CURRENT PERIOPERATIVE MANAGEMENT OF DIABETIC PATIENTS FROM GENERAL SURGERY WARDS

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Abstract: *The purpose of this paper is to analyze the current perioperative management of diabetes taking into account the guidelines recommendations and the findings of the studies published so far. The prevalence of diabetes is increasing among the population in all age groups. Diseases requiring surgery are common in diabetic patients. The paper correlated the information available to date on the perioperative treatment of diabetes, the postoperative complications and the most frequent errors committed on the management of diabetic patients, aspects with important practical implications. Although hyperglycemia has a significant clinical impact on perioperative morbidity and mortality, glycemic targets and perioperative management have not been well established yet. Further studies are needed to clarify these issues.*

Cuvinte cheie: *diabet zaharat, tratament perioperator*

Rezumat: *Scopul acestei lucrări este de a analiza managementul perioperator actual al diabetului zaharat ținând cont de recomandările ghidurilor și rezultatele studiilor publicate până în prezent. Prevalența diabetului zaharat este în creștere în rândul populației, în toate grupele de vârstă. Afecțiunile care necesită intervenție chirurgicală la pacienții cu diabet zaharat sunt frecvente. În lucrare s-au corelat informațiile existente până în prezent despre tratamentul perioperator al diabetului zaharat, complicațiile postoperatorii și erorile frecvente de management al pacienților diabetici, aspecte cu importante implicații practice. Deși hiperglicemia are un impact clinic semnificativ asupra morbidității și mortalității perioperatorii, țintele glicemice și managementul perioperator nu au fost încă bine stabilite. Sunt necesare studii suplimentare care să clarifice aceste aspecte.*

Diabetes is an epidemic disease, (1) whose prevalence in the population is increasing. Prevalence of diabetes worldwide was estimated, for all age groups, at 2.8% in the year 2000 and it will increase to 4.4% in the year 2030.(2)According to studies conducted by Yiling j. Cheng et al, the prevalence of type 2 diabetes in the American population has increased in the last two decades in all age groups, but especially among adults older than 65 years.(3) Patients with diabetes are hospitalized more frequently and have a longer duration of hospitalization than patients without diabetes.(1) The hospitalization risk of diabetic patients increases with age, duration of diabetes and number of disease complications.(4) Although in the past, hyperglycemia was considered secondary in importance to the condition that caused hospitalization, now more data proves that proper management of hyperglycemia leads to improved clinical outcomes.(1,5) The conditions that require surgery are very common in diabetic patients, especially related to complications of diabetes or associated comorbidities. In America, 15-20% of annual surgical procedures are performed in patients with diabetes.(4)

According to research conducted by LLChauah et al., most evidences related to mortality and morbidity in patients with type 2 diabetes undergoing surgery are coming from cardiac surgery. There are few records from non-cardiac surgery and from bariatric surgery.(6) Although the prevalence of diabetic patients undergoing surgery is high and hyperglycemia has a clinically meaningful impact on perioperative morbidity and mortality, perioperative management and perioperative glycemic targets have not been well established yet.(7)

Defining concepts of hyper and hypoglycemia in hospitalized patients

Following the recommendations of American Diabetes Association from the year 2014,(5) hyperglycemia in hospitalized patients is defined as any blood glucose greater than 140 mg/dl. It can occur in a patient previously diagnosed with diabetes, in an undiagnosed diabetic patient or it can be a transient hyperglycemia linked to the hospitalization, in which case blood sugar levels normalizes after discharge.

The differentiation between undiagnosed diabetes and transient hospital hyperglycemia can be done by determining glycated hemoglobin and it will be certainly resolved after discharge and follow-up the patient in ambulatory. It should be noted that no randomized clinical trials have demonstrated improved outcomes of new hospitalized diabetes cases or improved hospital glycemic management of patients already diagnosed with diabetes by using glycated hemoglobin.(8) Among hospitalized patients with hyperglycemia, a HbA1c value above 6% was reported to have 100% specificity and 57% sensitivity for the diagnosis of diabetes, whereas a HbA1c value of less than 5.2% practically exclude the diagnosis of diabetes.(9)

Hospital hypoglycemia is defined as blood glucose below 70 mg/dl. Severe hypoglycemia in a hospitalized patient is defined as blood glucose below 40 mg/dl.

In diabetic patients, surgery can be emergency or scheduled. It is considered a major surgery the interventions which last more than one hour and require general anesthesia.(10)

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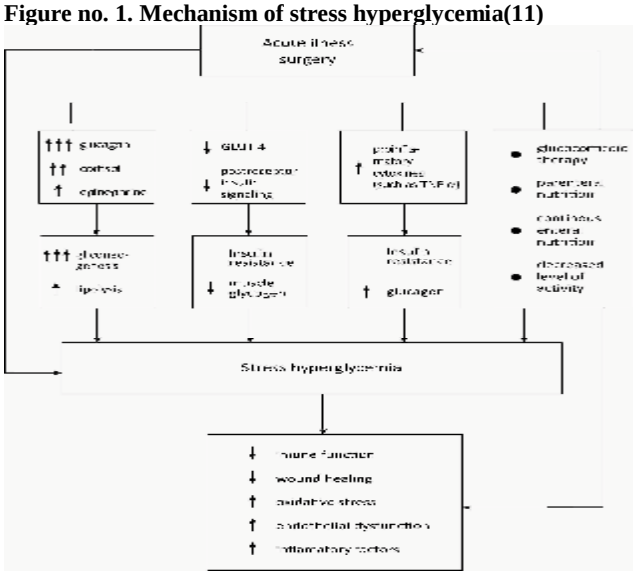
The mechanism by which hyperglycemia influences perioperative morbidity and mortality

Perioperative "stress" hyperglycemia appears from increasing counter regulatory hormones (corticosteroids and catecholamine), proinflammatory cytokines and causes related to hospitalization and treatment (decreased physical activity, cortisone therapy, parenteral nutrition). Increased glucose leads to impaired immune function, inducing a prothrombotic and proinflammatory status, endothelial dysfunction and increased oxidative stress (figure no. 1).(11)

Figure no. 1. Mechanism of stress hyperglycemia(11)



Perioperative glycemic targets in diabetic patients

Current recommendations (1,5) refers to all inpatients, whether or not they undergo surgery. For critically ill patients initiating insulin therapy is recommended at a glucose higher than 180 mg/dl and it is recommended to target a blood glucose between 140-180 mg/dl. For patients who are not critically ill, it is recommended a fasting glucose less than 140 mg/dl and a random glucose less than 180 mg/dl, as long as these targets can be achieved safely. As with outpatient, clinical judgment should prevail and targets should be individualized depending on glycemic control before admission, severity of illness for which the hospitalization has been made, clinical and nutritional status of the patient.

A meta-analysis published in the year 2013 (7) corroborated the data from several studies, most of which were from cardio vascular surgery. The aim was to determine what extent the intensity of perioperative glycemic control correlates with the outcome of the surgery (postoperative mortality, the incidence of atrial fibrillation, infections and stroke). Results showed that patients who received moderate glycemic control, with target blood glucose between 150-200mg, had the greatest reduction in mortality rates and in the incidence of perioperative stroke, compared with the patients in studies with a more relaxed glycemic targets (blood glucose> 200mg/dl). The patients who had a tight glycemic control (blood glucose <150 mg / dl) did not have an additional benefit on the targeted outcomes.

Postoperative blood glucose levels higher than 200 mg/dl are associated with prolonged hospitalization and an increased risk of postoperative complications, including wound infections and cardiac arrhythmias.(8) On the other hand, the NICE-SUGAR study, the largest prospective randomized trial to date conducted in a group of patients hospitalized in the intensive care units showed that intensive glycemic control with a target blood glucose between 81mg/dl and 108 mg/dL increases morality compared to the standard target blood glucose less than 180 mg/dl[12].(12) The study was conducted on critically ill patients, most of them (> 95%) requiring mechanical ventilation, hospitalized in surgical and medical ICU. The study did not deny the importance of glycemic control in patients hospitalized in ICU, but it suggested that it may not be necessary to achieve a glycemic target less than 140 mg/dL and that a glycemic target less than 110 mg/dl can be even dangerous.(5) A meta-analysis published in 2009,(13) which included 26 clinical trials, together with NICE-SUGAR study, showed that intensive treatment of hyperglycemia increases the risk of hypoglycemia and has no benefit on mortality, except inpatient from surgical intensive care unit who received a reduction in mortality. In addition to these findings, another study,(14) published in 2014, which followed intensive glycemic control versus standard glycemic control in a group of patients undergoing hepatobiliary-pancreatic surgical interventions showed that a target blood glucose between 80 mg/dl and 110 mg/dl is associated with a lower surgical wound infections, compared with a target blood glucose between 140 mg/dl and 180 mg/dl.

Monitoring of blood glucose in hospitalized patients

Following the recommendations of the American Association of Clinical Endocrinologists and American Diabetes Association, (1) the monitorization of the capillary blood glucose should be done before meals and at bedtime for most hospitalized patients who are eating. In patients which are receiving continuous enteral or parenteral nutrition, glucose monitoring should be done every 4-6 hours. If patients receive intermittent enteral or parenteral nutrition, blood glucose monitoring should be individualized and frequently enough so that no high glycemic variations occur. In the case of continuous infusion of insulin therapy, blood sugar should be measured frequently, at an interval ranging from 30 minutes to 2 hours depending on the patient's blood glucose stability.

Perioperative treatment of diabetic patients

Following the recommendations of American Association of Clinical Endocrinologists, from the year 2012,(8) perioperative treatment choice is based on the type of diabetes, type of surgery, the treatment received before the surgery and the metabolic control of the patient prior to surgery. The success of any perioperatory diabetic regimen is to monitor frequently blood glucose level, for early detection of changes in blood glucose.

Insulin therapy is the preferred treatment for correction of hyperglycemia in all hospitalized patients.(4)

All patients with type 1 diabetes and type 2 diabetic patients undergoing major surgery should receive perioperative insulintherapy.(7) Patients with type 2 diabetes which are on diet may not need special therapeutic intervention for glycemic correction in case of a minor surgery. In case of a major intervention, if glucose is out of targets continuous intravenous infusion of insulin and dextrose is recommended. For minor interventions, patients with type 2 diabetes on treatment with antidiabetic medication will stop the medication in the morning of the surgery for minor and they will resume the medication with refueling. If these patients will present perioperative hyperglycemia, it is recommended the correction by low doses of short-acting insulin (regular insulin or rapid-acting insulin analog) subcutaneously. Oral antidiabetic medication may be resumed after the refueling has started. A special mention must be made for metformin, which will be stopped with 12 hours before the surgery and it will be readministrated only after the confirmation that the postoperative renal function is preserved (10) (table no. 1).

Table no. 1. Perioperative management of diabetes

Diabetes Type	Minor surgical interventions		Major surgical intervention	
	Good metabolic control	Insufficient control (perioperative hyperglycemia)	Good metabolic control	Insufficient control (perioperative hyperglycemia)
T1DM	insulinotherapy - continuous intravenous infusion of insulin / insulin subcutaneous- basal/bolus regimen			
T2DM with insulinotherapy	insulinotherapy - continuous intravenous infusion of insulin / insulin subcutaneous- basal/bolus regimen			
T2DM with antidiabetic medication	interruption / resumption antidiabetic medication	rapid insulin subcutaneously (low dose for correction)	insulinotherapy - continuous intravenous infusion of insulin / insulin subcutaneous- basal/bolus regimen	
T2DM on diet	no special intervention for diabetes	rapid insulin subcutaneously (low dose for correction)	no special intervention for diabetes	insulinotherapy - continuous intravenous infusion of insulin / insulin subcutaneous- basal/bolus regime

Table no. 2. Indication of continuous infusion of insulin in patients with diabetes or high blood sugar (4)

Indication	Level of evidence
Diabetic ketoacidosis or hyperosmolar hyperglycemic status	A
General preoperative, intraoperative and postoperative care	C
Postoperative period after cardiac surgery	B
Organ transplantation	E
MI and cardiogenic shock	A
Stroke	E
Exacerbated hyperglycemia during high-dose glucocorticoid therapy	E
Status "nothing by mouth" in type 1 diabetes	E
Critically ill surgical patients requiring mechanical ventilation	A
Strategy for determining the dose of insulin before initiation or reinitiation subcutaneous insulin therapy in patients with diabetes type 1 or 2	C

For patients admitted pre and/or postoperative in the intensive care units, continuous intravenous insulin infusion is the preferred method of treatment[1.] The indications of the continuous infusion of insulin in hospitalized patients[4] are shown in table no. 2.

The basal basal-bolus regimen is the most appropriate way to administrate insulin subcutaneously.(1,4,8) Sliding scale insulin, which assumes the administration of regular human insulin four times per 24 hours, according to a preset protocol, proved to be less effective, because it leads to high blood glucose variations and it can be even dangerous in patients with type 1 diabetes, because it can precipitate the occurrence of diabetic ketoacidosis.(4,5,8)

Surgery RABBIT2 study (15)showed that basal-bolus regimen with insulin glargine once daily and insulin glulisine before meals improves glycemic control and reduces postoperative complications, versus sliding scale insulin in diabetic patients undergoing surgery. Basal-bolus regimen involves administration of the basal insulin once (glargine or detemir) or twice daily (detemir or NPH), nutritional bolus administration (regular human insulin or fast insulin analogue) and additional correction boluses (regular human insulin or fast insulin analog) according to a predetermined protocol, when fasting or bedtime blood glucose levels are not within the targets. If the patient does not eat, will be administrate only basal insulin and the nutritional boluses will be omitted. There are many protocols proposed for perioperative insulin administration. Table no. 3 shows the protocol for the administration of insulin in hospitalized patients proposed in the guidelines of the American Association of Clinical Endocrinologists in 2012.(8)

Preoperative will be administrated a percentage of the usual dose of basal insulin (NPH, detemir or glargine) and, if it is necessary, correctional boluses (regular insulin or rapid-acting insulin analogues). In patients with type 1 diabetes, a study by Mucha GT et al. showed that administration of the entire dose of basal insulin (glargine insulin) in patients who are not eating can be done safely, without risk of hypoglycemia. It is suggested, however, that for well-controlled type 1 diabetic patients a slight reduction, of 10-20%, it can be make. In the case of NPH insulin, which has a different pharmacokinetic than long-acting insulin analogues, it is indicated a dose reduction with 25-50% and administration of the correctional boluses when the blood glucose is out of the targets. The administration of a percentage of basal insulin can be done safely before surgery even in patients who are hospitalized in the morning of surgery.(8)

Postoperative complications associated with poor glycemic control

The most studies from this area were focused on patients undergoing cardiac surgery and on critically ill patients, hospitalized in ICU.(17) In their case, hyperglycemia in the perioperative period is associated with increased rates of deep sternal incision infections, increased in-hospital complications and mortality, and the improvement of the glycemic control lowers the rate of postoperative complications, decreased length of hospital stay and mortality. There are few observational studies conducted in patients undergoing general surgery interventions, aimed to follow in what extent the perioperative glycemic control correlates with postoperative complications. According to research conducted by Frisch et al.(16) in a group of patients undergoing non-cardiac surgery interventions, perioperative hyperglycemia was associated with increased length of hospital stay and increased days of hospitalization in the intensive care unit, with a statistically significant larger number of cases of pneumonia, surgery wound infections, sepsis/ bacteremia, urinary tract infection, acute myocardial infarction and acute renal failure. The authors have shown that hyperglycemia in a patient undiagnosed with diabetes yet is associated with a worse clinical outcome in comparison with hyperglycemia in patients previously diagnosed with diabetes.

This difference was observed and reported by other researchers.(18,19) Kotagal and col.(20) retrospectively analyzed more than 40,000 patients undergoing general surgery interventions, vascular and spine surgery, between 2010-2012 (The Surgical Care and Outcomes Assessment Program) and showed that hyperglycemia is a risk factor for postoperative adverse events in undiagnosed diabetic patients, but not in those with diabetes. They have made several assumptions for these seemingly paradoxical data, the most plausible being the lack insulin treatment in non-diabetic patients or the fact that hyperglycemia indicates a higher level of stress in non-diabetic patients compared with those previously diagnosed with diabetes.

Glycated hemoglobin (HbA1c) is an indication of long-term glycemic control, meaning a chronic hyperglycemia. The studies presented above followed the relationship between acute hyperglycemia in the perioperative period and postoperative complications. A study published in 2014, conducted by P. Underwood et al.,(21) pursued the relationship between preoperative HbA1c value and the clinical outcome in patients with diabetes undergoing major non-cardiac surgery. The results showed that a value of HbA1c higher than 8% was associated with increased length of hospital stay, regardless of the value of blood glucose from the day of hospitalization. Prospective studies are needed in this area, in order to establish with certainty a HbA1c threshold value from where chronic hyperglycemia may have a negative impact on the postoperative evolution of diabetic patients.

Common errors and improvement approaches of the glycemic perioperative management

Too intensive treatment of hyperglycemia or, conversely, a treatment with too tolerant targets, from fear of hypoglycemia, may have adverse consequences and is a cause for concern on hospital patient safety.(1)

The most common clinical conditions that increase the risk of hyperglycemia or hypoglycemia in hospitalized patients are shown in table no. 4.(1) In order to avoid them and the transition from clinical inertia to a good management, that achieves glycemic control safely for patients, resources / actions / order / well-established algorithms are required: administrative support (appropriate glucometers, tests) and educational support (doctors, nurses) in order to implement a uniform method for determining and evaluating bedside monitoring of blood glucose results, standardized communication between medical team members, protocols and standardized methods of insulin prescription.(1,8) In each hospital, it is important to establish a clear protocol for correction of hypoglycemia, which can be implemented by nurses.(8)

Table no. 3. Example of a basal-bolus insulin regimen for non-critically ill patients with type 2 diabetes (8)

- Discontinue oral or injectable diabetes medication
- Starting insulin: total daily dose
  - 0.2-0.3 U/kg of body weight in patients older than 70 yr and/or glomerular filtration rate less than 60mil/min/m^2
  - 0.4 U/kg of body weight for patients who have blood glucose concentration between 140 mg/dl and 200mg/dl
  - 0.5 U/kg body weight for patients with blood glucose above 200 mg/dl
- Total daily dose is distributed as approximately 50% basal insulin and 50% nutritional insulin.
- Prandial insulin is divided equally, at the 3 principals meals. Prandial insulin is holded if the patient is not able to eat.
- Correction dose – regular insulin or rapid-acting insulin analog

Glycemia (mg/dl)	Insulin-sensitive	Usual	Insulin-resistant
141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

- If the patient is able to eat, the correction dose is administrated before each meal and at bedtime following the "usual" column
- If the patient is not able to eat, is elderly or has impaired renal function, the correction dose is administrated following the "insulin-sensitive" column
- If the patient is treated with more than 80U/day before admission or he is in treatment with corticosteroids, the correction dose is administrated following the "insulin-resistant" column

Table no. 4. Clinical situations that increase the risk of hypo / hyperglycemia in the hospital

Changes in calories and carbohydrates intake (postoperative status of "nothing by mouth", enteral nutrition, parenteral nutrition)
Changes in clinical status or medication (e.g. corticosteroids, inotropic and vasopressor etc.)
The inability of physicians to make appropriate treatment adjustments based on daily blood glucose monitoring
Extended use of a "sliding scale insulin" as the only method of antihyperglycemic treatment
Lack of coordination between glucose determination, insulin and meals
Lack of coordination between the medical teams in the throughput of patients between different departments of the hospital
The use of long acting sulfonylureas for the elderly and those with renal or hepatic
Errors in writing and transcribing types and doses of insulin

CONCLUSIONS

Diabetes is a risk factor for postoperative complications. Acute hyperglycemia in the perioperative period is associated with adverse clinical consequences. Careful, fair and standardized glucose management in the perioperative period is necessary, in order to decrease the risk of postoperative complications. In patients with diabetes undergoing general surgery interventions, further studies are needed to define optimal glycemic targets and the most effective strategies by which these goals can be achieved.

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