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# Perioperative Management of Diabetes Mellitus: A Review

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## Abstract

**Introduction:** Diabetes Mellitus (DM) is frequently observed in surgical patients and relates to an increase in perioperative morbidity and mortality. Disease, anesthesia and surgery result in dysglycemia (hypo and/or hyperglycemia), which is one of the worse prognostic factors. The objective of this study is to review the specific needs of the diabetic surgical patient in the perioperative period, regarding its optimization.

**Methods:** Scientific studies (n=89) were obtained through PubMed, Google Scholar and Google, between 2008 and 2018.

**Results:** Actions proposed in order to reduce perioperative complications in the diabetic patient. Preoperative period: an anesthetic evaluation, discontinuation of OADs and fast-acting insulin, prioritization of diabetics in the surgery list, cancellation of non-urgent procedures when there are metabolic abnormalities and poor glycemic control and promotion of gastric emptying due to gastrointestinal autonomic dysfunction. Intraoperative period: the use of IV perfusion of insulin for glycemic control in major surgeries, the use of glycoside sera in cases of prolonged fasting and/or IV insulin perfusion, hourly glycemic monitoring, a glycemic goal between 80-180 mg/dl with correction of hyperglycemias with insulin, and the use of a rapid-sequence intubation when there is risk of aspiration. Postoperative period: the early return to oral nutrition and the restitution of OADs and insulin with the onset of food intake, multimodal analgesia and antiemetic prophylaxis, the correct transition from IV perfusion to subcutaneous insulin and pre-discharge therapeutic optimization.

**Discussion:** Several studies have shown a correlation between dysglycemia and postoperative morbidity and mortality. Nevertheless, the ideal glycemic range and the best glycemic management strategy remain indeterminate.

**Conclusion:** Studies that establish specific measures and universal cut-offs are scarce. There is a need for clearer and guidelines to minimize perioperative complications. It is also important that diabetic patients have the capacity to manage their own disease, to facilitate their optimization in the surgical context.

**Keywords:** Diabetes mellitus; Perioperative management; Anesthesia; Preoperative; Postoperative; Surgery

## Introduction

Diabetes Mellitus (DM) is a chronic disease of high prevalence and increasing incidence, particularly in developed or developing countries, and has been identified as a major cause of global mortality in the last decade [1,2]. In 2015, the estimated prevalence of DM was 8.5% in the world population, and 13.3% in the Portuguese population [3,4]. This multifactorial epidemic is due to the increasing age of the population and the increase of obesity and sedentarism, and is expected to continue to increase if some lifestyle habits (such as diet) are not modified [2,5].

DM is the most common multisystem endocrine-metabolic disease, characterized by a deregulation in carbohydrate metabolism where hyperglycemia predominates, and, if untreated, can become debilitating due to chronic failure of several organs [6]. It is classified based on its pathophysiological mechanism, in four clinical types of distinct etiology: type 1 DM, which results from the immune-mediated destruction of the cell and leads to absolute insulin deficiency, with type 1 diabetics having a compulsory need for insulin; the type 2 DM, which is associated with progressive loss of insulin secretion by the cell and insulin resistance, being it possible for type 2 diabetics to be controlled with diet, oral antidiabetic (ADO) and/or insulin; the gestational DM, diagnosed in the 2nd/3rd trimester of pregnancy; and the 4th category which includes a broad spectrum of specific types from other causes, such as genetic defects of cells, diseases of the exocrine pancreas, endocrinopathies and drugs [6,7]. Type 1 and type 2 DM are the most frequent types; however, type 2 is the most common (90-95% of cases) and most often develops in elderly and/or obese adults, although there is an increase in the diagnosis of young patients [1,2]. Type 1 DM mainly affected pediatric patients, but is now frequently diagnosed in adults [8].

The diagnosis of DM is established based on plasma glucose values, namely: fasting blood glucose ≥ 126 mg/dl, or glucose 2 h after oral glucose tolerance test (OGTT) ≥ 200 mg/dl, or HbA1c ≥ 6.5%, or casual blood glucose ≥ 200 mg/dl in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis (polyphagia, polydipsia, polyuria, fatigue and weight loss). Thus, another group of patients, known as pre-diabetic patients, can be classified into two groups: with impaired glucose tolerance (glycemia 2 h after OGTT between 140 and 199 mg/dl) or with fasting glucose anomaly (glycemia between 100 and 125 mg/dl in the fasted state) [7].

In DM there are several progressive physiological changes, thus, some organs and systems must be emphasized in the anesthetic approach: musculoskeletal, renal, neurologic, and cardiovascular [9].

### Musculoskeletal system

Chronic hyperglycemia promotes non-enzymatic glycosylation of proteins and leads to abnormal cross-linking of joint glycogen, which will limit joint mobility, triggering Stiff Joint Syndrome or diabetic cheiroarthropathy, which mainly affects the temporomandibular, atlanto-occipital and cervical spine joints. Diabetic scleredema is characterized by a non-depressible hardening of the skin in the neck and upper back regions and, associated with reduced joint mobility, limits the angles of movement of the neck and may hinder orotracheal intubation [9].

### Renal system

A significant 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 diabetics without adequate glycemic control [9].

### Neurologic system

The neurological effects of DM increase the risk of cerebrovascular accidents (CVA) and the presence of hyperglycemia is a strong predictor of worse prognosis in the various forms of acute brain injury [9]. Approximately 10% of diabetics also have symptoms of peripheral diabetic neuropathy, a multifactorial polyneuropathy that is mainly due to inflammation, oxidative stress and mitochondrial dysfunction caused by chronic hyperglycemia, which causes neuronal damage and decreased conduction velocity and nerve fiber reactivity [10]. These nerve fibers are also more susceptible to ischemic injury, such as when under stress due to chronic ischemic hypoxia [9].

Autonomic diabetic neuropathy is a common complication of DM and is frequently undiagnosed, affecting the gastrointestinal, genitourinary and cardiovascular systems [9]. It occurs in 17% of type 1 diabetics and 22% of type 2, and is characterized by resting tachycardia, exercise intolerance (fatigue and syncope), orthostatic hypotension, asymptomatic involvement of the coronary arteries, arrhythmias and sudden cardiac death. Autonomic gastrointestinal neuropathy causes symptoms such as dysphagia, gastroparesis and profuse diarrhea alternating with intestinal constipation. Autonomic genitourinary neuropathy main clinical manifestations are neurogenic bladder and sexual dysfunction [11]. Impaired neurovascular function, loss of autonomic response to hypoglycaemia (as happens after a few hours of perioperative fasting), and affected thermoregulatory response to hypothermia during anesthesia are also possible [5,9].

### Cardiovascular system

Diabetics are at increased risk of hypertension, coronary artery disease, peripheral arterial disease, silent myocardial ischemia, QT interval abnormalities (with potential and fatal ventricular arrhythmias), systolic and diastolic heart failure, congestive heart failure, and sudden death. Through several mechanisms, hyperglycemia promotes vasodilation and induces a pro-inflammatory, prothrombotic and pro-atherogenic state, responsible for these common vascular complications. These patients also have high intraoperative cardiovascular instability, since neuropathy predisposes them to bradycardia, hypotension and cardiorespiratory arrest during general anesthesia, and not the normal response (vasoconstriction and tachycardia) to the vasodilating effects of anesthesia. DM also predisposes to the development of a specific cardiomyopathy, which leads to diastolic dysfunction. This disease is, therefore, especially in insulin-dependent patients, an independent risk factor for adverse cardiac events, with cardiovascular disease being the cause of death in 80% of diabetics [5,9,12].

The estimated incidence of diabetics requiring surgery is about 25%, which explains why DM is frequently observed in surgical patients [11]. As the incidence of this disease continues to increase, and diabetics more often suffer from macro and microvascular complications (including retinopathy, nephropathy and neuropathy) and other comorbidities, their increased need for surgery and/or other surgical procedures, compared to non-diabetic patients, is understandable [13]. DM leads to increased morbidity, perioperative mortality (50% higher than non-diabetic patients) and use of resources, leading to more frequent and prolonged hospitalizations [9,14]. The determinants of worse prognosis of diabetics in the perioperative period are many, namely: hypoglycemia and hyperglycemia; comorbidities, including micro and macrovascular complications; the acute complications of diabetes; the complex medication regimens; errors in insulin prescription; the peri and postoperative infections; failure in identifying patients with diabetes; the lack of adequate institutional therapeutic protocols; and the lack of knowledge from health professionals about the correct approach [9,15]. Acute disease, anesthesia and surgery result in metabolic disturbances that alter glucose homeostasis, and this dysglycemia (hypo and/or hyperglycemia) in the surgical patient with diabetes is one of the factors with the worst prognosis [16,17].

### Hyperglycemia

Hyperglycemia is defined as glycemia>140 mg/dl in the hospitalized patient [18]. During surgery and postoperative period, depending on the type of anesthesia and surgery/procedure, nutritional and fluid support and anatomical location, glycemia increases significantly and may be responsible for perioperative complications [19]. As the ability to respond to the need for insulin is reduced or absent in patients with diabetes or pre-diabetes, the risk of developing hyperglycemia during or after surgery is greater [20]. However, even in people without DM, surgical stress can lead to transient hyperglycemia (by an adaptive mechanism) that normalizes after stabilization of the acute event, but which in some cases may lead to later disease development [19,21]. This stress hyperglycemia is more pronounced on the 1st postoperative day but may persist for 9 to 21 days after surgery [19]. Stress is the main etiology of perioperative hyperglycemia, followed by iatrogenic causes such as discontinuation of medication for the treatment of DM, drugs (such as some anesthetics, immunosuppressants and glucocorticoids), immobilization and advanced age of the patient. Thus, hyperglycemia results mainly from peripheral insulin resistance (which may last days after surgery) and from relative hypoinsulinemia, triggered by the release of pro-inflammatory mediators and counter-regulating hormones (catecholamines, cortisol, glucagon, and growth hormone), which promote gluconeogenesis and catabolism of proteins and fats, and which is triggered by stress, tissue trauma, fasting and pain [1,2,22]. This combination constitutes a serious problem of maintenance of glucose homeostasis, particularly in diabetics with poor prior metabolic control [2,13]. Thus, in extreme cases, acute complications of DM can be precipitated due to metabolic decompensation, resulting in diabetic ketoacidosis in type 1 diabetics and hyperosmolar hyperglycaemic syndrome in type 2 diabetes [9]. In addition, persistent hyperglycemia, as well as sustained hyperglycemia (estimated by the evaluation of glycosylated hemoglobin) are also risk factors for the occurrence of endothelial dysfunction and decreased phagocytic activity, postoperative sepsis, acute renal injury, alteration in operative wound healing (deleterious effects in the formation of collagen), cerebral and/or coronary ischemia, infections (surgical and nosocomial), hospitalization time and mortality [1,2,22,23]. Thus, hyperglycemia accounts for 66% of postoperative complications and 25% of perioperative deaths, and is therefore an independent marker of poor prognosis and mortality [2,24].

### Hypoglycemia

Hypoglycemia (<70 mg/dl) is common in hospitalized diabetics (especially in the first 7 days of hospitalization) and is caused by the relative excess of insulin or insulin secretagogues compared to carbohydrate intake, occurring more frequently in type 1 DM or long-term type 2 DM [17,22,25]. Severe hypoglycemia is defined as plasma glucose <40 mg/dl or when it is low enough for the individual to require the help of others [25]. Since glucose is the metabolic substrate required for the brain, this hypoglycemic state leads to neuroglycopenia and may result in somnolence, confusion, convulsions, irreversible neurological damage, and coma, and is also associated with an increase in mortality, length of hospital stay, risk of infection, difficulty in healing, prolongation of the QT interval, ischemia and angina, cardiac arrhythmias and sudden death in the surgical patient [16,26]. During general anesthesia or sedation, the symptoms of hypoglycemia are masked and, therefore, the prevention of their occurrence is of high importance [23].

The objective of this work is to systematically review the specific needs of DM in the perioperative period and its effective approach, gathering the latest information regarding the optimization of the diabetic surgical patient.

## Methods

This study was elaborated from scientific articles obtained through the bibliographic research carried out on the PubMed, Google Scholar and Google platforms between October 2018 and December 2018. The combinations of terms used in this research were: Diabetes anesthesia surgery, Diabetes postoperative anesthesia, Diabetes preoperative anesthesia, Diabetes perioperative management, Diabetes anesthesia management, Diabetes anesthesia. The types of articles used in this work were the following: reviews, systematic reviews, case reports, guidelines, observational studies. Articles published between 2008 and 2018 and written in English or Portuguese, were included. This research resulted in a thousand and one articles. Articles referring to groups of individuals or specific pathologies, such as children, elderly and individuals with cardiac pathology, as well as those that addressed other types of DM besides type 1 and 2 DM, that were focused on specific surgery procedures and animal studies were excluded.

With the application of these inclusion and exclusion criteria, one hundred and sixty-six publications were obtained. The articles were initially selected by the reading of the abstract and later by its complete reading. Lastly, other articles were also analyzed, by consulting the bibliographic references of those initially selected, which also took into account the year of their publication. In the end, we used eighty-nine scientific articles in this bibliographic review.

## Results

Given the increased risk of complications and the need for specific care, a correct evaluation and perioperative approach of the patient with DM is crucial [11]. This approach may take on some differences, depending on the type of DM, the evolutionary state of the disease, the age group and whether there are target organ lesions, and comprises 3 phases: preoperative, intraoperative and postoperative [1,2].

### Preoperative

There are some things to be considered in a diabetic, during this period, concerning diet, medication, and level of diabetes control and associated pre-existing complications [27]. In elective surgery, the objectives are to ensure that DM is as well controlled as possible and to avoid delays in surgery, minimizing the fasting period, ensuring normoglycemia and altering as little as possible the normal routine of the patient [15].

### Anesthesia consultation

The guidelines recommend that diabetics, when identified and proposed for elective surgery, should be evaluated and observed prior to anesthesia [28,29]. If they have been referenced by primary care, the latter should convey information about the patients to the surgical team and, if possible, the patients should also be optimized by them [15], since according to the Society for Ambulatory Anesthesia (SAMBA) [23], the desirable glycemic control should ideally be achieved in the weeks prior to surgery. Thus, it is suggested that this consultation should begin with a detailed clinical history of the type of DM and the dose of antidiabetic therapy (OADs and insulin), the duration, complications and comorbidities known, evaluation of prior metabolic control (through glycemic self-monitoring, mean blood glucose values and HbA1c value) and the presence of recent hypoglycemia (frequency, time of day, perception and severity) [22,23].

Therefore, if HbA1c dosing has not been done in the past 3 months or patients report poor glycemic control, and since a single blood glucose measurement provides little information about control in a stabilized diabetic, HbA1c's assessment will reflect the mean glycemia in the last 3 to 4 months, being a good indicator of long-term glycemic control [8,30,31]. A measure of HbA1c <7% gives us the assurance that the patient has a well-controlled diabetes [29].

Moitra et al. [32], in research with diabetics, also concluded that Hb1Ac levels predict pre and postoperative blood glucose levels, and Gustafsson et al. [33], in a similar study, have shown that the preoperative measurement of HbA1c may in fact identify patients at high risk of postoperative hyperglycemia, elevated C-reactive protein and postoperative complications. Therefore, when it is elevated, it may be necessary to postpone elective surgery for medical optimization, with the guidelines advising this postponement in cases with HbA1c ≥ 8.5-9%, a decision that should be made based on the presence of comorbidities and risk of surgical complications [1,22]. On the other hand, HbA1c <5% probably indicates severe recurrent hypoglycemias, being it usually advisable to postpone surgery [13]. However, there may be situations in which it is not possible to promote glycemic control preoperatively, being it possibly acceptable to proceed with surgery after explaining all risks to the patient and evaluating these risks and the urgency of the procedure [15,34].

When unidentified as diabetic, surgical patients should be screened for all possible risk factors for undiagnosed DM, such as obesity, metabolic syndrome, diabetogenic drugs, personal history of gestational DM or transient hyperglycemia, family history of DM and suggestive symptoms. When there is a suspicion, HbA1c dosing should be considered because pre-diabetes or undiagnosed diabetes increase the risk of perioperative complications due to acute glycemic instability and unrecognized chronic complications [8,13]. If this test is not performed in this consultation because the patient does not have criteria, it may be performed during hospitalization after hyperglycemia is observed [16].

In the consultation, instructions should also be given on the management of antidiabetic medication on the day of surgery and the night before, the control of perioperative dysglycemia and the likely effects of surgery on this glycemic control. Patients should also be advised of the possibility of changes in the days following the procedure [15]. Patients should be informed that smoking cessation is recommended and that, on the eve of surgery, they should maintain their usual diet [8,29]. According to the European Society of Anaesthesiology (ESA) [35], it is recommended that diabetics be without solid food intake within 6 hours prior to elective surgery (if the risk of aspiration is very high, the fasting period may be prolonged) [8]. They should also be advised to take their usual medication and therapy for hypoglycaemic seizures [22,23].

It is also important to assess the patient's ability to perceive and manage their own diabetes as this will guide the perioperative therapeutic targets and, if he is able to monitor glycemic levels and follow medication adjustment instructions, the glycemic targets are more easily reached [23,31]. The American College of Cardiology (ACC) and the American Heart Association (AHA) [36] also recommend the execution of an electrocardiogram (ECG) in all diabetics, except for procedures with low surgical risk. The fasting lipid profile, hepatic and renal function, and electrolytes (sodium, potassium) are also mandatory preoperative tests [29].

## Management of antidiabetic treatment

With proper guidance, diabetics should be allowed to maintain control and continue self-administration of their medication [15]. OADs have a slow onset and long duration of action and may lead to unexpected and drastic clinical variations in hospitalized patients [29]. Metformin is a renal excreted biguanide, that can cause hemodynamic instability and decrease in intraoperative renal perfusion, which also predisposes to lactic acidosis, being it classically recommended that it be discontinued within 24 to 48 hours prior to surgery or elective radiological procedure [8,37]. The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) [31] do not recommend its use in hospitalized patients because of the risk of renal damage, hemodynamic instability and possible need for contrast administration in procedures. However, some recent guidelines state that metformin can be safe and continued until the night before surgery if there is no altered renal function (glomerular filtration rate (GFR) <30 ml/min) or a significant risk of acute kidney injury (dehydration, procedures with risk of renal hypoperfusion and tissue hypoxia, use of contrast, etc.), where there is a need for close monitoring in the use of nephrotoxic drugs [1,15,16,22].

Due to the possibility of ketoacidosis in fasting diabetics on SGLT-2 inhibitors (dapaglifozin and canaglifozin), these drugs are suspended in the perioperative period [22].

Insulin secretagogues, such as sulfonylureas (glibenclamide, glimepiride, gliclazide and glipizide) and meglitinides (repaglinide and nateglinide), are usually withdrawn in the morning of surgery, due to the risk of hypoglycemia in fasting patients or with impaired renal function [8,15,16]. However, if the patient misuses sulphonylurea on the day of surgery, the procedure may still happen, with careful monitoring of blood glucose and need for glucose infusion if the patient is on an empty stomach [37]. Alpha-glucosidase inhibitors (acarbose, miglitol) decrease glucose absorption after meals, having no effect on preoperative fasting states, with its discontinuation being recommended until the patient returns to oral intake [37]. Thiazolidinediones (pioglitazone and rosiglitazone) are also discontinued on the day of surgery, as they may cause fluid retention in the postoperative period [37,38]. Injectable GLP-1 agonist OADs (exenatide and liraglutide) can be maintained on the day of surgery if necessary, as well as DPP-4 inhibitors (sitagliptin and linagliptin), as there is no risk of hypoglycemia even in fasted patients, however, this type of drug reduces postprandial blood glucose and its effects will be reduced in preoperative fasting patients, also causing gastroparesis, and are therefore often withdrawn on the day of surgery, with the safety and efficacy of its use in surgical patients still being studied [16,38].

Basal insulin (long duration) is generally used to maintain stable glycemic levels between meals and is not associated with hypoglycemia even during fasting [23]. Demma et al. [38], in a recent study with type 2 diabetics treated with glargine insulin once a day, concluded that the group that administered 60-87% of the normal dose of this insulin in the afternoon before surgery had the highest percentage of cases (78%) within the target range of glycemia values between 100 and 180 mg/dl (P<0.001) and a lower number of cases of hypoglycemia, compared to the group that did not administer insulin or that administered the normal dose. Thus, in order to avoid hyperglycemia and ketoacidosis, many guidelines, such as AACE/ADA[31], EndocrineSociety[39,40], SAMBA [23] and Joint British Diabetes Societies [34] recommend, even in euglycemic, the continuation of basal insulin (glargine or detemir) in the usual dosage (or 80% of the dose, if at risk of morning hypoglycaemia) in the night before surgery, or 75-100% of the dose (depending on the risk) if administered in the morning of the surgery [41].

For other types of insulin, guidelines recommend that patients, in the morning of the surgery, take 50-75% of the intermediate insulin dose (NPH), or the total dose if administered the night before (or 75%-80% of the dose, if risk of morning hypoglycaemia), and advise against the administration of fast-acting insulin in the morning of surgery [13,23,34,41]. SAMBA [23] warns that preoperative insulin management plans should take into account the level of glycemic control because, for example, patients with strict control, more unstable values or the use of complex insulin regimens, are at higher risk of hypoglycemia during fasting. These adjustments in medication should also take into account the fasting and surgery time and the expected time to start normal feeding after surgery [23].

In emergency surgeries, by definition, there is no opportunity for a plan to be performed, and modification of the patient's normal medication is only possible if the patient is physiologically well and the procedure is scheduled, as in minor trauma surgery [15]. In ambulatory surgery, OADs can be continued if the patient is controlled [13].

### Surgical admission plan

Diabetics should preferably be scheduled for the start of the surgical shift or as early as possible in order to minimize the fasting period and the risk of hypoglycaemia [15,28]. According to the Joint British Diabetes Societies [34], when possible, admission should be planned for the day of surgery if given all the information to the patient about the management to do in the ambulatory. Diabetics undergoing major surgery should be hospitalized the day before or when they start fasting, in order to initiate insulin infusion [29].

In diabetics, ambulatory surgery should be considered as it allows to reduce the risk of iatrogenic complications, however, these should be well controlled and able to manage their own diabetes, have easy access to emergency care if they need to, and surgery should be achievable in this context [1,29]. According to SAMBA [23], the decision to go through with ambulatory surgery in patients with poor glycemic control should be made together with the surgeon and should take into account the comorbidities and potential risks of surgery. These surgeries follow the protocols of minor surgeries [29]. Urgent surgeries follow the protocols of major surgeries [26].

### Preoperative evaluation

Preoperative urine collection II is recommended for the detection of asymptomatic urinary infections and proteinuria associated with acute postoperative renal failure in patients with risk factors (advanced age, type 1 DM, pre-existing renal disease, etc.) [29]. Adequate preoperative hydration (with water up to 2 hours prior to surgery) and initiation of fluid replacement on the morning of surgery (≥ 2 hours before induction) helps prevent postoperative dehydration [13,23].

If there are symptoms of dehydration, diabetic ketoacidosis or hyperosmolar hyperglycemic state, gasimetry and electrolytes should always be requested [8]. Diabetics undergoing emergency surgery are rarely well metabolically controlled, and the evaluation should include pH, creatinine and urea, and the volumetric status (hydration, blood pressure, urinary debit and capillary filling), in addition to glycemia and electrolytes, with potassium and acidosis alterations being the priority corrections [29].

### Blood glucose monitoring

Especially in patients undergoing long procedures and with a high metabolic impact, blood glucose levels should be monitored at admission in the preoperative area [8,16]. In insulin-dependent patients, frequent monitoring of blood glucose should be performed to ensure that the values are within the normal range, and glycemic analysis with test strip should be performed every 2 to 4 hours in all fasting patients [26,38].

### Hypoglycemia

Preventive measures of hypoglycemia include the identification of patients at increased risk (under intensive therapy, with oscillating glycemic profile or tight glycemic control, history of frequent hypoglycemia, and elderly patients as they are naturally less symptomatic), their monitoring and the appropriate preoperative changes in antidiabetic therapy [23,42]. Patients should be advised to carry a form of glucose that can be administered in the event of hypoglycemia during fasting and that does not lead to the cancelling of surgery, such as sugar-rich drinks [15,23]. ESA [35] defines safe administration of these beverages as up to 2 hours prior to elective surgery. However, researchers are always reluctant to give these formulations to diabetics due to possible effects on blood glucose and gastric emptying. Gustafsson et al. [42], in a study performed with diabetics, concluded that the intake of a carbohydrate-rich drink is safe, without risk of hyperglycemia and preoperative aspiration, when performed in the 180 minutes prior to anesthesia, since these patients did not show signs of delay in gastric emptying.

Glucose pills may also be used in case of hypoglycemia, although some anesthesiologists do not recommend its use within 6 hours prior to surgery [15,23]. Thus, if the patient presents with hypoglycemia in the last minutes before surgery, especially if type 1 diabetic, this should be corrected with 3-9 g of intravenous (IV) glucose, and surgery should proceed with regular monitoring of glycemia [16,29]. In case of severe hypoglycemia, elective surgery may have to be postponed [13].

### Hyperglycemia

Discontinuation of antidiabetic medication, inadequate long-term glycemic control, and preoperative response to stress may be the cause of preoperative hyperglycemia. This should be corrected before surgery with fast acting insulin (safer due to shorter duration of action) in sliding scale (supplemental or corrective insulin scheme based on a stratified adjustment scale), usually by subcutaneous administration, but it can be administered intravenously in case of more invasive procedures, and, if controllable, surgery should not be cancelled [8,23,29,38].

There is no consensus as to when surgery should not be performed due to hyperglycemia, but according to SAMBA and other recommendations, surgeries, except for life-threatening procedures, should be postponed for at least 12 hours in patients with compromised metabolic status (diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, severe dehydration, etc.), metabolic abnormality should be corrected and glycemia should be restored before surgery [16,23]. Thus, if glycemia>250-300 mg/dl, the presence of ketosis (ketonemia or significant ketonuria) and signs of hyperglycemic hyperosmolar state should be evaluated [15]. In case of glycemia <250-300 mg/dl and in the absence of findings of metabolic changes of this type, sliding-scale insulin infusion should be used and if levels drop as expected within one hour, insulin treatment continues and surgery can proceed normally [16]. Recommendations usually advise the postponement of non-urgent surgeries in case of persistent hyperglycemia above 300-500 mg/dl, there being no sufficient evidence to suggest a specific cut-off [16,37,43,44]. As diabetics tend to maintain an increase in perioperative morbidity and mortality, their identification in the surgical setting is imperative, however, about one-third remain undiagnosed and untreated prior to surgery, being detected only upon admission [13,37]. In the presence of hyperglycemia without previous diagnosis of DM, this may be due to hyperglycemia of stress, and the determination of HbA1c may allow to make this distinction [31].

### Management of the continuous subcutaneous insulin infusion system

The use of insulin infusion pumps (fast acting insulin in continuous infusion and administration of bolus at meals) has increased in recent years, mainly in type 1 DM, and hence the importance of a better knowledge about its perioperative approach [8]. The use of an infusion pump has been demonstrated to be successful in the control of diabetes in hospital context [45,46]. Corney et al. [46], carried out an investigation with ambulatory controlled diabetics with continuous insulin infusion pumps, which were grouped according to the intraoperative insulin infusion method and which revealed that the group that suspended the infusion pump experienced a higher percentage of intraoperative blood glucose ≥ 179 mg/dl (84.2%). There was no significant difference in mean intraoperative blood glucose between the infusion pump group and the IV infusion group (P=0.128).

Thus, the authors indicate that in minor elective procedures, especially shorter procedures (<2 hours) and/or with short fasting period, the patient can maintain insulin therapy by this administration route. In high-risk surgeries (urgent or with a long fasting period), the IV infusion regimen will be immediately established [8,22]. In addition, if the site of administration to the skin may prevent the surgical approach, discontinuation of this system and preoperative implementation of an alternative administration (subcutaneous or IV) is advised [8]. In preparing for surgery, it is recommended to optimize the basal insulin dose in order to maintain stable fasting blood glucose values, to change the infusion system, to test its function the day before surgery, and to place the catheter far from the surgical field. On the day of surgery, this baseline rate should be maintained, and if there was no appropriate dose adjustment, the flow rate could be reduced by 20% to avoid hypoglycaemia [22,23]. A specialist in this area should be involved in these decisions to assist in the evaluation and management of these infusion pumps [40,47].

### Musculoskeletal system

Standard airway assessment techniques are appropriate in DM but do not identify all difficulties in intubation, and it is advisable to use the prayer sign (both hands together and with the palms facing, being positive when there is an inability to approach them) to identify, in patients with long-term DM, the existence of diabetic cheiroarthropathy and the difficulty of intubation, placement of venous access and positioning of the patient [8,13]. Kundra et al. [48], to evaluate the perioperative morbidity associated with the positivity of this test, carried out a recent study with 501 diabetics that showed that in the group with positive prayer sign the average hours of ventilation was superior in relation to the negative test group (9.52 ± 6.46 h vs. 7.42 ± 8.01 h, respectively, P=0.013) and that the mean length of hospital stay was also higher (8.22 ± 1.35 vs. 7.43 ± 1.18 days, P<0.0001).

### Renal system

Preoperative assessment of the albumin-creatinine ratio and glomerular filtration rate is essential in major surgery, emergencies or if the patient presents with poor glycemic control. In the presence of chronic diabetic renal disease, it is necessary to avoid the perioperative administration of nephrotoxic agents and hemodynamically optimize the patient for blood pressure averaging between 60-70 mmHg in order to maintain renal perfusion [49,50].

### Neurological system

The evaluation of the existence of autonomic cardiac dysfunction involves simple tests using the Valsalva maneuver and evaluation of changes in heart rate and blood pressure when moving from supine position to sitting or in response to deep breathing. These tests allow assessing the degree of neuropathy and are usually performed together with a simple ECG. If neuropathy is diagnosed (confirmation by two abnormal tests or presence of symptoms), drugs that induce orthostatic hypotension should be avoided and the QT interval should be evaluated [51,52]. Gastroparesis, with delay in emptying and gastric dilation, is characteristic of the autonomic gastrointestinal neuropathy and a risk factor for aspiration and consequent chemical pneumonitis, bacterial contamination and infection. During the anesthetic consultation, the patient should be questioned about classic clinical manifestations (anorexia, nausea, vomiting, abdominal pain, feeling of premature infarction, etc.), and if clinically suggestive, gastric antrum should be measured and residue should be identified by ultrasound. Some recommendations to reduce the risk of regurgitation and aspiration during induction of anesthesia include avoiding solid food intake and promoting gastric emptying in the preoperative period with a prokinetic such as metoclopramide or erythromycin [8,13].

The assessment of autonomic genitourinary function, and particularly bladder dysfunction, should be performed in any diabetic with recurrent urinary tract infections, pyelonephritis, incontinence or a palpable bladder, and should include renal function, uroculture, ultrasound, and more invasive exams if necessary [11]. In diabetic patients submitted to local-regional techniques, it is prudent to evaluate the extent of autonomic, motor and sensory neuropathy, since this may aggravate the hypotension associated with neuroaxial blocks [29].

### Cardiovascular system

A preoperative cardiovascular assessment should be performed with blood pressure and heart rate measurements, search for signs and symptoms of heart failure, cerebrovascular and peripheral vascular disease, as well as the presence of signs of diabetic foot and peripheral neuropathy [8]. Joint British Diabetes Societies [34] recommend pressure relief in case of high-risk feet and avoidance of anti-embolism stockings in case of vascular disease or peripheral neuropathy. According to the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) [53], the evaluation of heart disease with more specific and/or more invasive examinations should be performed only in patients at high cardiovascular risk (with macroproteinuria, renal failure, arterial disease, etc.). Patient positioning should also be slow and controlled to avoid a sudden drop in blood pressure [11].

## Intraoperative

The intraoperative period begins when the patient enters the operating room and continues until he is transferred to the recovery room [1]. The objective of intraoperative care is to maintain a good glycemic control and a normal concentration of electrolytes, while also optimizing cardiovascular function and renal perfusion [15].

### Glycemic control

Clinicians should take into account the time taken to complete the procedure when determining the intraoperative glycemic control strategy [38]. Given the action profile and the multiple contraindications to the in-hospital use of OADs, insulin therapy with continuous infusion or bolus is the correct option for the perioperative control of glycemia in diabetics, and some studies even consider that it has other therapeutic properties (anti-inflammatory, vasodilator, protective of ischemic lesions, etc.) [29]. As subcutaneous insulin, if used in these cases, may be associated with a decrease in its absorption in case of hypothermia or peripheral vasoconstriction, undergoing major surgery (with prolonged fasting period, long duration of surgery, periods of inadequate tissue perfusion and/or emergency surgeries), glycemia should be controlled through IV infusion of insulin (regular insulin diluted in a saline solution), which should be started preoperatively if possible [1,29,38]. This IV regular insulin remains physiologically active for approximately one hour but has a half-life of 7 minutes, which allows for an adequate glycemic control, countering unexpected changes in blood glucose [38].

Typically, in DM type 1, lower insulin doses are required compared to insulin-treated type 2 DM, in order to obtain adequate glycemic control [2]. Thus, in type 1 diabetics, the rate of insulin infusion starts at about 0.5-1 U/hour, while the infusion rate typically increases in type 2 DM or poorly controlled diabetics, from 1-2 U/h up to about 2-3 U/hour or more. However, there are several algorithms that can be used to adjust the rate of insulin infusion [22,37], with insulin requirements being generally much higher, for example, in cardiac procedures [37]. Sliding-scale subcutaneous insulin, used for hyperglycemia, should not be used as monotherapy in the perioperative management of DM, because of the high risk of hypoglycemia and inferior glycemic control [1,54].

According to the Joint British Diabetes Societies [34], if the fasting period is short, and the patient is controlled and able to manage diabetes after surgery, a correct modification and manipulation of the antidiabetic medication may be sufficient to allow glycemic control in elective surgery, with no need for insulin infusion. Thus, in minor surgery (short surgery, for example), if preoperatively controlled (fasting glycemia<180 mg/dl), they take intraoperative rapid correction insulin only if necessary, IV in bolus or subcutaneous. If uncontrolled, they should also initiate IV infusion of insulin [1,22,29].

Fluid and electrolyte management

Adequate intraoperative administration of crystalloids (assuming no contraindications, such as congestive heart failure) helps prevent postoperative dehydration [23]. During surgery, the replacement fluids should not contain glucose unless there is low blood glucose, as the tendency is for hyperglycemia. However, it is important to avoid hyperchloremic metabolic acidosis, being it advisable do administrate, at 100-125 ml/hr, Hartmann's solution (Ringer's lactate) or other isotonic crystalloid solution (0.9% NaCl, for example) in order to optimize intravascular volume [15,22]. Hartmann's solutions are recognized as safe in administration to diabetics and do not contribute to clinically significant hyperglycemia [55].

However, if prolonged fasting is predicted and if patients are taking IV insulin infusions, 5-10% glycated sera should be given at 100-125 ml/h to avoid catabolism, hunger ketosis and hypoglycemia [29]. Administration of electrolytes may also be necessary, especially to avoid insulin-induced hypokalemia, and potassium should be evaluated every 4 hours in the perioperative period (or every 1 hour if there are changes in insulin flow), and if necessary, KCL may be administered with electrocardiographic monitoring [13,26]. In addition, there is a continuous Glucose-Insulin-Potassium (GIK) infusion technique, which has been supported as inotropic and metabolic therapy in severe critical disease states, and as an alternative to the IV infusion regimen of insulin [56]. However, this method is not authorized for individual manipulation of glucose or insulin levels and is best suited for maintenance of glycemia after reaching a specific target, with the use of IV insulin infusion having more advantages (such as flexibility in independent adjustment), and therefore GIK is usually used when the IV insulin infusion technique is not possible [34,37].

## Target glycemic range

The management of perioperative glucose levels revolves around a few goals: to reduce morbidity and mortality, to avoid severe hypo and hyperglycemia, to maintain fluid and electrolyte balance, to prevent ketoacidosis, and to establish safe glycemic targets [38].

However, there is controversy regarding the target glycemic range to be achieved during the intraoperative period. Early studies in this area suggested that intensive glycemic control (80-110 mg/dl) had a positive prognostic impact, but there is currently evidence that it should not be widely recommended [22,57]. According to the ADA's most current recommendations [58], the glycemic target should be between 80-180 mg/dl and more specifically <180 mg/dl in the critical patient and <140 mg/dl in the stable patient [31]. However, this value should take into account several factors such as the duration and degree of surgical invasion, the type of anesthesia and the predicted time of fasting and resumption of antidiabetic medication. In patients with a history of poor metabolic control, SAMBA [23] recommends maintenance of preoperative baseline values instead of attempting to normalize blood glucose levels because they have symptoms of hypoglycemia at normal blood glucose levels, mainly if type 2 diabetics.

## Blood glucose monitoring

Adequate blood glucose monitoring is critical in maintaining patient safety, facilitates insulin titration, and allows the early detection of hypoglycemia [23]. Blood glucose measurements should ideally be performed using arterial and venous blood instead of capillary blood and point-of-care devices (POCs), as these may show results altered by poor peripheral perfusion, hypovolemia, shock, hypothermia and/or acid-base disorders [8,13]. Several studies recommend against the use of POC in the perioperative period and the preferential use of glycemic measurements through central-laboratory devices (CL), since the latter have better accuracy [59,60]. Thus, the use of POC may not be appropriate in patients undergoing major surgery [8], however, in physiologically stable patients, they correlate well with laboratory values [61] and therefore, in general, during surgery, glycemic levels are monitored through POC (test strip for measurement of capillary glycemia, for example) with demonstrated hospital accuracy [37]. However, POCs also tend to overestimate glycemic values during periods of hypoglycemia compared to laboratory values, and values <70 mg/dl should be an alert [23].

The guidelines recommend that blood glucose be monitored intraoperatively every hour (or every 2 hours in stable patients) during major surgery or minor surgery in poorly controlled insulin takers, and at least once in minor surgery [13,29]. It should be monitored more frequently in emergency surgeries or if the values are outside the target range or suffer a sharp variation (for example, every 15-30 minutes if there is hypoglycemia or changes in the rate of insulin infusion) [13,37]. It should also be evaluated before induction of anesthesia [15].

## Hypoglycemia

Hypoglycemia is more likely in the intraoperative period due to fasting, and during anesthesia it may not be recognized, which explains the need for frequent monitoring and its early detection [16]. If glycemia ≤ 70 mg/dl, the IV infusion of insulin should be discontinued and reevaluated within 5-10 minutes and if it persists initiate 3-9 g of IV hypertonic glucose and evaluate glycemia 15-20 minutes later. The guidelines state that insulin infusion can be resumed at a lower rate of perfusion when glycemia>100 mg/dl in two consecutive measurements [16,22,29].

## Hyperglycemia

In case of intraoperative hyperglycemia (≥ 180 mg/dl) in minor surgical procedures (ambulatory or short), it should be corrected with sliding-scale insulin, preferably subcutaneously (for ease and efficacy in the correction), and in major surgeries by increasing the IV infusion rate. If two doses of subcutaneous insulin do not allow reaching the target glycemic range, IV infusion should also be initiated, since repeated doses of subcutaneous insulin are associated with the risk of insulin stacking and consequent hypoglycaemia [15,16,23,40]. In diabetics, fast-acting subcutaneous insulin should be given up to a maximum of 6 U [15,16]. This administration is done according to sliding-scale protocols, assuming that 1 U should lower about 50 mg/dl of glucose, or according to the patient's insulin sensitivity factor (ISF=1800/total daily insulin dose; corrective insulin=(glycemia-130)/ISF), being careful not to administer the new dose until the peak of action of the previous dose has passed (about 2-4 h) so that hypoglycaemia does not occur [1,22].

## Management of the continuous subcutaneous insulin infusion system

In the operative room, the anesthesia team assumes responsibility for the infusion pump, and must control the connection with the device [1,22]. Blood glucose should be checked every hour and, if necessary, corrective insulin should be given. However, if uncontrolled hyperglycemia, it may be necessary to convert to IV insulin infusion [1,22]. In case of hypoglycemia, an infusion of glucose should be administered, and if this persists, the switch should be made to infusion of IV insulin with glycated serum [1].

## Type of anesthesia

It is crucial that the anesthetic technique used allows a rapid post-surgical recovery in order to prevent hypo or hyperglycemic coma, and the selection should be made based on the coexistence of other diseases [37]. Most IV induction anesthetics have an insignificant effect on blood glucose, with the exception of the inducing agent Etomidate, which is known to cause less hypotension and fewer hangover-like effects in the recovery and which, by suppressing cortisol secretion, also leads to a decrease in glycemic response to surgery. If used at high doses during surgery, benzodiazepines decrease ACTH secretion, stimulate growth hormone secretion, and also reduce sympathetic stimulation. On the other hand, volatile anesthetic agents, such as halothane and isoflurane, inhibit the normal insulin production triggered in a dose-dependent manner by glycemia, resulting in a hyperglycemic response [37].

Thus, the type of anesthesia influences the hyperglycemic response during surgery. While the most commonly used anesthetic agents cause hyperglycemia, epidural or local anesthesia tends to have a nominal effect on glucose metabolism by inhibiting the release of catecholamines, preventing glycemia elevation, and allowing sympathetic efferent blockade, attenuating the normal hyperglycemic response to surgical stress [37]. Li et al. [61], in a recent meta-analysis, showed that, compared to general anesthesia, the combination of general and epidural anesthesia was associated with better intraoperative glycemic control, and one of the studies showed that it could even decrease glycemic values.

In general, the response to neuromuscular blocking agents is normal in diabetics, but in patients with neuropathies or irregular transmission through the neuromuscular junction, hemodynamic instability due to severe hypotension (the same effect as is induced by general anesthesia) and possible increase of the risk of neuropathy after peripheral nerve block may occur [11,37], and these patients should always be examined for signs of existing polyneuropathy [13]. However, loco-regional techniques are not contraindicated in diabetics and have some advantages, such as avoiding orotracheal intubation (which may be difficult), allowing the evaluation of the central effects of hypoglycemia and the recovery of oral intake earlier by decreasing nausea and vomiting [29].

## Renal system

In the presence of chronic diabetic renal disease, hemodynamic monitoring is recommended to evaluate the volume and guide the need for vascular filling and administration of vasopressors in case of risk of instability (surgical hemorrhage, for example) [50]. The administration of anesthetic agents should also take into account the pharmacokinetic and pharmacodynamic changes resulting from this chronic renal failure [13].

## Neurological system

The hemodynamic response to intubation is altered in diabetics with autonomic neuropathy, and therefore, must be executed with careful monitoring, titrated anesthesia and minimal manipulation of the airway [11]. In patients with a high risk of gastroparesis and consequent aspiration, it is important to consider the use of a rapid-sequence intubation [62,63].

## Cardiovascular system

In diabetics with autonomic cardiac neuropathy, hemodynamic status influences the titration of anesthesia, requiring continuous monitoring of blood pressure and heart rate, electrocardiogram to identify rhythm disturbances and ischemic changes, and central venous pressure to assess volume. In these patients with autonomic neuropathy and cardiovascular instability, but subject to neuraxial central anesthesia, ultrasound-guided nerve block is safer [11].

## Postoperative

**Resumption of food intake:** Diabetics undergoing major surgery resume oral ingestion more than 4 hours after surgery, and those undergoing minor surgery less than 4 hours after surgery [29]. If the patient is unable to tolerate oral nutrition for a long period of time, total parenteral nutrition should be considered, and enteral nutrition should be resumed as soon as possible as it has a lower infection rate, lower cost, earlier restoration of normal bowel function and reduced hospitalization time [64]. However, in patients treated with intra-operative IV insulin, it will be more advisable to continue the infusion of insulin together with an infusion of glucose until they are able to tolerate oral feeding [37].

**Control of pain, nausea and vomiting:** According to the Association of Anaesthetists of Great Britain and Ireland [15], post-operative multimodal analgesia should be used along with appropriate antiemetic prophylaxis to allow an early return to normal diet and antidiabetic regimen, promoting a more precocious hospital discharge.

One of the most important and validated antiemetics for perioperative use is dexamethasone, which increases the risk of hyperglycemia, and at the dose of 4 mg is considered more antiemetic than at the dose of 8 mg, being it recommended to use the first dose in combination with another antiemetic such as droperidol or a 5-HT3 antagonist [8,13,23]. Glycemic measurement should be ensured every hour, up to 4 hours after dexamethasone administration, and corrected for hyperglycemia if necessary [15].

Poorly controlled pain is also a risk factor for hyperglycemia, especially in uncontrolled diabetics, with common analgesics not affecting glycemic control and able to be used without modifying the indication or dose. The use of local anesthesia is also associated with better postoperative pain control, although the interference of hyperglycemia in the immune system also makes postoperative epidural abscesses more likely [13,29].

**Blood glucose monitoring:** Shortly after surgery, capillary glycemia should always be evaluated [16,22]. In major surgeries, blood glucose should continue to be monitored hourly until 4 hours postoperatively, every 2 hours thereafter, and after stabilization, it may be changed to intervals of 4-6 hours [16,29]. In subjects undergoing minor surgery, it should be monitored at the end of the fast or 4 hours after surgery [29].

**Target glycemic range:** According to the guidelines, the postoperative target glycemic range is 140-180 mg/dl [37]. However, if patients are monitored in an ICU after surgery due to surgical complications or comorbidities, the hyperglycemic response to stress (mean blood glucose of 180-220 mg/dl) should be taken into account and a strategy with more tolerant glycemic management should be developed [65].

**Hypoglycemia:** The risk of hypoglycemia remains up to 3-4 hours after the last regular insulin dose and up to 1.5 hours after the last rapid insulin dose, and its occurrence should be monitored (glycemic values and suggestive symptoms) [13,42]. When capillary glycemia ≤ 70 mg/dl and there is no contraindication for oral feeding, the patient should ingest about 15g of sugar (in a glass of water or through a juice, for example) and measure glucose 15 minutes later, repeat if levels remain low and, if necessary, IV hypertonic glucose may be administered [16,22]. If glycemic levels are low and oral feeding is not indicated or the patient is unconscious, IV infusion of glucose or administration of subcutaneous glucagon (if there is no IV access) should be done immediately [23,37].

**Hyperglycemia:** Due to the stress associated with surgery, postoperative complications and the side effects of anesthesia, there is usually an elevation of glycemia and difficult glycemic control in the postoperative period [8,37]. If blood glucose>180 mg/dl, corrective insulin should be administered [16]. If glycemia>250-300 mg/dl in patients treated with insulin, the presence of ketosis should be investigated and, if present, hydration and rapid insulin analogue should be rapidly initiated. If present in type 2 diabetics, electrolytes should be dosed to confirm the presence of hyperosmolar syndrome and refer to the intensive care unit (ICU) [13].

Management of antidiabetic treatment: When the patient is able to safely resume food intake without nausea or vomiting, the infusion of IV insulin may be terminated and the glycemic control procedures applied before surgery may be restored, being it possible that they have to be adjusted as a result of stress or altered caloric intake [37].

The basal-bolus scheme is the most adequate and safe for the postoperative period [13,66]. The literature recommends that the transition from IV to subcutaneous insulin occurs early (after the patient has stable glycemia and without vasopressor drugs) and with overlapping of the two types of insulin, to assure a basal insulin concentration in type 1 diabetic, preventing ketoacidosis, and to increase glycemic control in type 2 diabetics [37,38]. An insulin-dependent diabetic should continue IV infusion of insulin at least 30 to 60 minutes after the first dose of fast acting subcutaneous insulin (administered with a meal) [1,15], and at least 2 to 4 hours after the administration of long-acting insulin (if it had been stopped) [16]. In this transition, the subcutaneous basal insulin dose corresponds to approximately 50-80% of the total dose of IV insulin administered within 24 hours of intraoperative [29,38,67]. Postprandial insulin requirements for rapid insulin bolus should be assessed according to how the patient is being nourished [37]. The recommendations of ADA and AACE [31] are that, of the total subcutaneous dose (80% of IV dose of insulin), 70% is given as baseline and 30% as a prandial dose in the postoperative period. In type 2 diabetics or non-diabetic patients, whose blood glucose levels were controlled with low insulin infusions (≤ 2 U/h), no transition is needed, with just adequate glycemic monitoring and subcutaneous insulin correction boluses being maintained if necessary. Type 2 diabetics treated with insulin also initiate the usual prescription of insulin when they resume oral intake [16,21].

If IV infusion of insulin was given in a short period of time, to a patient not previously treated with insulin, but postoperative glycemic levels remain high, it is correct to initiate insulin at the daily dose of 0.5-1 U/kg (50% long action and 50% fast analogue) [13]. Concerning OADs, the guidelines advise the commencement of preoperative doses at the beginning of food intake (since most of the hypoglycemic agents act after food intake), and it may be necessary to reduce or delay the intake of sulfonylureas if food intake is likely to be reduced [15,23]. The exception is metformin, which, when there is suspicion of renal hypoperfusion or 24 hours after major surgery, is resumed only after evaluation of renal function and verification of a GFR>60 ml/min, provided there is no risk of metabolic acidosis [29,68]. Documentation of adequate renal function is also required in the resumption of SGLT-2 inhibitors if renal dysfunction is suspected [22].

In the case of diabetics without previous diagnosis, the possibility of initiation of OAD and dietary recommendations is advised, and a consultation for primary health care should be scheduled within 1 month [13]. Decisions regarding the ambulatory DM treatment regimen should be based on renal function, dietary intake, general functional status and type of surgical procedure performed [8], and the patient should be involved in this planning of postoperative care [15].

**Management of the continuous subcutaneous insulin infusion system:** If the patient maintained the system intraoperatively, in the postoperative period he should start prandial bolus according to the usual scheme, once he starts oral ingestion [22]. If it has not been maintained, the pump must be reconnected if the patient is able to handle it independently. If the patient is not autonomous, it is mandatory to start a bolus-basal scheme with subcutaneous insulin [13].

**Pre-discharge evaluation:** Before discharge, the capillary glycemia should be checked [22,23]. If glycemia ≤ 180 mg/dl, ambulatory medication can be resumed and the patient can be discharged; if glycemia>180 mg/dl, rapid insulin bolus should be given and discharge should be postponed until stabilization; and if glycemia>300 mg/dl, discharge is contraindicated and the patient is admitted for IV infusion of insulin [13]. Discharge should not be delayed only because of poor glycemic control and consideration should be given to the patient's ability to manage diabetes at home, being it advisable for care teams to educate the diabetic patient [34].

Some studies and recommendations are in favor of using the HbA1c value to guide the treatment regimen at discharge, and patients with an acceptable glycemic control (HbA1c < 7-8%) can be maintained with pre-hospitalization treatment, if there are no contraindications, and patients with suboptimal control should intensify therapy (add and/or increase OADs and/or basal insulin) [16]. The need for ambulatory support and involvement of the primary care team in the discharge planning should be assessed [34].

### Neurological system

Orthostatic hypotension may be precipitated postoperatively, being it mandatory to do continuous monitoring of blood pressure, oxygen supplementation and adequate analgesia within 24 hours after any intervention [11].

## Discussion

The combination of an increased incidence of the disease and an inadequate perioperative approach to diabetes has led to an increased rate of surgical complications, mortality, and treatment costs [1].

It is commonly reported that perioperative glycemic control contributes to reducing the morbidity and mortality of diabetics [22]. In fact, there appears to be a correlation between glycemia and postoperative morbidity and mortality, with glycemia levels <180 mg/dl usually associated with a lower risk of poor surgical outcomes [13]. Several studies have even shown that the risk of complications and mortality is related to the severity of hyperglycemia, with increased risk even in non-diabetic patients [69,70].

Abdelmalak et al. [70] demonstrated that preoperative glycemia is associated with mortality in the first year (P<0.001). Frisch et al. [68] also concluded that the risk of death increases in proportion to perioperative glucose levels (P=0.008) and that perioperative hyperglycemia is associated with an increase in length of hospital stay (P=0.001), a greater number of postoperative cases of pneumonia, systemic and urinary tract infection (P=0.001), acute renal failure and acute myocardial infarction (P=0.005). McConnell et al. [71] Also concluded that postoperative hyperglycemia is associated with a higher percentage of surgical site infection. More recently, Kotagal et al. [69] also reported a dose-response relationship between glycemic levels and compound adverse events, especially in diabetics. Kwon et al. [72] identified a dose-effect relationship between the efficacy of glycemic control with insulin and prognosis, and concluded that assessment of perioperative glycemia and insulin administration in hyperglycemia are important goals.

Thus, the prognostic impact of this hyperglycemia justifies its early detection through regular glycemic measurements and its correction, especially in patients at high surgical risk [13].

Further to this, several studies have also shown the relationship between high values of preoperative HbA1c and surgical outcomes. A recent study by Narayan et al. [73] showed that an HbA1c ≥ 6.5% was associated with a significant increase in the incidence of deep sternal wound infection (P=0.04) and respiratory complications (P=0.01) in patients undergoing coronary bypass. Kallio et al. [74] also had similar conclusions, showing an increase in the rate of complications and a prolongation of hospitalization in patients with uncontrolled DM and HbA1c (P<0.001), being there a progressive decrease in complications with tighter control of Hb1Ac. In other studies, preoperative values of HbA1c ≥ 6.5% are also associated with a postoperative glycemic variability, an increase in major adverse events [75,76] and a decrease in intraoperative insulin sensitivity [77-79].

Thus, glycemic control has been increasingly recognized as a perioperative goal in surgical patients [37], and it is advisable to postpone elective surgeries when the value of glycemia and HbA1c is very high [13]. However, there is no consensus regarding the optimal HbA1c concentration, nor sufficient evidence to recommend the postponement of elective surgeries from a specific value of HbA1c or fasting glycemia [16,23].

The literature supports the prevention of hyperglycemia and also hypoglycemia, but the ideal range between these two points remains equally undetermined [13] and several studies evaluating tight perioperative glycemic control have had inconsistent results [23].

In general, it is currently accepted that perioperative normoglycemia (80-120 mg/dl), like hyperglycemia, increases morbidity and mortality by increasing the rate of hypoglycemia, and that moderate perioperative glycemic control (140-180 mg/dl) is the one with better results (although it requires complex insulin protocols that are difficult to implement) [13].

Bhamidipati et al. [77] showed that moderate glucose (127-179 mg/dl) was associated with lower mortality (P=0.02) and lower incidence of major complications (P < 0.001), similar to Duncan et al. [78] who have shown that blood glucose levels between 140 and 170 mg/dl are associated with a decreased risk of adverse events. In a study conducted in an ICU by Finfer et al. [80] it was also shown that intensive glycemic control (target range 81 to 108 mg/dl) increased cardiovascular mortality (P=0.02) and the number of hypoglycemic seizures (P < 0.001), while target values ≤ 180 mg/dl resulted in a decrease in mortality. Another study conducted in an ICU [81] and another meta-analysis [82] also concluded that strict glycemic control was associated with a much higher risk of hypoglycemia with no improvement in mortality.

Thus, AACE and ADA [31] now advise less aggressive therapy for blood glucose targets between 140-180 mg/dl, contrary to previous recommendations. The Society of Critical Care Medicine [83] also places 150 mg/dl as a glycemic target in all non-cardiac patients, and values <180 mg/dl are accepted by some authors [34,40].

Likewise, the optimal and best glycemic management strategy remains undetermined, and there is no consensus regarding how hyperglycemia should be controlled in surgical patients, being there no sufficient evidence in the literature to guide the use of insulin in an insulin-dependent patient, and a lack of cut-off values [23,26]. For example, in 2009 the Society of Thoracic Surgeons guidelines [84] recommended the use of insulin infusion for hyperglycemia>180 mg/dl, whereas in 2012 the Critical Care Society reported that patients with blood glucose>150 mg/dl should be treated to keep values below this [83].

There is also insufficient evidence on the preoperative management of OADs and insulin [23]. It is recognized that various recommendations offer a large number of different preoperative instructions regarding antidiabetic medication in the day before and in the day of surgery, and the fear of hypoglycemia often leads to inappropriate practices of stopping all medication in diabetics [16]. For example, it has been recommended that OADs be discontinued the day before surgery because of the risk of hypoglycemia and other complications [23,40], but, on the other hand, for example, the Joint British Diabetes Societies [34] state that metformin may be maintained on the day of surgery if there is no renal injury and the Society for Ambulatory Anesthesia [23] states that metformin should be taken the day before but not on the day of surgery.

Given this, according to SAMBA [23], there are many areas that require future studies and for which the current information is insufficient and conflicting, being it necessary to develop adequate and well-designed studies to make safer and more universal recommendations.

Overall, with the use of careful glycemic management strategies, surgical outcomes are similar in diabetics and non-diabetics [37]. Therefore, according to Monteiro et al. [22], the implementation of institutional protocols that promote adequate preoperative assessment, the selection of safe glycemic targets and the minimization of risk factors for postoperative complications, improve the prognosis of these patients.

In this context, Udovcic et al. [85] revealed in an investigation that, after the introduction of guidelines, there was in fact an increase in the pre-operative ($P<0.01$) and intraoperative ($P<0.01$) glycemic monitoring, increased use of insulin during the whole perioperative period ($P<0.01$) and significantly lower pre and postoperative glycemic mean values ($P<0.01$). A similar study by Shah et al. [84], also showed that the Hb1Ac value was measured in a higher percentage in a group evaluated after the implementation of guidelines ($P<0.01$), as well as pre and intraoperative blood glucose monitoring ($P<0.001$), and an increase in the use of perioperative insulin ($P \leq 0.04$) as well as lower pre and postoperative blood glucose mean levels ($P<0.01$) were also observed. McCavert et al. [86] also demonstrated that glycemic optimization, based on the use of a hospital protocol, was associated with a 25.4% reduction in perioperative complications, and the authors recommended the use of pre-defined guidelines in all diabetics.

That being said, it is urgent to elaborate proposals of new protocols, to evaluate them and to implement them in all hospital institutions, as well as reevaluating them periodically [29].

Finally, another main problem is that the prevalence of undiagnosed DM, mainly type 2 DM (usually asymptomatic), and is high in hospitalized patients [13]. A study by Abdelmalak et al. [87] showed that, of the 33923 surgical patients analyzed and known as non-diabetic, 10% were undiagnosed diabetics and 11% had pre-diabetes. Sheehy et al. had similar results, having concluded that undiagnosed DM and pre-diabetes are common. That is why correct preoperative evaluation is equally essential in these patients [88].

## Key Learning Points

### Preoperative

- The authors recommend a preoperative anesthetic evaluation with medical optimization, risk stratification and an adapted surgical plan.
- Discontinuation of OADs and fast-acting insulin on the day of surgery is generally advised, and basal and intermediate insulins are usually continued.
- It is essential to identify all diabetics and prioritize them in the list of surgeries, minimizing the fasting time to about 6 hours.
- The authors stress the need for frequent glycemic monitoring to ensure that glycemia is in the target range.
- According to the guidelines, hyperglycemia should be corrected with sliding scale fast acting insulin, and hypoglycemia with sugar-rich drinks, glucose tablets or IV glucose, depending on the time remaining for surgery.
- Cancellation of non-urgent procedures should be considered if patients exhibit metabolic abnormalities (ketoacidosis, hyperosmolar hyperglycemic syndrome or dehydration), glycemic measurements above 300-500 mg/dl, and/or HbA1c ≥ 8.5-9% or <5%.
- In the preparation of the diabetic it is also advised to do prayer sign evaluation (to identify difficulty in intubation), cardiovascular evaluation, hemodynamic optimization when there is risk of renal dysfunction, and the promotion of gastric emptying with metoclopramide or erythromycin in case of autonomic gastrointestinal disfunction.

### Intraoperative

- The authors recommend the use of IV infusion of regular insulin for glycemic control in major surgeries, and the use of corrective rapid insulin (IV or subcutaneous), if necessary, in minor surgery.
- Fluid replacement should be done with Hartmann's solutions, but in the case of prolonged fasting and/or IV insulin infusion, 5-10% glycosated sera should be given.
- The guidelines advise blood glucose monitoring every hour (or every 2 hours if patients are stable) and more often when values are outside the target range or suffer variations.
- According to the most current recommendations, the glycemic target should be between 80-180 mg/dl.
- In case of hyperglycemia, in minor surgery it is described that this should be corrected with sliding-scale rapid subcutaneous insulin (up to a maximum of 6 U) and in major surgeries by increasing the IV infusion rate; if hypoglycemia is suspected, IV infusion of insulin should be suspended and, if necessary, hypertonic glucose IV should be initiated.
- Loco-regional techniques, although they may be associated with hemodynamic instability in patients with neuropathy, appear to have advantages over general anesthesia, such as a lower risk of hyperglycemia.
- In patients at high risk for gastroparesis and consequent aspiration, it is important to consider the use of a rapid-sequence intubation.

### Postoperative

- Early return to oral nutrition is recommended (more than 4 hours after major surgery and less than 4 hours after minor surgery).
- Multimodal analgesia and antiemetic prophylaxis are also advised to allow a rapid return to a normal dietary and therapeutic routine, as well as an earlier hospital discharge.
- According to the guidelines, the target glycemic range in this period is 140-180 mg/dl.
- When the patient is able to safely resume food intake, the OADs and insulin can be restored, with the basal-bolus insulin regimen being the most appropriate and there being a need for continuation of IV perfusion (at least 30-60 minutes), in the transition to subcutaneous

insulin, after the first dose of rapid insulin to ensure a basal insulin dose.

- In the event of hypoglycemia and if there is no contraindication to oral feeding, the patient should ingest sugar or, if necessary, hypertonic IV glucose should be administered; if oral feeding is not indicated or the patient is unconscious, IV infusion of glucose or administration of glucagon are advised.
- In case of hyperglycemia, supplemental corrective insulin can be used to restore glycemic values according to the target range.
- Before discharge, capillary blood glucose should be checked and the HbA1c value should be used to determine whether pre-hospitalization treatment should be maintained or whether it should be intensified.

## Conclusion

DM is a constantly growing public health problem and is therefore also very common in surgical patients. However, both diagnosed and undiagnosed DM, negatively affect surgical outcomes. In this group of patients, the main objective of the perioperative period is to prevent dysglycemia. For this purpose, it has been recommended, in the preoperative period, to do medical optimization and risk stratification, with the execution of a surgical plan appropriate to the patient; in the intraoperative period, the use of IV insulin infusion and frequent glycemic monitoring with correction of hyper and hypoglycemia, in order to maintain glycemic targets of 80-180 mg/dl; and in the postoperative period, an early return to oral nutrition and to the initial therapeutic regimen of the diabetic, as well as a pre-discharge therapeutic optimization.

However, this review shows that there are still controversies in this subject and a great shortage of studies that support specific measures and establish universal cut-offs in these so demanding patients from a surgical point of view. Therefore, although no single scenario describes what to do with diabetics undergoing surgery, this review leads to the belief that there should be clearer and more appropriate guidelines regarding the perioperative approach and the control of hyperglycemia from preoperative to postoperative, with attention to the specific needs of these patients, based on better evidence and carried out by multidisciplinary teams. This would not only allow minimizing perioperative complications, promoting better glycemic control and avoiding cancellation of surgeries, but also decrease the percentage of undiagnosed DM.

With this review, it is also concluded that it is increasingly important that patients with DM have more and better capacity to manage their own disease, so as to facilitate their optimization in the surgical context, which is already, in it, a constant challenge.

## References

1. L du Toit, T Biesman Simons, N Levy, J A Dave (2018) A practical approach to managing diabetes in the perioperative period. S A fr Med J 108: 369-375.
2. Sílvia M, Fernando R, Pereira de M, Alves de MJJ, Beatriz C (2008) Perioperative approach of the diabetic patient. Int Med 15: 49-60.
3. Portuguese Society of Diabetology (2016) Report of the National Diabetes Observatory: Diabetes Facts and Figures-the Year 2015.
4. World Health Organization (2016) Global report on diabetes.
5. Kadoi Y (2010) Perioperative considerations in diabetic patients. Curr Diabetes Rev 6: 236-246.
6. Leung V, Toolsie KR (2017) Perioperative Management of Patients with Diabetes. Health Serv Insights 10: 1178632917735075.
7. Classification and Diagnosis of Diabetes:Standards of Medical Care in Diabetes-2018. Diabetes Care 41: S13-S27.
8. Miller JD, Richman DC (2016) Preoperative evaluation of patients with Diabetes mellitus. Anesthesiol Clin 34: 155-169.
9. Pontes JPJ, Mendes FF, Vasconcelso MM, Batista NR (2018) Evaluation and perioperative management of patients with diabetes mellitus. A challenge for the anesthesiologist. Rev Bras Anesthesiol 68: 75-86.
10. Ten Hoope W, Looije M, Lirk P (2017) Regional anesthesia in diabetic peripheral neuropathy. Curr Opin Anaesthesiol 30: 627-631.
11. Moningi S, Nikhar S, Ramachandran G (2018) Autonomic disturbances in diabetes: Assessment and anaesthetic implications. Indian J Anaesth 62: 575-583.
12. Oakley I, Emond L (2011) Diabetic cardiac autonomic neuropathy and anesthetic management: review of the literature. AANA J 79: 473-479.
13. Cosson E, Catargi B, Cheisson G, Jacqueminet S, Ichai C, et al. (2018) Practical management of diabetes patients before, during and after surgery: A joint French diabetology and anaesthesiology position statement. Diabetes Metab 44: 200-216.
14. Thompson BM, Stearns JD, Apsey HA, Schlinkert RT, Cook CB (2016) Perioperative Management of Patients with Diabetes and Hyperglycemia Undergoing Elective Surgery. Curr Diab Rep 16: 2.
15. Barker P, Creasey PE, Dhatariya K1, Levy N, Lipp A, et al.(2015) Peri-operative management of the surgical patient with diabetes 2015: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia 70: 1427-1440.
16. Duggan E, Klopman MA, Berry AJ, Umpierrez G (2016) The Emory University Perioperative Algorithm for the Management of Hyperglycemia and Diabetes in Non-cardiac Surgery Patients. Curr Diab Rep 16: 34.
17. Stubbs DJ, Levy N, Dhatariya K (2017) The rationale and the strategies to achieve perioperative glycaemic control. BJA Education 17: 185-193.
18. Bajwa S, Baruah MP, Kalra S, Kapoor MC (2015) Interdisciplinary position statement on management of hyperglycemia in peri-operative and intensive care. J Anaesthesiol Clin Pharmacol 31: 155-164.
19. Duggan EW, Carlson K, Umpierrez GE (2017) Perioperative Hyperglycemia Management: An Update. Anesthesiology 126: 547-560.
20. Polderman JA, van Wilpe R, Eshuis J, Preckel B, Hermanides J (2016) Ambulatory anesthesia: optimal perioperative management of the diabetic patient. Dovepress 3: 13-22.
21. Pichardo-Lowden A, Gabbay RA (2012) Management of hyperglycemia during the perioperative period. Curr Diab Rep 12: 108-118.
22. Monteiro AM, Alves M, Marques O (2016) Diabetes and ambulatory surgery-protocol of perioperative performance. Portugese J Endocrinol Diab Metabol 11: 262-267.
23. Joshi GP, Chung F, Vann MA, Ahmad S, Gan TJ, et al. (2010) Society for Ambulatory Anesthesia consensus statement on perioperative blood glucose management in diabetic patients undergoing ambulatory surgery. Anesth Analg 111: 1378-1387.
24. Schroeder SM (2014) Perioperative management of the patient with diabetes mellitus: update and overview. Clin Podiatr Med Surg 31:1-10.
25. Dhatariya K, Levy N, Hall GM (2016) The impact of glycaemic variability on the surgical patient. Curr Opin Anaesthesiol 29: 430-437.
26. Berhe YW, Gebregzi AH, Endalew NS, Guideline on peri-operative glycemic control for adult patient with diabetic mellitus: Resource limited areas. International J Surg Open 9: 1-6.
27. Power M, Ostrow CL (2008) Preoperative diabetes management protocol for adult outpatients. J PeriAnestha Nurs 23: 371-378.
28. Bodnar TW, Gianchandani R (2014) Preprocedure and preoperative management of diabetes mellitus. Postgrad Med 126: 73-80.
29. Pereira MJSF, Lisboa M (2009) Diabetes and Surgery: Recommendations of good clinical practice in the perioperative control of the diabetic patient. Revista Portuguesa de Cirurgia 9: 39-50.
30. Becker DE (2009) Preoperative Medical Evaluation: Part 2: Pulmonary, endocrine, renal, and miscellaneous considerations. Anesth Prog 56: 135-145.

31. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, et al. (2009) American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. Diabetes Care 32: 1119-1131.

32. Moitra VK, Greenberg J, Arunajadai S, Sweitzer B (2010) The relationship between glycosylated hemoglobin and perioperative glucose control in patients with diabetes. Can J Anaesth 57: 322-329.

33. Gustafsson U,Thorell A, Soop M, Ljungqvist O, Nygren J (2009) Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. Br J Surg 96: 1358-1364.

34. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, et al. (2014) 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 64: e77-e137.

35. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, et al. (2011) Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 28: 556-569.

36. Meneghini LF (2009) Perioperative management of diabetes: translating evidence into practice. Cleve Clin J Med 76: S53-S59.

37. Sudhakaran S, Surani SR (2015) Guidelines for Perioperative Management of the Diabetic Patient. Surgery Research and Practice.

38. Demma LJ, Carlson KT, Duggan EW, Morrow JG, Umpierrez G (2017) Effect of basal insulin dosage on blood glucose concentration in ambulatory surgery patients with type 2 diabetes. J Clin Anesth 36: 184-188.

39. Umpierrez GE1, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, et al.(2012) Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 97: 16-38.

40. Rosenblatt SI, Dukatz T, Jahn R, Ramsdell C, Sakharova A, et al. (2012) Insulin glargine dosing before next-day surgery: comparing three strategies. J Clin Anesth 24: 610-617.

41. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, et al. (2009) Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 94: 709-728.

42. Gustafsson UO, Nygren J, Thorell A, Soop M, Hellström PM et al. (2008) Pre-operative carbohydrate loading may be used in type 2 diabetes patients. Acta Anaesthesiol Scand 52: 946-951.

43. Kannan S, Satra A, Calogeras E, Lock P, Lansang MC (2014)Insulin Pump Patient Characteristics and Glucose Control in the Hospitalized Setting. J Diabetes Sci Technol 8: 473-478.

44. Alexanian SM, McDonnell ME, Akhtar S (2011) Creating a Perioperative Glycemic Control Program. Anesthesiol Res Pract.

45. Lansang MC, Modic MB, Sauvey R, Lock P, Ross D, et al. (2013) Approach to the adult hospitalized patient on an insulin pump. J Hosp Med 8: 721-727.

46. Corney SM, Dukatz T, Rosenblatt S, Harrison B, Murray R, et al. (2012) Comparison of insulin pump therapy (continuous subcutaneous insulin infusion) to alternative methods for perioperative glycemic management in patients with planned postoperative admissions. J Diabetes Sci Technol 6: 1003-1015.

47. Bailon RM1, Partlow BJ, Miller-Cage V, Boyle ME, Castro JC, et al. (2009) Continuous subcutaneous insulin infusion (insulin pump) therapy can be safely used in the hospital in select patients. Endocr Pract 15: 24-29.

48. Kundra TS, Kaur P, Manjunatha N (2017) Prayer sign as a marker of increased ventilatory hours, length of intensive care unit and hospital stay in patients undergoing coronary artery bypass grafting surgery. Ann Card Anaesth 20: 90-92.

49. Ichai C, Vinsonneau C, Souweine B, Armando F, Canet E et al. (2016) Acute kidney injury in the perioperative period and in intensive care units (excluding renal replacement therapies). Ann Intensive Care 6: 48.

50. Dimitropoulos G, Tahrani AA, Stevens MJ (2014) Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 5: 17-39.

51. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, et al. (2011) Cardiovascular autonomic neuropathy in diabetes: Clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 27: 639-653.

52. Authors/Task Force Members, Rydén L, Grant PJ, Anker SD, Berne C, et al. (2013) Esc Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the Easd: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (esc) and developed in collaboration with the European Association for the Study of Diabetes (easd). Eur Heart J 34: 3035-3087.

53. Hirsch IB (2009) Sliding scale insulin—time to stop sliding. JAMA 301: 213-214.

54. Simpson A K, Levy N, Hall G (2008) Peri-operative iv fluids in diabetic patients--don't forget the salt. Anaesthesia 63: 1043-1045.

55. Puskarich MA, Runyon MS, Trzeciak S, Kline JA, Jones AE (2009) Effect of glucose – insulin – potassium infusion on mortality in critical care settings: a systematic review and meta-analysis. J Clin Pharmacol 49: 758-767.

56. Abdelmalak BB, Lansang MC (2013) Revisiting tight glycemic control in perioperative and critically ill patients: when one size may not fit all. J Clin Anesth 25: 499-507.

57. Mraovic B, Schwenk ES, Epstein RH (2012) Intraoperative Accuracy of a Point-of-Care Glucose Meter Compared with Simultaneous Central Laboratory Measurements. J Diabetes Sci Technol 6: 541-546.

58. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2018. Diabetes Care 41: S144-S151.

59. Rice M, Pitkin A, Coursin DB (2010) Glucose measurement in the operating room: more complicated than it seems. Anesth Analg 110: 1056-1065.

60. Akhtar S, Barash P, Inzucchi SE (2010) Scientific principles and clinical implications of perioperative glucose regulation and control. Anesth Analg 110: 478-479.

61. Li X, Wang J, Chen K, Li Y, Wang H, et al. (2017) Effect of different types of anesthesia on intraoperative blood glucose of diabetic patients: A PRISMA-compliant systematic review and meta-analysis. Medicine 96: e6451.

62. McGrane S, Atria NP, Barwise JA (2014) Perioperative implications of the patient with autonomic dysfunction. Curr Opin Anesthesiol 27: 365-370.

63. Seres DS, Valcarce M, Guillaume A (2013) Advantages of enteral nutrition over parenteral nutrition. Therap Adv Gastroenterol 6: 157-167.

64. Marik PE, Bellomo R (2013) Stress hyperglycemia: an essential survival response. Crit Care 17: 305.

65. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, et al. (2011) Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 34: 256-261.

66. Avanzini F, Marelli G, Donzelli W, Busi G, Carbone S, et al. (2011) Transition From Intravenous to Subcutaneous Insulin: Effectiveness and safety of a standardized protocol and predictors of outcome in patients with acute coronary syndrome. Diabetes Care 34: 1445-1450.

67. Lipska KJ, Bailey CJ, Inzucchi SE (2011) Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 34: 1431-1437.

68. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, et al. (2010) Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 33: 1783-1788.

69. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, et al. (2015) Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 261: 97-103.

70. Abdelmalak BB, Knittel J, Abdelmalak JB, Dalton JE, Christiansen E, et al. (2014) Preoperative blood glucose concentrations and postoperative outcomes after elective non-cardiac surgery: an observational study. Br J Anaesth 112: 79-88.

71. McConnell Y, Johnson P, Porter G (2009) Surgical site infections following colorectal surgery in patients with diabetes: association with postoperative hyperglycemia. J Gastrointest Surg 13: 508-515.
72. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, et al. (2013) Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg 257: 8-14.
73. Narayan P, Kshirsagar SN, Mandal CK, Ghorai PA, Rao YM, et al. (2017) Preoperative Glycosylated Hemoglobin: A Risk Factor for Patients Undergoing Coronary Artery Bypass. Ann Thorac Surg 104: 606-612.
74. Kallio PJ, Nolan J, Olsen AC, Breakwell S, Topp R, et al. (2015) Anesthesia preoperative clinic referral for elevated Hba1c reduces complication rate in diabetic patients undergoing total joint arthroplasty. Anesth Pain Med 5: e24376.
75. Subramaniam B, Lerner A, Novack V, Khabbaz K, Paryente-Wiesmann M, et al. (2014) Increased glycemic variability in patients with elevated preoperative HbA1C predicts adverse outcomes following coronary artery bypass grafting surgery. Anesth Analg 118: 277-287.
76. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, et al. (2010) The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. J Clin Endocrinol Metab 95: 4338-4344.
77. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, et al. (2011) Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 141: 543-551.
78. Duncan AE, Abd-Elsayed A, Maheshwari A, Xu M, Soltesz E, et al. (2010) Role of intraoperative and postoperative blood glucose concentrations in predicting outcomes after cardiac surgery. Anesthesiology 112: 860-871.
79. De La Rosa Gdel C, Donado JH, Restrepo AH, Quintero AM, González LG, et al. (2008) Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. Crit Care 2008. 12: R120.
80. Finfer S (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360:1283-1297.
81. Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS (2012) Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 40: 3251-3276.
82. Wiener R, Wiener D, Larson R (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis.
83. Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, et al. (2009) The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. Ann Thorac Surg 87: 663-669.
84. Shah M, Apsey HA, Stearns JD, Schlinkert RT, Seifert KM, et al. (2014) Guidelines to improve perioperative management of diabetes mellitus: an example of a successful quality initiative. Diabetes Manag 4: 327-337.
85. Udovcic M, Castro JC, Apsey HA, Stearns JD, Schlinkert RT, et al. (2015) Guidelines to improve perioperative management of Diabetes mellitus: assessment of the impact of change across time. Endocrine Pract 21: 1026-1034.
86. McCavert M, Mone F, Dooher M, Brown R, O'Donnell ME (2010) Peri-operative blood glucose management in general surgery-a potential element for improved diabetic patient outcomes-an observational cohort study. Int J Surg 8: 494-498.
87. Abdelmalak B, Abdelmalak JB, Knittel J, Christiansen E, Mascha E, et al. (2010) The prevalence of undiagnosed diabetes in non-cardiac surgery patients, an observational study. Can J Anaesth 57: 1058-1064.
88. Sheehy AM, Benca J, Glinberg SL, Li Z, Nautiyal A, et al. (2012) Preoperative "NPO" as an opportunity for diabetes screening. J Hosp Med 7: 611-616.