The diabetic surgical patient

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Purpose of review

This review summarizes the current progress in disease classification, pathophysiology and management of diabetes mellitus with a special focus on treatment modalities and recommendations for the practicing anesthesiologist.

Recent findings

The revised classification of diabetes mellitus emphasizes disease cause and eliminates any reference to age-of-onset and insulin therapy. Hyperglycemia has emerged as an important marker of outcome in the operating room. Intensive insulin therapy promises to reduce health risk in the surgical and critical care setting. Perioperative β-blocker and statin therapy are likely to reduce cardiac morbidity and mortality in diabetic patients. Promotility therapy (with metoclopromide) intended to reduce the aspiration risk of diabetic gastroparesis is likely over-utilized and may only be indicated for diabetics with poor glucose control and high hemoglobin A1c levels.

Summary

According to World Health Organization projections, anesthesiologists can expect to care for more diabetic patients than ever before. Diabetes and its associated complications present unique challenges to the perioperative physician. As biomedical research continues to unravel the genetic, cellular and molecular mechanisms of this complex metabolic disease, our specialty must be prominently involved in the design and testing of innovative treatments to protect the diabetic patient from the risks of surgery and anesthesia.

Keywords

anesthesiology, diabetes, hyperglycemia, outcome, perioperative

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Abbreviations

GIK glucose–insulin–potassium
MI myocardial infarction

0952-7907

Introduction

The ill effects of diabetes mellitus on human health were first documented on Egyptian papyrus as early as 1550 BC by the physician Hesy Ra [1]. Today, diabetes remains a serious health risk of growing epidemic proportions. Apart from genetic causes, lifestyle and diet of the prosperous Western societies have contributed significantly to the incidence and severity of this disorder. Historical evidence for the important role of environmental factors exists in the work of French physician Bouchardat [2], who noted that severe food rationing during the years of the Franco–Prussian war in the 1870s correlated with the disappearance of glycosuria in diabetic patients. Diabetes has become one of the major causes of early-onset illness and increased mortality in many countries, and its prevalence is expected to double by 2030 [3]. This common syndrome is associated with rising hospital admissions, longer and more complex hospital stays and a corresponding acceleration of healthcare costs [4]. Diabetes mellitus is a disorder characterized by abnormal carbohydrate metabolism, which causes hyperglycemia. Left untreated, diabetes is a debilitating disease, which leads to acute and chronic organ dysfunction and failure. The comorbidities of diabetic patients and the demands of glycemic control during the perioperative period present unique challenges in the care of the diabetic surgical patient. In this review, our goal is to summarize the current progress in disease classification, pathophysiology and management of diabetes mellitus with a special focus on treatment modalities and recommendations for the practicing anesthesiologist.

Pathophysiology and disease classification

According to recent recommendations by the American Diabetes Association and the World Health Organization, diabetes mellitus should be classified by the underlying disease cause rather than by age-of-onset (i.e. juvenile-onset compared with adult-onset diabetes) or treatment modality (i.e. insulin-dependent compared with non-insulin-dependent diabetes) [5]. Type 1 diabetes, characterized by insulin deficiency, is the result of an autoimmune-mediated destruction of pancreatic β cells. In contrast, peripheral insulin resistance is the hallmark of the more common Type 2 diabetes and is often coupled with a failure to secrete insulin. Proposed mechanisms for insulin resistance include an increased level of nonesterified fatty acids, inflammatory cytokines, adipokines and mitochondrial dysfunction [6•,7•]. Failed insulin secretion is thought to result from

pancreatic β cell dysfunction due to glucotoxicity, lipotoxicity and amyloid formation [6•]. Obesity has become a major health risk and increasing evidence marks it as a risk factor for the development of Type 2 diabetes [8]. Specifically, weight gain and abdominal or visceral fat, independent of body mass index, are associated with an increased risk of diabetes [9]. Consumption of fast food and sugar-sweetened beverages has also been implicated in the development of diabetes [10,11]. Recent studies [12] suggest that adipose tissue functions as an endocrine organ to produce hormones and inflammatory mediators that suppress insulin signaling.

Hyperglycemia, perioperative metabolism and patient outcome

Hyperglycemia has emerged as a marker of outcome in diverse settings. In the nonoperative fields, several studies [13–15] have demonstrated a correlation between blood glucose and the development of congestive heart failure in diabetic and nondiabetic patients after a myocardial infarction (MI). After ischemic stroke, the presence of hyperglycemia is associated with reduced functional capacity, decreased penumbral salvage and an increased final infarction size [16,17]. After trauma, nondiabetic patients with hyperglycemia had a greater risk for longer hospital stay, an increased infection rate and mortality [18]. Elevated blood glucose is often a result of the stress response, and its presence can provide the practitioner with insight into the severity of a patient's illness. In this context, it will be critical to distinguish between hyperglycemia as a marker of acute illness and its potential as a reversible, treatable and independent variable of outcome.

In surgical patients, according to several observational studies [19,20], hyperglycemia increased hospital stay, intensive care unit (ICU) admission, postoperative infections, neurological events and the risk of in-hospital mortality. Patients with new hyperglycemia (a group likely composed of patients with undiagnosed diabetes, prediabetes or hyperglycemia from the stress of illness) had higher in-hospital mortality than patients with known diabetes and hyperglycemia. Blood glucose values were not statistically different between groups [20].

Hyperglycemia, or the diabetic condition, impairs many physiological processes involved in the recovery from surgery. The catabolic and sympathetic response to trauma and surgery has been well described [21]. The metabolic consequences of surgery, characterized by elevations in circulating catecholamines, growth hormone, glucagon and cortisol levels with a concomitant depression in insulin levels, promote hepatic glycogenolysis and gluconeogenesis. Hyperglycemia and insulin resistance marks this metabolic profile [22]. The metabolic response may be pronounced among diabetics undergoing surgery. When the protein and glucose catabolic response to abdominal surgery in Type 2 diabetics was compared with the response of nondiabetics with isotopic markers of catabolism, patients with Type 2 diabetes had higher plasma glucose concentrations postoperatively, with higher glucagon levels and lower insulin levels. Protein catabolism after colorectal surgery was increased in patients with diabetes [23•]. The administration of carbohydrates preoperatively has been shown to reduce postoperative insulin resistance and diminish protein losses [24,25•]. In addition to insulin infusions, minimally invasive surgeries and epidural anesthesia have been proposed to reduce perioperative insulin resistance and hyperglycemia [22, 26]. The metabolic responses to surgery are exaggerated in diabetics, and preventing the insulin resistance of stress and providing adequate analgesia may blunt this response.

Glycemic control

The comorbidities of diabetic patients and the difficulties associated with glycemic control during the perioperative period present unique challenges in the monitoring and treatment of the diabetic surgical patient. Glycemic control during the perioperative period is difficult to predict because multiple factors affect blood sugar and pancreatic function, including the stress of surgery, acute illness, anorexia, anesthetic masking of hypoglycemic symptoms and NPO (*nil per os*) status.

Glycemic control in the intensive care setting

The emphasis on strict perioperative glycemic control has been advocated primarily in the intensive care setting [27–29]. Strict glucose control leads to improved survival with a concomitant decrease in the incidence of infections, neuropathies and renal failure [28,29]. The benefits of intensive insulin therapy to treat hyperglycemia, however, may not occur during the initial phase of critical illness or injury. Results from a recent trial by Van den Berghe and her colleagues [30••] suggest that intensive insulin therapy in the medical ICU may worsen outcomes in patients who stayed in the ICU for less than 3 days. In fact, the data suggest that patients who stayed in the ICU for more than 3–5 days derived the greatest benefit [29,30••]. This result is not surprising to those who believe that the initial hyperglycemia of critical illness is a protective and adaptive response, which serves to deliver glucose to poorly perfused tissues that are hypermetabolic [21,31,32].

Intraoperative glycemic control

The clinical benefits of intraoperative glycemic control in cardiac surgery patients have recently been reported in two studies. Lazar *et al.* [33••] randomly allocated

patients to tight glycemic control using a glucose–insulin–potassium (GIK) infusion or standard therapy using intermittent subcutaneous insulin. Both regimens were initiated before anesthesia and continued for 12 h after surgery. Diabetic patients who received a short course of GIK had a lower incidence of atrial fibrillation, shorter postoperative stay, fewer recurrent wound infections and fewer episodes of recurrent ischemia with better survival rates for the 2 years after surgery. In the second study [34••], persistent intraoperative hyperglycemia, despite an insulin protocol, was associated with worsened cardiac, neurologic, renal and respiratory outcomes. What remains unclear is whether greater insulin administration in the second study would have reduced morbidity in the patients with persistent intraoperative hyperglycemia. Preoperative and postoperative blood glucose concentrations, however, were unremarkable in patients with and without postoperative morbidity. Lack of strict glucose control intraoperatively may have contributed to adverse outcomes.

Normoglycemia, particularly during cardiopulmonary bypass (CPB), is difficult to maintain. Large amounts of insulin are often required to counter the disrupted glucose–insulin relationship of CPB. Consequently, in the postoperative period, patients may be at increased risk of hypoglycemia [35]. With the recent emphasis on strict glucose control, several protocols have been offered for intraoperative glucose management [33••, 34••,36•,37]. In one protocol the initial insulin resistance before CPB is counteracted with a fixed insulin infusion, an insulin clamp and a titrated dextrose infusion to achieve normoglycemia. Preoperative hyperglycemia and renal failure may predict difficulty in intraoperative glucose control. As achieving intraoperative normoglycemia is difficult in diabetics with initial blood glucose values of more than 300 mg/dl, glucose control in advance of surgery might facilitate intraoperative management [38•]. Insulin clearance decreases with renal failure, so frequent glucose monitoring and a low insulin infusion rate may prevent intraoperative hypoglycemia in patients with compromised renal function [38•]. A simple cost-effective glucose–insulin infusion regimen to achieve normoglycemia among diabetic patients scheduled for elective surgery has been established to control glucose with less hypoglycemia [37]. Tight glucose control has also been achieved through the administration of a GIK solution to improve perioperative outcomes [33••].

The benefits of insulin treatment may also result from its anabolic, anti-inflammatory and anti-apoptotic effects. In addition, insulin may improve dyslipidemias and prevent endothelial dysfunction and hypercoagulability in critically ill patients [39•]. Furthermore, advocates of strict intraoperative glucose control cite studies that show the harmful effects of acute hyperglycemia on the immune system. Acute, short-term hyperglycemia compromises the immune system by depressing chemotaxis, phagocytosis and complement function. Elevated glucose levels alter the inflammatory response to stress and compromise endothelial function resulting in vasoconstriction [40].

Diabetes and perioperative outcome

Some studies [41–43] have suggested that diabetics do not have a greater risk of perioperative complications in the short term. In contrast, other studies [44–47] have demonstrated a poorer prognosis among diabetics particularly after cardiac surgery. In a large retrospective analysis of patients with ankle fractures [48], diabetes was associated with increases in hospital mortality, postoperative complications, length of hospital stay and total hospital charges. In a retrospective analysis of 179 consecutive diabetic patients who had noncardiac surgery, cumulative mortality at 1 year was 24%. Predictors of death among diabetic patients included ischemic heart disease, urgent surgery, American Society of Anesthesiologists physical status score and hyperglycemia. A preoperative diagnosis of ischemic heart disease was associated with an overall postoperative mortality of 44%. The mortality of diabetics was largely attributable to cardiovascular events [49]. A prospective regional cohort study [50] examined the effect of diabetes and associated comorbidities on long-term survival after coronary artery bypass graft surgery. Long-term survival of diabetics after cardiac surgery was strongly affected by the presence of peripheral vascular disease and renal failure. In diabetics with renal failure, peripheral vascular disease or both, the 10-year survival rate was 40%. These data may be used to provide prognostic information to diabetics prior to surgery. Taken together, these results emphasize the magnified effect of diabetes on cardiac morbidity and mortality and the need to provide adequate cardiac protection in this vulnerable group of patients.

Additional therapies

The perioperative use of β blockers has been advocated for patients at increased cardiac risk [51–54]. Nonetheless, the rationale for use of β blockers in diabetics before major noncardiac surgery was recently questioned in the Diabetic Postoperative Mortality and Morbidity (DIPOM) trial [55]. These investigators reported no difference in the incidence of primary cardiac endpoints (MI, unstable angina and congestive heart failure) or all-cause mortality between diabetics treated with oral metoprolol or placebo. Significant limitations in the design and execution of this trial have been cited, however, and include treatment duration and compliance, under-dosing, drug formulation and impaired drug

absorption after surgery. In contrast, the available cumulative evidence from multiple smaller β-blocker intervention trials suggests an overall positive trend towards perioperative cardioprotection, especially in high-risk patients [56–58]. This conclusion was recently supported by the currently largest observational study assessing the effect of perioperative β-blockade on hospital mortality after major noncardiac surgery in a cohort of 663 635 patients across 329 hospitals in the United States [59]. This study demonstrated that perioperative β-blocker therapy resulted in a significant reduction of in-hospital deaths among high-risk, but not low-risk patients. Taken together, until the results of the POISE (Perioperative Ischemic Evaluation) study become available, it appears prudent to use perioperative β blockade in diabetic patients according to the recommendations of the American Heart Association and American College of Cardiology [60].

In several observational studies, statin therapy is rapidly emerging as a risk-reducing therapy for cardiovascular events [61–63]. In a prospective randomized trial [64••], the short-term administration of atorvastatin therapy to patients before vascular surgery, irrespective of patients' cholesterol levels, reduced the incidence of cardiovascular events in the first 6 months after surgery, including death from cardiac causes, nonfatal acute MI, ischemic stroke and unstable angina. Given the cardiovascular consequences of diabetes, the preoperative medical management of diabetic patients undergoing surgery should evaluate their risk of perioperative myocardial insult and include the judicious use of β blockers and perhaps statin therapy.

Diabetes and the cardiovascular system

Understanding the pathogenesis of atherosclerosis is essential to appreciating the magnified risk of morbidity and mortality in diabetics during the perioperative period. At the cellular level, hyperglycemia is associated with an altered cellular redox state, oxidant stress, decreased bioavailability of nitric oxide (NO), harmful low-density lipoprotein oxidation and activation of procoagulant peptides [65]. The accumulation of advanced glycation endproducts (AGEs) in diabetes promotes cellular dysfunction and disrupts vascular wall homeostasis through inhibition of endothelial-dependent vasodilation [66•]. In addition, engaging the receptor for AGEs (RAGE), a cell surface immunoglobulin, can potentially convert short-term proinflammatory signals into long-term maladapted cellular responses [66•,67•]. Through these and other mechanisms, hyperglycemia impairs vasodilatation and induces a chronic proinflammatory, prothrombotic and proatherogenic state as the basis for the commonly observed vascular complications in diabetics [68]. Diabetes also impairs glucose metabolism in the myocardium. Alterations in glucose oxidation increase levels of free fatty acids, oxygen consumption and accumulation of free radicals, inhibit glucose utilization, decrease contractility and predispose to arrhythmias [69].

A diagnosis of diabetes has the same predictive value for a perioperative cardiovascular event as a history of a MI, a positive stress test, Q waves on an electrocardiogram or congestive heart failure [60,70]. Patients with diabetes but without previous MI carry the same level of risk for coronary events as nondiabetic patients with previous MI [71]. In fact, patients with diabetes are considered risk equivalents for coronary artery disease mandating intensive anti-atherosclerotic therapy [72].

In a large retrospective meta-analysis [73], an increase in HbA1c was associated with a greater risk of cardiovascular events. Interestingly, elevation of HbA1c was associated with cardiac morbidity and mortality independent of a diagnosis of diabetes. These results suggest that the risk for coronary heart disease correlates with glucose control regardless of whether or not a patient is diabetic [74•]. The association between long-term glucose control and cardiovascular events during the perioperative period has not been adequately studied. Although diabetes is an independent intermediate risk factor in patients who undergo noncardiac surgery, further research examining HbA1c as a predictor of risk for perioperative morbidity is warranted. These data may be used to stratify patients into high-risk, intermediate and low-risk categories.

Diabetes and the nervous system

The neurological effects of diabetes increase the risk of stroke, and the presence of hyperglycemia is a strong predictor of poor outcome in many forms of acute brain injury [75,76]. In animal models, elevated blood glucose levels have been shown to increase blood–brain barrier permeability, disrupt cellular metabolism and promote neuronal acidosis. In a recent retrospective analysis of patients with acute ischemic stroke [77•], normalization of blood glucose values to less than 130 mg/dl within 48 h of admission resulted in a 4.6-fold decrease in mortality. Stroke risk, on the other hand, seems to correlate with chronic glucose control. A recent large community-cohort study of diabetics and nondiabetics [78•] found an association between HbA1c levels and stroke risk in both subject groups.

An association between elevated blood glucose levels and the development of vasospasm following a subarachnoid hemorrhage has also been demonstrated [79]. One of the fundamental principles in the initial management of cerebral perfusion pressures is the modification of cerebral vascular tone through adjustments in carbon dioxide levels. In diabetic patients, however, vasomotor

response to carbon dioxide may be impaired under propofol anesthesia. In fact, the vasodilatory response to hypercapnia, measured by transcranial Doppler, was impaired in diabetics compared with nondiabetics. The degree of impairment correlated with the patient's HbA1c [80]. This finding poses interesting questions regarding the role of long-term glucose control in the regulation of cerebral vasoreactivity in diabetics. In a small retrospective analysis of patients undergoing image-guided stereotactic brain biopsy, diabetes was an independent risk factor for biopsy-associated morbidity. Even though a causal relationship between glucose control and outcomes remains unclear, hyperglycemia on the day of surgery predicted morbidity among diabetics and increased the risk of neurological complications fourfold [81].

Abnormalities from autonomic neuropathy of the enteric nervous system are common among diabetics [82]. Both short-term hyperglycemia and poor long-term glycemic control delay gastric emptying, which may lead to an increased gastric fluid volume [83]. In response to this concern, the use of promotility agents in diabetic patients has evolved into a common practice, which is currently supported by the Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration [84]. A recently conducted prospective trial [85••], however, demonstrated that 8 h of fasting before surgery resulted in similar and clinically inconsequential gastric fluid volumes among control subjects and Type 1 and Type 2 diabetics. These authors seriously questioned the need for universal prokinetic therapy in all diabetic patients and suggested limiting its use to poorly controlled diabetics with elevated hemoglobin A1c values (over 9%).

Conclusion

Anesthesiologists will frequently face several perioperative challenges to safely guide diabetic patients through surgery. Preoperative laboratory studies such as blood glucose values and glycosylated hemoglobin can serve as markers of outcome and identify patients at risk for short-term or long-term morbidity. Aggressive management of hyperglycemia preoperatively may be warranted to diminish the incidence of intraoperative and postoperative elevations of blood glucose. Tight glucose control in the perioperative period awaits further advances in affordable real-time monitoring technology and treatment protocols, but promises to benefit the diabetic and nondiabetic patient. As a diagnosis of diabetes is a coronary artery disease equivalent, the use of β blockers and statin therapy may be justified in diabetics during the perioperative period.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 351–353).

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