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REVIEW ARTICLE

Evaluation and perioperative management of patients with diabetes mellitus. A challenge for the anesthesiologist[☆]



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Abstract Diabetes mellitus (DM) is characterized by alteration in carbohydrate metabolism, leading to hyperglycemia and increased perioperative morbidity and mortality. It evolves with diverse and progressive physiological changes, and the anesthetic management requires attention regarding this disease interference in multiple organ systems and their respective complications. Patient's history, physical examination, and complementary exams are important in the preoperative management, particularly glycosylated hemoglobin (HbA1c), which has a strong predictive value for complications associated with diabetes. The goal of surgical planning is to reduce the fasting time and maintain the patient's routine. Patients with Type 1 DM must receive insulin (even during the preoperative fast) to meet the basal physiological demands and avoid ketoacidosis. Whereas patients with Type 2 DM treated with multiple injectable and/or oral drugs are susceptible to develop a hyperglycemic hyperosmolar state (HHS). Therefore, the management of hypoglycemic agents and different types of insulin is fundamental, as well as determining the surgical schedule and, consequently, the number of lost meals for dose adjustment and drug suspension. Current evidence suggests the safe target to maintain glycemic control in surgical patients, but does not conclude whether it should be obtained with either moderate or severe glycemic control.

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PALAVRAS-CHAVE

Diabetes melito;
Anestesia;
Cuidados
perioperatórios;
Hipoglicemiantes;
Insulina;
Hemoglobina
glicosilada

Avaliação e manejo perioperatório de pacientes com diabetes melito. Um desafio para o anesthesiologista

Resumo O diabetes melito (DM) é caracterizado por alteração no metabolismo de carboidratos que leva à hiperglicemia e ao aumento da morbimortalidade perioperatória. Cursa com alterações fisiológicas diversas e progressivas e, para o manejo anestésico, deve-se atentar para a interferência dessa doença nos múltiplos sistemas orgânicos e suas respectivas complicações. Anamnese, exame físico e exames complementares são importantes no manejo pré-operatório, com destaque para a hemoglobina glicosilada (HbA1c), que tem forte valor preditivo para complicações associadas ao diabetes. O planejamento cirúrgico tem como objetivos a redução do tempo de jejum e a manutenção da rotina do paciente. Pacientes portadores de DM Tipo 1 precisam receber, mesmo em jejum perioperatório, insulina para suprir as demandas fisiológicas basais e evitar cetoacidose. Já os pacientes portadores de DM Tipo 2, tratados com múltiplos fármacos injetáveis e/ou orais, são suscetíveis ao desenvolvimento de um estado hiperosmolar hiperglicêmico (EHH). Assim, o manejo dos hipoglicemiantes e dos diferentes tipos de insulina é fundamental, além da determinação do horário cirúrgico e, conseqüentemente, do número de refeições perdidas para adequação de doses ou suspensão dos medicamentos. As evidências atuais sugerem o alvo de manutenção da glicemia seguro para os pacientes cirúrgicos, sem concluir se deve ser obtido com controle glicêmico intensivo ou moderado.

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Introduction

In surgical patients, the presence of diabetes mellitus (DM) or hyperglycemia is associated with increased morbidity and mortality, with a perioperative mortality rate up to 50% higher than in the non-diabetic population.¹ There are multiple reasons for these adverse outcomes, such as failure to identify diabetic or hyperglycemic patients; multiple comorbidities including micro and macrovascular complications; complex polypharmacy and insulin prescription errors; increased perioperative and postoperative infections; associated episodes of hypoglycemia and hyperglycemia¹; a lack of (or inadequate) institutional protocols for management of diabetic or hyperglycemic inpatients; and inadequate knowledge of diabetes and hyperglycemia management amongst staff providing care.²

Material and methods

We searched multiple databases, including Medline via PubMed (January 1966 to August 2016), The Cochrane Library and Lilacs (from 1982 to August 2016). After a bibliographical survey, the articles with better methodological design were selected. We also use the evidence-based updates from the UpToDate and Medscape domains. There was no language restriction.

Searches were performed between May and August 2016. The following strategies were used for searches in PubMed:

1. "Diabetes Mellitus" [All Fields] AND "Anesthesia" [All Fields], "Diabetes Mellitus" [All Fields] AND "Perioperative Period" [All Fields], "Glycemic Control" [All Fields] AND "Perioperative Care" [All Fields],

"Glycemic Control" [All Fields] AND "Anesthesia" [All Fields], "Diabetes Mellitus" [All Fields] AND "Anesthesia" [All Fields] AND "Perioperative" [All Fields];

2. "Diabetes Mellitus" [MeSH Terms] AND "Anesthesia" [MeSH Terms], "Diabetes Mellitus" [MeSH Terms] AND "Perioperative Period" [MeSH Terms], "Anesthesia" [MeSH Terms] AND "Diabetes Mellitus" [MeSH Terms] AND "Perioperative Period" [MeSH Terms], "Diabetes Mellitus" [MeSH Terms] AND "Perioperative Care" [MeSH Terms];
3. "Diabetes Mellitus" [MeSH Terms] OR ("diabetes" [All Fields] AND "mellitus" [All Fields]) OR "diabetes mellitus" [All Fields] AND ("anaesthesia" [All Fields] OR "anesthesia" [MeSH Terms] OR "anesthesia" [All Fields]) AND Perioperative [All Fields].

Physiological changes and anesthetic implications

Diabetes mellitus is a disease characterized by abnormality in carbohydrate metabolism, which evolves with hyperglycemia. If left untreated, it is a debilitating disease, leading to chronic organ failure and dysfunction. Type 1 diabetes (DM1) results from the destruction of insulin-producing pancreatic β -cells by an autoimmune mechanism, causing complete deficiency in insulin secretion. Type 2 diabetes (DM2), the most common form of diabetes, is a consequence of peripheral resistance to insulin action and is frequently associated with progressive failure in insulin secretion over the years, resulting from dysfunction in pancreatic β -cells due to glycototoxicity, lipotoxicity, and amyloid formation.³

The diagnostic criteria for diabetes mellitus are listed in [Table 1](#).

Table 1 Diagnostic criteria for diabetes mellitus according to the American Diabetes Association – 2015.⁴

1. Glycosylated hemoglobin (HbA1c) $\geq 6.5\%$ ^a OR
2. Fasting glucose $\geq 126 \text{ mg.dL}^{-1}$ ^a (no caloric intake for at least 8 h) OR
3. Glycemia after 2 h – oral GTT $\geq 200 \text{ mg.dL}^{-1}$ ^a OR
4. Patients with classic symptoms of hyperglycemia or hyperglycemic crisis, with random glycemia $\geq 200 \text{ mg.dL}^{-1}$

GTT, glucose tolerance test.

^a In the absence of unambiguous hyperglycemia, the results should be confirmed by test repetition.

With the broader screening of blood glucose, another group of patients known as pre-diabetics has also been identified. They can be classified into two main classes: impaired fasting glucose and glucose intolerance. Positive screening of these patients includes: fasting blood glucose between 100 and 125 mg.dL^{-1} ; glycemia 2 h after oral glucose tolerance test (GTT) between 140 and 199 mg.dL^{-1} ; or HbA1c between 5.7 and 6.4%.⁵

The physiological changes in diabetic patients are multiple and progressive and, for anesthetic management, the following organs and systems must be emphasized: musculoskeletal, kidney, neurological, and cardiovascular.

Musculoskeletal system

Chronic hyperglycemia leads to non-enzymatic glycosylation of proteins and abnormal collagen cross-links in joints, limiting mobility and leading to the so-called stiff joint syndrome (SJS). Temporomandibular, atlanto-occipital, and cervical spine joints may be affected.⁶ Diabetes sclerodema is characterized by firm, wood-like, non-compressible nuchal edema and upper dorsum regions and, associated with reduced joint mobility, may limit the neck range of motion and hinder orotracheal intubation.⁷

Kidney

A relevant proportion of patients with DM have diabetic nephropathy. This chronic complication is characterized by the development of albuminuria and progressive reduction of renal function in patients without adequate glycemic control. In general, patients with this complication are at greater risk of perioperative morbidity and mortality. Therefore, albuminuria screening in these patients would contribute to further assessment of the risk of acute renal failure (ARF).⁸

In the presence of hypovolemia, intraoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) may impair redistribution of renal blood flow and worsen renal function. This is especially important when concomitantly using drugs that modulate the renin-angiotensin-aldosterone system (RAAS).⁸ Therefore, caution should be exercised in the use of NSAIDs in patients with DM, who may already have some degree of kidney failure. Moreover, the use of NSAIDs also increases the risk of edema, which may be aggravated when given concomitantly with the class of oral antidiabetic drugs known as glitazones.²

Likewise, cyclooxygenase type 2 (COX-2) inhibitors may affect kidney function in at-risk patients, including those with diabetic nephropathy. In a review of the literature,

ARF and/or severe electrolyte changes (particularly hyperkalemia and metabolic acidosis) were clearly triggered by celecoxib or rofecoxib.⁹ In Brazil, there is a lack of studies on the safety of parecoxib for perioperative venous use and its impact on the kidney function of this population.

Neurological system

Neurological effects of diabetes increase the risk of cerebrovascular accident (CVA) and the presence of hyperglycemia is a strong predictor of worse outcomes in various forms of acute brain injury.¹⁰ A prospective study found association between HbA1c levels and risk of CVA in diabetic and non-diabetic patients.¹¹ In fact, the vasodilator response to hypercapnia, measured by transcranial Doppler, was reduced in diabetic patients compared to non-diabetic patients. The degree of reduction was correlated with the HbA1c levels of patients.¹² This finding raises interesting questions about the role of long-term glycemic control in the regulation of cerebral vascular reactivity in diabetic patients.

Nerve fibers in diabetic patients may be more susceptible to ischemic injury, as they are already under stress from chronic ischemic hypoxia. Local anesthetics may be neurotoxic. To avoid nerve damage in these patients caution should be exercised regarding total dose and concentration of local anesthetics used in regional anesthesia.⁸

Autonomic neuropathy

Diabetic autonomic neuropathy is a common DM complication often undiagnosed. This complication may affect the gastrointestinal, genitourinary, and cardiovascular systems. The main clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, intestinal constipation, gastroparesis, bladder dysfunction, impaired neurovascular function, and loss of autonomic response to hypoglycemia. For anesthetic management, in addition to cardiovascular autonomic alterations, it is important to remember that reduced esophageal motility and gastroparesis may lead to vomiting and aspiration of gastric content.⁸ Acute or chronic hyperglycemia increases the gastric emptying time and may increase the volume of gastric contents.¹⁰

Cardiovascular system

Diabetic patients are at increased risk of hypertension, coronary artery disease (CAD), silent myocardial ischemia, systolic and diastolic heart failure, and congestive heart failure.⁸ Through several mechanisms, hyperglycemia impairs vasodilation and induces a proinflammatory, prothrombotic, and proatherogenic state, which are the basis for vascular complications commonly found in diabetic patients.¹³ Patients with diabetes but no prior acute myocardial infarction (AMI) have the same risk of coronary events as a non-diabetic patient with previous AMI.¹⁴ In fact, diabetic patients are considered to be at increased risk for CAD—intensive use of antiatherosclerotic therapy is mandatory.¹⁵ The American Heart Association (AHA) guidelines on perioperative cardiovascular evaluation of patients undergoing non-cardiac surgery report diabetes, especially in patients receiving insulin therapy, as an independent risk factor for adverse cardiac events.¹⁶

Preoperative assessment and importance of HbA1c

In DM patients, clinical history should clarify the type of diabetes (DM1, DM2, gestational DM or other types), glycemic control, diagnostic time (predictor of chronic complications), drug therapy (oral, noninsulin injectable antidiabetic drugs or insulin), dose and dosing time of medications.¹⁷

The occurrence and frequency of hypoglycemia should be questioned, as they interfere with preoperative management of medications, in addition to the frequency of hospitalization related to glycemic control (acute decompensation). Patient's ability to measure his blood sugar and understand the principles of diabetes therapy should be evaluated, as it influences the perioperative management of these patients.¹⁷

Other risk factors for atherosclerosis should be investigated (smoking, hypertension, dyslipidemia, family history, sedentary lifestyle), presence of recent infections that may alter perioperative glycemic control (skin, feet, genitourinary tract, dental), and use of drugs for other comorbidities.¹⁸

An important concern in diabetic patients is the significant number of patients with DM2 who are unaware of the diagnosis and only become aware of it at the time of surgery. A study with patients undergoing non-cardiac surgeries found an undiagnosed DM rate of 10% and impaired fasting glycemia of 11%.¹⁹ Another study showed that 24% of patients referred from primary care to elective surgery had a DM diagnosis or impaired fasting glycemia discovered on the day of surgery.²⁰ Interestingly, patients with undiagnosed DM were more likely to require resuscitation, reintubation and longer postoperative mechanical ventilation, and higher perioperative mortality compared to patients without DM and patients with previously diagnosed DM.²¹ These findings, together with those of other investigators, suggest that undiagnosed DM is an even greater risk factor for perioperative morbidity and mortality than previously diagnosed DM. The increased risk may be related to several factors, including inadequate preventive care and less aggressive therapy by the care team.⁵

Physical examination includes blood pressure assessment with emphasis on the search for orthostatic hypotension, a potential sign of autonomic neuropathy. Dilated fundus examination may provide an idea of the risk of a patient developing postoperative visual loss, especially after prolonged prosthetic column surgery and after cardiac surgery with cardiopulmonary bypass. Due to the homology between cerebral and retinal microcirculations, changes in retinal vasculature may reflect similar changes in cerebral vasculature. The presence of diabetic retinopathy may therefore also indicate impairment of cerebral microcirculation. Some studies have shown that diabetic retinopathy was a predictor of postoperative cognitive dysfunction due to impairment of coexisting cerebral circulation.²²

Stiff joint syndrome adds significant risk during airway management. On physical examination, the patient presents with an inability to move close the palm surfaces of the interphalangeal joints while pressing one hand against the other—positive "prayer signal". Airway evaluation should include the size of the thyroid gland, as patients with DM1 have an association of about 15% with other autoimmune

Table 2 Mean glycemia assessment for specific HbA1c values.

HbA1c (%)	Plasma mean glycemia	
	mg.dL ⁻¹	mmol.L ⁻¹
6	126	7.0
7	154	8.6
8	186	10.2
8.5	200	11.0
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

Adapted from Refs. 25,26.

diseases, such as Hashimoto's thyroiditis and Graves' disease.¹⁸

To assess the degree of subsequent nerve damage, the degree of preoperative neurological dysfunction should always be documented, particularly prior to regional anesthesia. In search of signs of skin lesion or infection, examining the skin (insulin injection site) and feet should be part of the evaluation routine.

Basic complementary investigation should include: resting electrocardiogram (ECG), assessment of kidney function (serum creatinine), electrolytes, fasting blood glucose and HbA1c (if not measured in the last two to three months). In individualized cases, additional investigations including non-invasive cardiac tests should be considered.²³

HbA1c provides a view of glycemic control over the last two to three months and has a strong predictive value for complications of diabetes.²⁴ High preoperative levels are associated with increased perioperative risk and constitute a good preoperative screening test.^{2,5,8} Table 2 shows the correlation between HbA1c and average blood glucose levels based on two large studies.^{25,26}

Studies have shown that poor glycemic control reflected through perioperative high levels of blood glucose and HbA1c are associated with worse surgical outcomes. These results were found in both elective and emergency surgeries including spinal,²⁷ vascular,²⁸ colorectal,²⁹ cardiac,^{30,31} trauma,³² thoracic,³³ orthopedic,³⁴ neurological and hepatobiliary surgeries.^{35,36} A study has shown that an increase in mortality greater than 50%, a 2.4-fold increase in the incidence of postoperative respiratory infections, incidence of duplicate AMI,^{1,2} and a nearly two-fold increase in the incidence of ARI are among the worst outcomes.³⁷

Due to the new evidence linking high levels of HbA1c as a marker of poor glycemic control and perioperative complications, a recent British guideline recommends that patients with DM referred from primary care for surgical evaluation should have their most recent HbA1c results included in their referral and that the HbA1c dosage should be requested from diabetic patients with scheduled surgery if they have not had a measurement recorded in the last three months.³⁸ In addition to the routine evaluation in diabetic patients without HbA1c measurement in the last three months, during preoperative evaluation of non-diabetic patients with DM risk factors (age > 45 years, hypertension, dyslipidemia, overweight, sedentary lifestyle, and history of

polycystic ovary, among others), some authors recommend routine measurements of HbA1c.^{4,8}

In fact, HbA1c measurement is the preoperative test indicated for patients diagnosed with DM or risk factors. On the other hand, in order to better evaluate glycemic control and diagnoses diabetes in those with unknown DM, some authors suggest the determination of HbA1c levels in the preoperative period of all patients undergoing major surgeries.³⁹ This approach is justified considering that hyperglycemic patients and/or patients with untreated DM in the preoperative period presented worse outcomes compared to patients with treated diabetes even with similar preoperative blood glucose values.^{1,21,40} Such approach may not only identify DM in these undiagnosed patients, but help in choosing the best time for elective surgery, considering that postponement could improve glycemic control and reduce complications.³⁹

On the other hand, a systematic review concluded that the preoperative blood glucose and HbA1c measurement in patients undergoing elective non-cardiac surgery is not necessary in asymptomatic and non-diabetic patients. In this group of patients, the HbA1c and blood glucose values would only be justified in those undergoing major vascular and orthopedic surgery because they are at higher risk.⁴¹

Impact of surgical stress and anesthesia on metabolic control

Several conditions in diabetic patients may result in worsening of hyperglycemia during the perioperative period.^{42,43} Surgical stress induces neuroendocrine response; glucagon, epinephrine, and cortisol (counterregulatory hormones) are the first secreted hormones. These hormones lead to a catabolic state, which contributes to perioperative hyperglycemia. In extreme cases, the increased counterregulatory hormones and consequent hyperglycemia may lead to a metabolic decompensation and result in diabetic ketoacidosis in patients with DM1 or in a hyperosmolar hyperglycemic nonketotic state (DM2).⁴⁴

Drugs used during surgery may also interfere with the degree of hyperglycemia in diabetic patients. Anesthetic agents and sedatives may affect glucose homeostasis via modulation of sympathetic tone.⁴² In fact, some anesthetic agents may reduce catabolic hormone secretion or change insulin secretion in DM2 patients with residual insulin secretion.⁸

General anesthesia may mask the common signs and symptoms of hypoglycemia, one of the main concerns of anesthesiologists in the perioperative period.⁸ The choice of anesthetic agent may affect glucose homeostasis. High doses of benzodiazepines and gamma-aminobutyric acid agonists (GABA) reduce the secretion of adrenocorticotrophic hormone (ACTH) and cortisol and may reduce the hyperglycemic response to surgery.⁸ Etomidate inhibits adrenal synthesis of steroids by blocking the 11 β -hydroxylase activity and triggers a reduction in hyperglycemic response to surgery.⁴⁵ Clonidine reduces sympathetic tone and norepinephrine release at nerve terminals. High dose of opioids appear to decrease the hyperglycemic response to surgery by reducing catabolic hormones.⁴⁶ In vitro studies have shown that inhalational anesthetics, such as halothane and isoflurane, inhibit the normal production of glucose-triggered insulin

in a dose-dependent manner and result in hyperglycemic response.⁴⁷

Regional anesthesia, including subarachnoid, epidural and other regional blockades, can modulate the secretion of catabolic hormones and insulin. The activation of sympathetic nervous system and hypothalamic-pituitary axis induced by surgical stress may be avoided by this type of anesthesia.⁴⁸ In patients with insulin resistance some authors have shown that regional anesthesia and epidural analgesia, compared to general anesthesia, may reduce the degree of insulin resistance in early postoperative period.⁴⁹ However, there are reservations and concerns regarding the use of regional anesthesia in DM patients, both for peripheral blocks and neuraxial approach techniques. DM is associated with several types of neuropathies; symmetrical distal polyneuropathy (diabetic polyneuropathy – DPN) and autonomic neuropathy are present in up to 50% of long-standing diabetic patients.^{7,22} DPN patients may be more susceptible to double-crush injury (increased susceptibility to nerve damage following low-grade secondary aggression, if we assume that diabetic fiber already has some degree of injury from chronic hypoxemia),⁵⁰ but the current clinical evidence is inconclusive. Animal studies have shown that nerve fibers of diabetic animals are more sensitive to the effects of local anesthetics and may be more susceptible to the neurotoxicity triggered by these drugs.^{51,52} Clinical studies suggest increased sensitivity to local anesthetics in diabetic patients undergoing peripheral nerve blocks.⁵³ Moreover, diabetic nerves are less sensitive to electrical stimulation, which theoretically would increase the risk of nerve injury by the needle when trying to locate the nerves with a peripheral nerve stimulator.⁵⁴ For these reasons, the American Society of Regional Anesthesia (ASRA)⁵⁵ recommendations for peripheral nerve blocks in very symptomatic patients are to limit the concentration and/or dose of the local anesthetic, avoid the use of epinephrine as an adjuvant, and use ultrasound as a guide to keep the needle tip away from the nerve. In addition, evidence has shown that diabetic patients are more likely to develop epidural abscesses and hemodynamic instability following neuraxial blocks (patients with autonomic neuropathy).²

Surgical planning

The main goals are to reduce fasting period, ensure normoglycemia (capillary blood glucose between 108 and 180 mg.dL⁻¹), and reduce patient disruption to the maximum. Ideally, the patient should be scheduled for the first hours of surgical map. If the patient's fasting time is limited to one missed meal, the option is to change his/her normal medication for diabetes. If longer periods of fasting are predicted, a variable rate intravenous insulin infusion (VRIII) should be used and a specialist assessment requested. On the day of surgery, the patient should receive written instructions on medication management, control of perioperative hypo- or hyperglycemia, and probable effects of surgery on diabetes control.²

Capillary glycemia should be checked on admission, prior to induction of anesthesia, and monitored regularly during the procedure (at least every hour, or more often if the results are outside the normal range).²

Management of oral and injectable non-insulin antidiabetic drugs

The glycemic control in diabetic patients consists of the balance between carbohydrate intake and its expenditure (for example, exercise). It also depends on which drug is used and how these drugs work. During fasting periods, some agents (sulfonylureas and glinides) reduce glucose concentration, which require dose modification and/or agent suspension. Other agents prevent increased glucose levels (metformin, glucagon-like peptide-1 [GLP-1] analogs, and dipeptidyl peptidase-4 [DPP-4] inhibitors) and may be continued without risk of hypoglycaemia.²

Metformin acts as an insulin sensitizer and inhibits gluconeogenesis. Some guidelines recommend discontinuing the use of metformin 24–48 h prior to surgery because of the risk of developing lactic acidosis and perioperative renal failure due to metformin accumulation.⁵⁶ As the evidence for this approach is weak and there is evidence that perioperative continuation of metformin is safe, a rational approach is to continue the perioperative use of metformin in all patients with a short fasting period, normal kidney function, and when contrast is not used.^{2,39} On the other hand, metformin should be discontinued when there is preexisting renal damage (glomerular filtration rate – GFR < 60 mL·min⁻¹ or increased creatinine),^{2,57} use of contrast or significant risk of ARF development. In such cases, discontinuation should occur on the day of surgery and for the next 48 h.²

During fasting, sulfonylureas stimulate insulin secretion and may lead to hypoglycemia. Because they have a longer half-life (2–10 h),⁵⁸ it is recommended to omit the dose on the day of surgery regardless of the procedure time.² Glinides' mechanism of action is similar to that of sulphonylureas and, for having a short half-life (1 h) and early action peak, they are used to control postprandial blood glucose—hypoglycemia with this type of drug is less common.¹⁷ Dose omission on the day of surgery should occur in the morning procedures. If surgery is performed in the afternoon and the patient has a meal in the morning, the pre-meal dose may be used.²

Similar to metformin, glitazones (or thiazolidinediones) act through peripheral sensitization to insulin. They are not associated with lactic acidosis, although they may be associated with water retention and possible worsening of postoperative edema and heart failure.⁵⁹ Consensus does not suggest this drug discontinuation during the perioperative period^{2,17,60,61}; it should be used on the day of surgery and attention should be given to the possibility of edema worsening and cardiac decompensation in patients at risk.²

Alpha-glycosidase inhibitors inhibit oligosaccharidase and disaccharidase enzymes and reduce glucose absorption after meals. On the day of surgery, the dose should be omitted in morning procedures. However, if the surgery is in the afternoon and the patient has had a meal in the morning, the pre-meal dose may be used,² if we consider that these drugs are not hypoglycemic and have a short half-life.¹⁷

The new incretinic drugs, represented by GLP-1 analogs and DPP-4 inhibitors, increase insulin secretion after glucose ingestion and reduce glucagon secretion.⁵⁸ It does not cause hypoglycemia, but may lead to delayed gastric emptying by increasing GLP-1.⁶⁰ Therefore, some authors suggest that it be discontinued on the day of procedure.^{8,60}

Notwithstanding, the most recent British guideline recommends its use until the day of surgery regardless of the procedure time.²

The sodium glucose co-transporter type 2 (SGLT2) protein inhibitors, present in the proximal convoluted tubule of the nephron, have recently been introduced for DM treatment. Because SGLT2 lead to glycosuria, it can generate osmotic diuresis with dehydration and hypotension; these effects are more common with the concomitant use of diuretics.⁶² Due to lack of experience with these drugs, it is recommended to omit the dose on the day of surgery, regardless of the procedure time.²

The management of oral antidiabetic drugs in patients who will undergo a short fasting period; that is, limited to a lost meal, is summarized in Table 3. All such drugs must be discontinued until the oral intake is reestablished.^{2,8}

Insulin management

Patients with DM1 are often treated with multiple insulin injection. The preferred regimen of physiologic insulin dosing (also called basal bolus) mimics endogenous insulin production by providing basal, prandial, and correction doses. Basal dose may be offered by a continuous subcutaneous insulin infusion through an insulin pump (based on a rate of rapid-acting insulin analogs) or through long-acting and non-peak insulin analogs. Basal insulin comprises approximately 50% of the patient's total daily dose of insulin, meeting the metabolic needs without causing hypoglycemia. Patients inject variable boluses of fast-acting insulin according to their carbohydrate intake at meals.⁶³

However, in DM2 patients, current treatment algorithms include the use of different types of oral hypoglycemic agents, non-insulin injectable drugs, and insulins.⁸ Long-acting, intermediate-acting or premixed insulin are optional regimens used most often by these patients to supplement oral drugs and endogenous insulin production, but may cause hypoglycemia during fasting. DM2 patients are insulin-resistant and usually require higher doses of insulin for the same level of glycemic control.

It is of fundamental importance to remember that basal metabolism uses approximately 50% of the daily insulin produced by an individual, even in the absence of food. Therefore, the patient should continue to receive a certain amount of insulin even when fasting. This is mandatory in DM1 patients, as they are insulin-deficient and prone to develop diabetic ketoacidosis. They need, therefore, a continuous exogenous supply of insulin. A common mistake is to treat these patients as DM2 patients who are not prone to ketosis. The latter are susceptible to develop an HHS, which may lead to severe volume depletion and neurological complications, although they may also develop ketoacidosis in response to extreme stress conditions.⁸

The types of insulin available for DM treatment are listed in Table 4, as well as their pharmacokinetics.

Long-acting insulin analogs, such as glargine, degludec or detemir are commonly used to maintain glycemic control between meals. Patients generally do not present with an increased risk of hypoglycemia with these analogs, even if

Table 3 Recommendations for perioperative use of oral and non-insulin injectable antidiabetic drugs.

Class (trade name)	Previous day	Day of surgery	
		Morning surgery	Afternoon surgery
<i>Biguanides</i> Metformin (Glifage®)		Regular use, unless contraindicated ^a	
<i>Sulphonylureas</i> Gliclazide (Diamicon®) Glibenclamide (Daonil®) Glimepiride (Amaryl®) Glipizide (Glucotrol®)	Regular use	Omit the dose regardless of the time	
<i>Glinides</i> Nateglinide (Starlix®) Repaglinide (Prandin®)	Regular use	Omit the morning dose	Take the morning dose (pre-meal) if the patient had breakfast
<i>Alpha-glucosidase inhibitors</i> Acarbose (Glucobay®)			
<i>Glitazones</i> Rosiglitazone (Avandia®) Pioglitazone (Actos®)	Regular use	Regular use (attention to patients at risk for cardiac congestion)	
<i>DPP-4 inhibitors</i> Sitagliptin (Januvia®) Vildagliptin (Galvus®) Saxagliptin (Onglyza®) Alogliptin (Nesina®) Linagliptin (Trayenta®)	Regular use	Regular use ² or omit the dose on the day of surgery (potential delay of gastric emptying) ³	
<i>GLP1 analogs</i> Exenatide (Byetta® Bydureon®) Liraglutide (Victoza®)			
<i>SGLT-2 inhibitors</i> Dapaglifozina (Forxiga®) Canaglifozina (Invokana®) Empaglifozina (Jardiance®)	Regular use	Omit dose on the day of surgery. Attention for concomitant use of diuretics.	

^a Use of radiological contrast, GFR < 60 mL·min⁻¹, elevated creatinine or significant risk of ARF.²

Adapted from Refs. 2,8,17.

they have not eaten, as seen in pre and postoperative fasting. The administration of the usual dose of these analogs on the day prior to surgery and on the day of surgery is recommended, unless there is a history of hypoglycemia or reduced caloric intake on the eve of the procedure.^{17,60} Some authors recommend reducing doses by 20–30% the night before or in the morning of surgery.^{2,63}

Combined treatment with insulin (intermediate-action or premixed) and oral antidiabetic drugs may cause hypoglycemia during fasting. Regarding intermediate-acting insulin, such as neutral protamine hagedorn (NPH) or neutral protamine lispro (NPL), given on the day before surgery, the dose given in the morning may be maintained; however, some authors recommend a 25% reduction in the dose given at night, particularly if there is a history of hypoglycemia. On the day of surgery, a reduction of 25–50% in the morning dose is recommended.^{2,8,17,60}

Premixed insulins are fixed combinations of fast-acting and intermediate-acting insulins.⁶³ It is not necessary to

change the dose on the day before surgery. However, on the day of surgery, they should be replaced by those of intermediate and fast action. To minimize the risk of hypoglycemia caused by the fast-acting component, the dose of each type of insulin should be given independently.⁶³ As for the intermediate-acting component, it is recommended to proportionally reduce the morning dose by 25–50%.^{2,17,60,63}

Short-acting insulin (regular insulin) or fast-acting analogs (aspart, glulisine, lispro) are intended to control meal-induced glycemic changes. It is therefore recommended that the dose remain unchanged the day before surgery. On the day of surgery, due to the risk of hypoglycemia, it is intuitive to avoid given these insulins while the patient is fasted.^{2,8,17,60,63}

In order to determine the preoperative management of insulin, besides knowing the insulin scheme used by the patient, it is essential to define the time scheduled for surgery and how many meals will be lost. In patients who will miss only one meal, glycemic control may be done by manip-

Table 4 Insulin type and pharmacokinetics.

Drug class: generic (trade name)	Onset	Peak effect	Duration
<i>Rapid acting analogs</i>			
Lispro (Humalog [®])	5–15 min	30–90 min	4–6 h
Aspart (Novolog [®] Novorapid [®])	5–15 min	30–90 min	4–6 h
Glulisin (Apidra [®])	5–15 min	30–90 min	4–6 h
<i>Short action</i>			
Regular (Novolin R [®] Humulin [®])	30–60 min	2–4 h	6–8 h
<i>Intermediate action</i>			
NPH (Novolin N [®] Humulin N [®])	2–4 h	4–10 h	10–16 h
Insulin zincica (Lente [®])	2–4 h	4–10 h	12–20 h
Extended zinc insulin (Ultralente [®])	6–10 h	10–16 h	18–24 h
<i>Long/basal action</i>			
Glargine (Lantus [®])	2–4 h	None	20–24 h
Detemir (Levemir [®])	2–4 h	None	20–24 h
Degludec (Tresiba [®])	2–4 h	None	≥42 h
<i>Pre-mixed (NPH + regular)</i>			
70% NPH/30% regular (Novolin 70/30 [®] , Humulin 70/30 [®])	30–90 min	Dual	10–16 h
50% NPH/50% regular (Humulin 50/50 [®])	30–90 min	Dual	10–16 h
<i>Pre-mixed (intermediate-acting + short-acting analogs)</i>			
70% Aspart Protamine suspension/30% Aspart (Novolog mix 70/30 [®])	5–15 min	Dual	10–16 h
75% Lispro Protamine suspension/25% Lispro (Humalog mix 75/25 [®])	5–15 min	Dual	10–16 h
50% Lispro Protamine suspension/50% Lispro (Humalog mix 50/50 [®])	5–15 min	Dual	10–12 h

Adapted from Ref. 17.

ulating the usual doses of insulin as previously mentioned and summarized in Table 5.^{2,17,60}

It is important to remember that evidence on the perioperative management of insulin is still scarce and there is no consensus among different guidelines. However, for surgeries requiring a long period of fasting with loss of more than one meal or large surgeries,^{2,61} the use of a variable rate intravenous insulin infusion (VRIII) is more indicated.

Variable rate intravenous insulin infusion (VRIII)

VRIII is preferred for patients who will miss more than one meal, those with DM1 who underwent surgery and did not receive basal insulin, those with poorly controlled diabetes (HbA1c > 8.5%), and for the majority of diabetic patients who require emergency surgery. VRIII should be given and monitored by qualified and experienced professionals.² Adequate glucose supply should be provided to prevent induction of catabolic state, fast ketosis, and insulin-induced hypoglycemia. It is recommended that blood glucose be measured at least every hour.⁸

There are numerous VRIII algorithms published in the literature, with insulin and glucose solutions infused alone or combined with glucose, insulin and potassium (GIK) solution. The injection regimen of choice is separate infusion of insulin and glucose in which glucose is given at a rate of 5–10 g.h⁻¹, and the insulin used is the short-acting insulin (1 mL.100⁻¹ U insulin in 99 mL of 0.9% SS).²³ Most DM1 patients require an infusion rate of 1–2 units.h⁻¹, while insulin-resistant DM2 patients may require higher rates.²³

An algorithm commonly followed calculates the initial rate of infusion by dividing the glycemic level (in mg.dL⁻¹) per 100 and then rounds up the result in units.h⁻¹ (e.g., a glucose of 210 divided by 100 = 2.1 units.h⁻¹). In the case of hypoglycemia, the infusion of insulin may be decreased; however, to avoid ketosis, the temptation to discontinue insulin infusion should be avoided in DM1 patients. In such cases, insulin infusion may be reduced to 0.5 units.h⁻¹ and the rate of glucose infusion increased to maintain glycemic targets.²³

The rate of insulin infusion should be titrated according to the procedure and degree of insulin resistance. For myocardial revascularization procedures, insulin requirements may increase up to 10-fold, especially after recovery from the hypothermia period; a three to five fold increase in the initial rate of insulin is required.²³

Which fluid to use in the perioperative period?

The goal is to avoid solutions with glucose, unless hypoglycemia is present.² The recommended solution for diabetic patients who do not require VRIII is Hartmann's solution (ringer lactate – RL), preferred for reducing 0.9% sodium chloride, as it reduces the risk of hyperchloremic acidosis.⁸ In diabetic patients, RL may lead to hyperglycemia. In fact, it has been shown that 1 L of RL solution increases plasma glucose by no more than 1 mmol.L⁻¹ (18 mg.dL⁻¹).⁶⁴ This does not contraindicate its use in diabetic patients.⁸

Table 5 Management of insulin therapy for patients undergoing short fasting period (up to a missed meal).

Type of insulin	Previous day	Day of surgery	
		Morning surgery	Afternoon surgery
Continuous subcutaneous insulin infusion (pump)	Maintain basal infusion or reduce 20–30% of baseline if history of frequent hypoglycemia		
Long-acting or basal insulin (glargine, detemir)	Morning application: maintain dose Night application: maintain dose or reduce 20–30% ^b	Morning application ^a : Maintain dose or reduce 20–30% if history of frequent hypoglycemia. Check blood glucose at admission	
Intermediate-acting insulin (NPH)	Morning application: maintain dose Night application: maintain dose or reduce 20–30% ^b	Reduce morning dose by 50% ^a ; check blood glucose at admission; keep evening dose unchanged after surgery (if already fed)	
Pre-mixed insulin	Maintain dose	Reduce morning dose intermediate insulin to 50%; omit the dose of fast/short-acting insulin. Check blood glucose at admission. Keep evening dose unchanged after surgery (if already fed)	
Fast-acting or short-acting insulin analogs	Maintain dose	Hold dose	Hold dose

^a On the day of surgery, the morning insulin should be given upon arrival at the health center.

^b History of hypoglycemia during dawn/morning.

Adapted from Refs. 2,17,61,64.

For patients receiving VRIII, the goal is to provide glucose as a substrate to prevent proteolysis, lipolysis and ketogenesis and to improve intravascular volume and maintain plasma electrolytes at normal values, particularly potassium. Fluids should be given at a rate appropriate to the patient's normal maintenance needs—typically 25–50 mL.kg⁻¹.day⁻¹ (about 83 mL.h⁻¹ for a 70 kg patient).² To avoid catabolism, glucose should be provided at a rate of about 5–10 g.h⁻¹.²³ Additional RL solution or other balanced isotonic crystalloid solution should be used to restore intravascular volume.²

Perioperative glycemic targets

There is strong recommendation^{2,17,60,65} to follow the implantation of the World Health Organization (WHO) surgical safety target, which establishes that the ideal in-hospital glucose range for non-critically ill diabetic patients should be 108–180 mg.dL⁻¹ (6–10 mmol.L⁻¹ in the USA, with the lower limit of 100 mg.dL⁻¹ or 5.6 mmol.L⁻¹). Adequate glycemic control reduces perioperative infection, morbidity, and mortality.^{1,40}

Some authors consider that a range of 72–216 mg.dL⁻¹ (4–12 mmol.L⁻¹) would be acceptable.⁶⁰ However, there are some arguments against using this broad range. The upper limit of 216 mg.dL⁻¹ (12 mmol.L⁻¹) is similar to the in vitro concentration, which results in a variety of changes in endothelial function, increased cytokine synthesis, and impaired neutrophil function that increase the risk of infection.⁶⁶ The lower limit of 72 mg.dL⁻¹ (4 mmol.L⁻¹) is close to the blood glucose values that induce symptoms of hypoglycemia in some diabetic patients.³⁹

Systematic reviews and meta-analysis have attempted to identify the benefits of intensive glycemic control in diabetic patients undergoing surgery. A meta-analysis concluded that moderate glycemic control, defined as a glycemic target between 150 and 200 mg.dL⁻¹ (8.3–11.1 mmol.L⁻¹), during or immediately after surgery, is associated with a reduced risk of mortality and stroke in DM patients compared to a liberal glycemic control, defined as a glycemic target >200 mg.dL⁻¹ (>11.1 mmol.L⁻¹). The results of this meta-analysis also showed that there were no differences in the outcomes between moderate and severe glycemic control, which was defined as glycemic targets between 90 and 150 mg.dL⁻¹ (5.6–8.3 mmol.L⁻¹).⁶⁷ These findings are supported by a recent Cochrane review, which concluded that there were no differences between intensive glycemic control, near-normal glycemia, and conventional control regarding postoperative outcomes, except for an increase in hypoglycemic events that occurred in patients treated with intensive control.⁶⁸

Chronically elevated glycemic levels should not be acutely reduced or normalized due to the potential for hypoglycemia and because significant fluctuations in blood glucose levels may increase perioperative morbidity and mortality.^{5,42}

When to postpone surgery?

In general, surgery should be postponed in patients with significant complications of hyperglycemia, such as dehydration, ketoacidosis or HHS.^{17,42} However, surgery may be indicated for patients with preoperative hyperglycemia, provided that the patient has adequate glycemic control

in recent months.¹⁷ Depending on individual circumstances, an upper limit of HbA1c between 8% and 9% is acceptable.⁸ The latest British guidelines recommend that surgery should be postponed in the presence of HbA1c above 8.5% (mean of 200 mg.dL⁻¹) in order to improve glycemic control and reduce complications.² For the Australian Society of Diabetes, HbA1c value should be above 9% (mean blood glucose of 215 mg.dL⁻¹) for postponing surgery.⁶¹

On a daily basis, these recommendations may be poorly practical if we consider that reducing HbA1c levels could take weeks/months⁶⁰ and that in certain cases it may not be possible to improve glycemic control in a timely manner, particularly if the reason for surgery, such as chronic infection, contribute to worse glycemic control or if the surgery is urgent. In these circumstances, it may be acceptable to continue surgery after explaining to the patient the increased risks.² In these patients, HbA1c would be a useful tool to enhance perioperative diabetic therapy in an attempt to reduce complications.⁸

Conclusion

DM patients are at increased risk for developing perioperative complications. Metabolic stress caused by the surgical procedure leads to an increase in the demand for insulin, which may cause decompensation and hyperglycemia. Prior to surgery, a thorough assessment of the characteristics of these patients, including treatment for DM, is critical. Perioperative management, particularly drug treatment, should be adjusted according to the patient's routine and surgical procedure characteristics (type and duration). If the fasting period is limited to a missed meal, the choice is to maintain or modify the way in which the medication is usually used. If longer periods of fasting are predicted, a variable rate intravenous insulin infusion (VRIII) should be used and a specialist assessment requested. Evidence on the perioperative management of medications is still scarce and there is no agreement between the different guidelines, therefore more clinical trials are needed to determine the best planning for the treatment of these patients.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in non-cardiac surgery. *Diabetes Care*. 2010;33:1783–8.
2. Barker P, Creasey PE, Dhataria K, et al. Peri-operative management of the surgical patient with diabetes 2015: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia*. 2015;70:1427–40.
3. Stumvall M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. 2005;365:1333–46.
4. Standards of medical care in diabetes – 2015. Classification and diagnosis of diabetes. *Diabetes Care*. 2015;38 Suppl. 1:58–16.
5. Sebranek JJ, Lugli AK, Coursin DB. Glycaemic control in the perioperative period. *Br J Anaesth*. 2013;111 Suppl. 1:i18–34.
6. Larkin ME, Barnie A, Braffett BH, et al. Musculoskeletal complications in type 1 diabetes. *Diabetes Care*. 2014;37:1863–9.
7. Wall R. Endocrine disease. In: Hines RL, Marschall KE, editors. *Stoelting's anesthesia and co-existing disease*. 6th ed. Philadelphia: Elsevier; 2012. p. 376–84.
8. Soldevila B, Lucas AM, Zavala R, et al. Perioperative management of the diabetic patient. In: Stuart-Smith K, editor. *Perioperative medicine – current controversies*. Switzerland: Springer; 2016. p. 165–92.
9. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med*. 2001;111:64.
10. Moitra VK, Meiler SE. The diabetic surgical patient. *Curr Opin Anaesthesiol*. 2006;19:339–45.
11. Selvin E, Coresh J, Shahar E, et al. Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Lancet Neurol*. 2005;4:821–6.
12. Kadoi Y, Hinohara H, Kunimoto F, et al. Diabetic patients have an impaired cerebral vasodilatory response to hypercapnia under propofol anesthesia. *Stroke*. 2003;34:2399–403.
13. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis. *JAMA*. 2002;287:2570–81.
14. Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary artery disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–34.
15. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–97.
16. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2215–45.
17. Joshi GP, Chung F, Vann MA, et al. Society for ambulatory anaesthesia consensus statement on perioperative blood glucose management in diabetic patients undergoing ambulatory surgery. *Anesth Analg*. 2010;111:1378–87.
18. Loh-Trivedi M, Croley WC. Perioperative management of the diabetic patient; 2015. <http://emedicine.medscape.com/article/284451-overview#a3> [accessed 27.08.16].
19. Abdelmalak B, Abdelmalak JB, Knittel J, et al. The prevalence of undiagnosed diabetes in non-cardiac surgery patients, an observational study. *Can J Anaesth*. 2010;57:1058–64.
20. Sheehy AM, Benca J, Glinberg SL, et al. Preoperative 'NPO' as an opportunity for diabetes screening. *J Hosp Med*. 2012;7:611–66.
21. Lauruschkat AH, Arnrich B, Albert AA, et al. Prevalence and risks of undiagnosed diabetes mellitus in patients undergoing coronary artery bypass grafting. *Circulation*. 2005;112:2397–402.
22. Kadoi Y. Anaesthetic considerations in diabetic patients. Part I: preoperative considerations of patients with diabetes mellitus. *J Anesth*. 2010;24:739–47.
23. Khan NA, Ghali WA, Cagliero E. Perioperative management of blood glucose in adults with diabetes mellitus; 2016 www.UpToDate.com
24. American Diabetes Association. Standards of medical care in diabetes – 2015. *Diabetes Care*. 2015;38 Suppl. 1:S33–40.
25. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. *Diabetes Care*. 2014;37:1048–51.

26. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31:1473–8.
27. Walid MS, Newman BF, Yelverton JC, et al. Prevalence of previously unknown elevation of glycosylated hemoglobin in spine surgery patients and impact on length of stay and total cost. *J Hosp Med*. 2010;5:10–4.
28. O'Sullivan CJ, Hynes N, Mahendran B, et al. Haemoglobin A1c (HbA1C) in non-diabetic and diabetic vascular patients. Is HbA1C an independent risk factor and predictor of adverse outcome? *Eur J Vasc Endovasc Surg*. 2006;32:188–97.
29. Gustafsson UO, Thorell A, Soop M, et al. Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. *Br J Surg*. 2009;96:1358–64.
30. Halkos ME, Lattouf OM, Puskas JD, et al. Elevated preoperative hemoglobin A1c level is associated with reduced long-term survival after coronary artery bypass surgery. *Ann Thorac Surg*. 2008;86:1431–7.
31. Alserius T, Anderson RE, Hammar N, et al. Elevated glycosylated haemoglobin (HbA1c) is a risk marker in coronary artery bypass surgery. *Scand Cardiovasc J*. 2008;42:392–8.
32. Kreutziger J, Schlaepfer J, Wenzel V, et al. The role of admission blood glucose in outcome prediction of surviving patients with multiple injuries. *J Trauma*. 2009;67:704–8.
33. Vilar-Compte D, Alvarez de Iturbe I, Martin-Onraet A, et al. Hyperglycemia as a risk factor for surgical site infections in patients undergoing mastectomy. *Am J Infect Control*. 2008;36:192–8.
34. Shibuya N, Humphers JM, Fluhman BL, et al. Factors associated with nonunion, delayed union, and malunion in foot and ankle surgery in diabetic patients. *J Foot Ankle Surg*. 2013;52:207–11.
35. Chuang SC, Lee KT, Chang WT, et al. Risk factors for wound infection after cholecystectomy. *J Formos Med Assoc*. 2004;103:607–12.
36. Ambiru S, Kato A, Kimura F, et al. Poor postoperative blood glucose control increases surgical site infections after surgery for hepato-biliary-pancreatic cancer: a prospective study in a high-volume institute in Japan. *J Hosp Infect*. 2008;68:230–3.
37. Underwood P, Askari R, Hurwitz S, et al. Preoperative A1C and clinical outcomes in patients with diabetes undergoing major noncardiac surgical procedures. *Diabetes Care*. 2014;37:611–6.
38. NICE Guideline. Preoperative tests (update): routine preoperative tests for elective surgery. London: National Institute for Health and Care Excellence (UK); 2016, nice.org.uk/guidance/ng45.
39. Aldam P, Levy N, Hall GM. Perioperative management of diabetic patients: new controversies. *Br J Anaesth*. 2014;113:906–9.
40. Kwon S, Thompson R, Dellinger P, et al. Importance of perioperative glycemic control in general surgery: a report from the surgical care and outcomes assessment program. *Ann Surg*. 2013;257:8–14.
41. Bock M, Johansson T, Fritsch G, et al. The impact of preoperative testing for blood glucose concentration and haemoglobin A1c on mortality, changes in management and complications in noncardiac elective surgery: a systematic review. *Eur J Anaesthesiol*. 2015;32:152–9.
42. Akhtar S, Barash PG, Inzucchi SE. Scientific principles and clinical implications of perioperative glucose regulation and control. *Anesth Analg*. 2010;110:478–97.
43. Bagry HS, Raghavendran S, Carli F. Metabolic syndrome and insulin resistance: perioperative considerations. *Anesthesiology*. 2008;108:506–23.
44. McAnulty GR, Robertshaw HJ, Hall GM. Anaesthetic management of patients with diabetes mellitus. *Br J Anaesth*. 2000;85:80–90.
45. Fragen RJ, Shanks CA, Molteni A, et al. Effects of etomidate on hormonal responses to surgical stress. *Anesthesiology*. 1984;61:652–6.
46. Belhoula M, Ciébiéra JP, De La Chapelle A, et al. Clonidine premedication improves metabolic control in type 2 diabetic patients during ophthalmic surgery. *Br J Anaesth*. 2003;90:434–9.
47. Lattermann RT, Schrickler U, Wachter M, et al. Understanding the mechanisms by which isoflurane modifies the hyperglycemic response to surgery. *Anesth Analg*. 2001;93:121–7.
48. Halter JB, Pflug AE. Effect of sympathetic blockade by spinal anaesthesia on pancreatic islet function in man. *Am J Physiol*. 1980;239:150–5.
49. Donatelli F, Vavassori A, Bonfanti S. Epidural anaesthesia and analgesia decrease the postoperative incidence of insulin resistance in preoperative insulin-resistant subjects only. *Anesth Analg*. 2007;104:1587–93.
50. Osterman AL. The double crush syndrome. *Orthop Clin N Am*. 1988;19:147–55.
51. Kalichman MW, Calcutt NA. Local anesthetic-induced conduction block and nerve fiber injury in streptozotocin-diabetic rats. *Anesthesiology*. 1992;77:941–7.
52. Willams BA. Toward a paradigm shift for the clinical care of diabetic patients requiring perineural analgesia: strategies for using the diabetic rat model. *Reg Anesth Pain Med*. 2010;35:329–32.
53. Gebhard RE, Nielsen KC, Pietrobon R, et al. Diabetes mellitus, independent of body mass index, is associated with a “higher success” rate for supraclavicular brachial plexus blocks. *Reg Anesth Pain Med*. 2009;34:404–7.
54. Sites BD, Gallagher J, Sparks M. Ultrasound-guided popliteal block demonstrates an atypical motor response to nerve stimulation in 2 patients with diabetes mellitus. *Reg Anesth Pain Med*. 2003;28:479–82.
55. Neal JM, Barrington MJ, Brull R, et al. The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine executive summary 2015. *Reg Anesth Pain Med*. 2015;40:401–30.
56. Duncan AI, Koch CG, Xu M, et al. Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. *Anesth Analg*. 2007;104:42–50.
57. The Royal College of Radiologists. Standards for intravascular contrast agent administration to adult patients. 2nd ed. London: The Royal College of Radiologists; 2010. Available from [https://www.rcr.ac.uk/docs/radiology/pdf/BFCR\(10\)4.Stand_contrast.pdf](https://www.rcr.ac.uk/docs/radiology/pdf/BFCR(10)4.Stand_contrast.pdf) [accessed 05.06.16].
58. Standards of medical care in diabetes – 2015. Approach to glycemic control. *Diabetes Care*. 2015;38 Suppl. 1: S41–8.
59. Sudhakaran S, Surani SR. Guidelines for perioperative management of the diabetic patient. *Surg Res Pract*. 2015; 2015:284063.
60. Dhatariya K, Levy N, Kilvert A, et al. NHS diabetes guideline for the perioperative management of the adult patient with diabetes. *Diabet Med*. 2012;29:420–33.
61. Australian Diabetes Society. Peri-operative diabetes management guidelines; 2012. <https://diabetessociety.com.au/documents/PerioperativeDiabetesManagementGuidelinesFINALCleanJuly2012.pdf> [accessed 10.06.16].
62. Ferreira VA. Avanços farmacológicos no tratamento do diabetes tipo 2. *Braz J Surg Clin Res (BJSJR)*. 2014;8:72–8.
63. Vann MA. Management of diabetes medications for patients undergoing ambulatory surgery. *Anesthesiol Clin*. 2014;32:329–39.
64. Simpson AK, Levy N, Hall GM. Peri-operative i.v. fluids in diabetic patients – don't forget the salt. *Anaesthesia*. 2008;63:1043–5.
65. Moghissi ES, Korytkowski MT, Di Nardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract*. 2009;15:353–69.

66. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest*. 2005;115:2277–86.
67. Sathya B, Davis R, Taveira T, et al. Intensity of peri-operative glycaemic control and postoperative outcomes in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract*. 2013;102:8–15.
68. Buchleitner AM, Martínez-Alonso M, Hernández M, et al. Peri-operative glycaemic control for diabetic patients undergoing surgery. *Cochrane Database Syst Rev*. 2012:CD007315.