a delayed action (20 min vs. 5 min for ultra-rapid analogues) and the duration of action is less adapted to meals (6 h compared to the post-prandial requirements of 3 h).

An insulin pump is often used for subcutaneous (SC) administration of insulin in T1D and sometimes in T2D. Programmable electronic pumps (the size of a mobile phone) contain an insulin reservoir and deliver insulin subcutaneously and continuously 24-h a day. The patient refills the reservoir (ultra-rapid analogue of insulin), which is connected to an infusion line and a cannula (6 or 9 mm), which is inserted subcutaneously. The catheter should be changed by the patient every three days to prevent alterations to the equipment and because diffusion of insulin then becomes less effective. The reservoir, the tube and the needle should be changed at the same time.

This system reproduces the basal-bolus scheme by discontinuous SC injections of slow-acting and ultra-rapid analogues of insulin: continuous infusion of a small amount of ultra-rapid insulin reproduces basal insulin and is the basal output. The amount is determined and programmed by a diabetologist and may be modified depending on the time of day (day, night). To reproduce a bolus, the output is accelerated using either a remote control or directly on the pump by the patient (1 IU bolus = 1 IU of ultra-rapid insulin analogue).

The system is reliable but the major risk is ketoacidosis if delivery of insulin is interrupted (catheter obstruction, line kinking but not triggering the pump alarm, needle withdrawal), empty reservoir; pump stopping...). If the dose of ultra-rapid insulin infused per hour is very low, the effect of the insulin will stop after approximately 2 hours. Sudden and total lack of insulin in a patient with T1D leads to ketoacidosis within a few hours. If the pump is removed, basal insulin should be replaced immediately either by a SC injection of slow-acting insulin or intravenous (IV) administration of ultra-rapid-acting insulin and an infusion pump. These aspects are developed further in Practical sheets P titled 'Administration of insulin intravenously with an infusion pump/SC insulin' and Q 'General basal-bolus scheme'.

If the patient develops hypoglycaemia, it is necessary to immediately administer 15 g of carbohydrate orally (see text entitled 'Postoperative period'). The pump should not be removed as the staff may forget to reconnect it, which would lead to ketoacidosis. If severe hypoglycaemia occurs, it is possible to stop the pump temporarily for 1–2 h maximum, but it is essential to restart it rapidly.

2. Unexpected dyglycaemia

2.1. Stress hyperglycaemia

2.1.1. Definition

The surgical procedure and its inherent metabolic effects induce a stressed state that causes perioperative hyperglycaemia, known as 'stress hyperglycaemia'. According to the American Diabetes Association, stress hyperglycaemia is defined as transient hyperglycaemia in a previously non-diabetic patient submitted to an acute illness or that has undergone an invasive procedure [2]. It is characterised by blood-glucose levels $\geq$ 1.80 g/L (10 mmol/L), with levels returning to normal ($<$ 1.26 g/L or 7 mmol/L) after removal of the stressor and withdrawal of glucose-lowering treatment, if it was started previously in a patient whose HbA1c was $<$ 6.5%.

2.1.2. Aggravating factors

The severity of stress hyperglycaemia depends on the type of surgery, the aggressiveness of the procedure and its duration [3–5]. Its prevalence varies between 30 and 80% depending on the type of surgery, with the highest prevalence observed during cardiac surgery. It is therefore not surprising that most studies conducted to assess perioperative glycaemic control have been carried out in the setting of cardiac surgery with extracorporeal circulation [5–12]. Other risk factors include catecholamine infusion, corticosteroid use, obesity, age, hypothermia, hypoxia, cirrhosis, trauma, extensive burns and sepsis.

2.1.3. Mechanisms of stress hyperglycaemia

The main mechanism responsible for perioperative stress hyperglycaemia is peripheral insulin resistance [13], which is an independent risk factor for morbidity and mortality [12]. In addition, stimulation of endogenous glucose production can also occur [14] and there is an increase in renal reabsorption of glucose [6] or a decrease in glucose clearance [15]. Stress hormones (glucagon, cortisol, catecholamines) and mediators of inflammation (interleukin 1 and 6) released during surgical stress may lead to perioperative insulin resistance [16]. Insulin resistance affects lipid metabolism with the increased release of free fatty acids [17], thus further aggravating insulin resistance.

Perioperative insulin resistance may last for several days after the invasive procedure and initially involves insulin-dependent peripheral tissues [18,19]. Perioperative blood loss, as well as prolonged immobilisation, both affect glucose metabolism by skeletal muscles and accentuate perioperative insulin resistance. Finally, prolonged perioperative fasting induces a decrease in hepatic glycogen supply and an increase in neoglucogenesis, lipid and protein metabolism, which, in turn aggravates perioperative insulin resistance [20].

2.1.4. Pathophysiological consequences of stress hyperglycaemia

Hyperglycaemia abolished ischaemic preconditioning [21] and resulted in endothelial dysfunction [22], decreased phagocytic activity of polymorphonuclear neutrophils [23] and increased the formation of lesions in the blood / brain barrier in a model of murine cerebral ischemia [24]. These deleterious effects of hyperglycaemia are caused by mitochondrial abnormalities in non-insulin-dependent cells where glucose transporters (GLUT 4) are over-expressed during stress [25].

Perioperative insulin resistance leads to the increased release of free fatty acids [17], which are potentially harmful to the myocardium, and modify protein metabolism, thus leading to increased protein catabolism and delayed healing [26]. Insulin therapy mitigates the consequences of insulin resistance, such as the postoperative neuro-hormonal response to stress [8] and the perioperative release of free fatty acids from peripheral tissues during surgery, with extracorporeal circulation in non-diabetic patients [27].

2.2. Stress hyperglycaemia or undiagnosed pre-existing dysglycaemia?

It is estimated that more than 500,000 patients have undiagnosed T2D in France. The prevalence is high among hospitalised patients due to their age and comorbidities. In a study of 40,836 inpatients, of whom 19% had known diabetes, 47% underwent perioperative screening of blood-glucose levels. Screening showed that 18% had blood-glucose levels $>$ 1.8 g/L (10 mmol/L). Hyperglycaemia was observed in 40% of diabetic and 6% of non-diabetic patients [28].

Hyperglycaemia revealed postoperatively does not distinguish patients with unknown diabetes before surgery from those with stress hyperglycaemia. However, measurement of HbA1c levels, which reflect glycaemic control over the previous 8–12 weeks, can distinguish between these two situations [29]. HbA1c $\geq$ 6.5% has been used as a diagnostic criterion for this purpose since 2009 in some countries [2] and identifies one-third more undiagnosed diabetic patients compared to using fasting blood-glucose $\geq$ 1.26 g/L (7 mmol/L). However, routine measurement of HbA1c is not recommended for the French general population due to its cost [1].

The simplest method is to detect undiagnosed dysglycaemia in the preoperative period (Practical Sheet C). Indeed:

- pre-diabetes found during preoperative evaluation signals a risk for stress hyperglycaemia and its complications;
- complications of undiagnosed diabetes may occur during the perioperative period due to acute glycaemic instability and/or unrecognised chronic diabetic complications (see text 'Preoperative period').

Thus, these risks should be identified and avoided wherever possible.

We propose that screening should be carried out in subjects with signs of diabetes (primary syndrome) or that are at very high-risk: i.e. metabolic syndrome, familial history of diabetes, previous acute coronary syndrome or cerebrovascular accident, previous treatment with diabetogenic drugs, history of gestational diabetes, previous transient hyperglycaemia [30]. We recommend screening by measuring fasting blood glucose and HbA1c levels. This position concerning the use of HbA1c as a diagnostic criterion for dysglycaemia has already been described in the recommendations for the management of patients with acute coronary syndrome [31]. The diagnostic criteria are summarised in Appendix 1.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix 1. Diagnostic criteria for dysglycaemia. Interpretation of fasting blood-plasma glucose levels and oral-glucose tolerance test (OGTT) results (2 h after ingestion of 75 g glucose) [1].

Glycaemia	OGTT (2 h after oral ingestion of 75 g glucose) g/L (mmol/L)		
Fasting glucose (g/L [mmol/L])	<1.40 (7.8)	1.40-1.99 (7.8-11.0)	≥2.00 (≥11.1)
<1.10 (6.1)	Normal	Glucose intolerance	Diabetes
1.10-1.25 (6.1-6.9)	Fasting hyperglycaemia	Fasting hyperglycaemia and glucose intolerance	Diabetes
≥1.26 (7.0)	Diabetes	Diabetes	Diabetes

Interpretation of HbA1c levels [2]

HbA1c	<5.7%	5.7-6.4%	≥6.5%
	Normal	Risk of developing diabetes	Diabetes

Measurement of HbA1c levels to diagnose dysglycaemia is not recommended in France [1].

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