The goal of this article is to present the importance of diabetes mellitus as comorbidity in patients submitting to different surgical procedures. The results of numerous studies that have been presented here showed worst surgical outcome in patients with bad diabetes control. This review considers the elements for preoperative evaluation and preparation of these patients (former therapy, longterm metabolic control, micro and macrovascular complications etc). According to existing data, the goals for preoperative preparation and the regimes for their achievement have been defined. Also, the regimes for blood glucose controle during intraoperative and postoperative period have been evaluated in this article.

Key words: preoperative preparation, diabetes mellitus, surgery, anesthesia

INTRODUCTION

Diabetes mellitus (DM) represents a heterogenous group of disorders with a common feature of absolute or relative lack of insulin. The disease is characterised by a variety of hormonally induced metabolic disorders, diffuse microvascular lesions and chronic end-organ complications.1 According to the American Diabetes Association (ADA) latest guidelines (2009): fasting blood glucose (BG) ≥7.0 mmol/l OR symptoms of hyperglycemia with random plasma glucose ≥11,1 mmol/l OR 2 hour plasma glucose ≥11,1 mmol/l during the OGTT, are diagnostic for DM.2

DM is the most commonly encountered endocrine/metabolic disease, with rising prevalence that in the past decades. Currently, 6.4% of population in developed countries is known to be diabetic, and the prevalence is predicted to increase to 7.7% to the year of 2030.3 Obese adolescents are particularly at risk (prevalence of diabetes among them is 4%, while 25% of them has impaired glucose tolerance).4

Due to advances in medical and surgical therapies and rising prevalence of diabetes in general population, more diabetic patients are subject to various kinds of surgeries or are likely to need some surgery because of diabetes complications. The estimated incidence of DM in general surgical population is around 15-20%, while it is over 50% among vascular surgical patients (scheduled for surgery because of chronic diabetes complications).5

THE IMPACT OF DM ON PERIOPERATIVE PERIOD

Patients with DM have an established association with adverse perioperative outcomes with an increased morbidity and mortality, which has been shown by a number of studies.

Large scale, retrospective study of Marshall and al, analyzing data of more than 1.000.000 patients grouped according to the quality of diabetic control, has shown that uncontrolled DM results in increase of surgical and systemic complications and mortality, as well.6 The other large, controlled clinical study, conducted among 108593 non-cardiac non-vascular surgical patients, revealed that patients with higher preoperative BG values had higher mortality.7 The lenth of hospital stay was higher among diabetics, due to more frequent postoperative complications, particularly wound infection and impaired healing.8 It is also well documented that good preoperative glycemic control significantly reduces postoperative wound infection and impaired healing.9 Infections constitute 2/3 of postoperative complications, being the principal cause of 20% postoperative deaths among diabetics.

Adverse outcome of surgery in diabetics can be explained by several mechanisms. Diabetics have decreased production and impaired reactivity of nitrous-oxide in the endothelium. Complement activation is decreased with
the concomitant increase in cytokine synthesis and endothelium adhesive molecules expression. Leukocyte function is also derailed with reduced capability for phagocytosis and chemotaxis, thus making diabetic patients more vulnerable to infection and inflammation. Impaired and prolonged wound healing is the result of decreased collagen formation and depleted leukocyte activity. Administration of insulin is crucial for early development of granulation tissue and subsequent fibroblast growth and collagen synthesis.10

It is postulated that glucose itself can be toxic. Hyperglycemia promotes reactions of non-enzyme glycosylation leading to abnormal protein formation, lowering wound’s tensile strength and elasticity. High BG levels can also induce production of microglobulins by the liver and increase blood viscosity leading to intracellular swelling by stimulating production of large nondiffusible molecules (ex. sorbitol)11.

The immediate perioperative factors causing increased perioperative risk in diabetics are: neuroendocrine stress response with catabolic hormone secretion, perioperative starvation, anesthetic techniques and drugs, altered consciousness during general anesthesia, ciliary disturbances with altered absorption of subcutaneous insulin and immobilisation.12

PREOPERATIVE EVALUATION OF PATIENTS WITH DM

Preoperative evaluation of diabetic patients has to be very thorough and guided by criteria shown in table 1.13

Assessment of long-term metabolic control of DM

Quality of long-term preoperative metabolic control of diabetes (2-3 months) is usually obtained by the level of glycosylated hemoglobin (HbA1c). Normal HbA1c is in the range of 3.5%-6%, while levels over 7% indicate that current therapy is being inadequate, or that patient is not taking it regularly. Those patients are expected to need higher doses of perioperative insulin and to have increased risk for perioperative complications. HbA1c >8% is indicative of bad metabolic control with expected worse outcome of surgery. Retrospective study of Dronge at al. analyzing 490 diabetic patients undergoing major noncardiac surgery has shown that good preoperative control (HbA1c <7%) is associated with decrease of infectious complications.9 More attention has been raised lately to HbA1c in perioperative risk assessment, and it was even thought about this variable to be included in diagnostic criteria for DM.

A detailed history of diabetic therapy is crucial during preoperative evaluation of diabetic patients. While type I DM is treated exclusively with various types of insulin, patients with type II DM can be treated with diet, oral hypoglycaemic agents (OH), and combination of OH and insulin. The attending physician should be familiar with type of patient’s insulin (regarding their duration of action), as well as with the types of OH (regarding their adverse effects, duration of action or interactions with other drugs).14

Insulin regimens in type I DM. The history of patient’s preoperative therapy should contain the information on total daily dose of insulin (TDD) which enables prediction of patient’s postoperative insulin requirements. If TDD is less than 30U, a good perioperative control is anticipated with usual insulin doses. TDD of insulin more than 80 U, it is usually associated with a higher degree of insulin resistance and possible difficulties with perioperative BG control.15

There are at least four groups of exogenous insulins regarding their time action profile. Rapid acting insulin analogues (Lispro, Aspart, Glulisine) have rapid onset (5-15 minutes) with peak effect after 60 minutes and duration of action of 4-5 hours. Short acting insulin (Regular) has onset of action in 30-60 minutes, peak after 2-4 hours and duration of 6-8 hours. Intermediate insulins (Isophane)

| TABLE 1 | ESSENTIAL COMPONENTS OF PREOPERATIVE EVALUATION OF DIABETIC PATIENTS |
|-----------------|--------------------------|------------------|-----------------|------------------|----------------|
| Components of preoperative evaluation | Consider |
| Characteristics of DM | Type of DM (1,2) | Duration of DM | Therapeutic regimen | BG (preprandial and 2h after meal, if possible), |
| Laboratory analyses | Urine analysis (albumin and ketons), BUN, creatinine, electrolytes, | Hemoglobin (+HbA1c) | Acute (DKA, HHS, hypoglycemia), |
| Complications of DM | Chronic: cardiovascular (CAD), hypertension, peripheral vascular disease, cerebrovascular disease, nephropathy, retinopathy, peripheral polyneuropathy |
| Assessment of comorbid conditions | Other therapy (except for diabetes) |
| Evaluation of airway | SJS (Prayer sign), Cervical spine, atlanto-occipital joint mobility |

Abbreviations: DKA-diabetic ketoacidosis; HHS-hyperglycemic hyperosmolar state; CAD-coronary artery disease; SJS-stiff joint syndrome
start acting after 2-4 hrs, with peak in 4-6 hrs and duration of 12-16 hrs. Finally, long-acting insulin analogues (Ul-
tralente, Glargine) act evenly after onset of aprox. 2 hrs,
with no peak of action throughout the 24 hour period.16

When determining total daily insulin requirement, it is
important to keep in mind that insulin secretion can be di-
vided into a basal and additional, stimulated secretion. Ba-
sal insulin secretion occurs even in the absence of oral in-
take and is is crucial for inhibition of catabolism and keto-
acidosis. Additional insulin secretion is controlled by va-
rious stimuli. The main stimulators of insulin secretion are
plasma glucose and fructose. The remainder, such as amino-acids,
gastrointestinal hormones (gastrine, cholecystokinine, se-
cretine, incretins), acetylholine and β-adrenergic agonists,
also play an important role. The most important inhibitors
of insulin secretion are cathecholamins (epinephrine and
norepinephrine), α-adrenergic agonists, cortisol, growth
hormone, glucagone, and some cytokines.10

It is, therefore, extremely important for diabetic pati-
ents to be provided with some basal insulin (usually in the
form of an intermediate insulin) in order to supress keto-
genesis and cover basal metabolic needs, even during star-
vation period.

Therapeutic regimen in patients with type 2 DM may in-
fluence anesthetic management, and so the details of the
pharmacological regimen, such as the type of drug, dose,
and administration mode should be ascertained during
preoperative assessment. It should be kept in mind that
some of oral antidiabetics can interreact with perioperati-
ve medications or influence postoperative glycoregula-
tion, causing prolonged and severe hypoglycemia, resul-
ting in adverse outcome of surgery.17

Oral hypoglycemic drugs (OH) act by different mecha-
nisms, having various side-effects which should be con-
sidered during preoperative evaluation. Sulphonylureas
and meglitinides stimulate insulin secretion, while bigu-
nides inhibit hepatic glucose production. Alpha-glucosi-
dase inhibitors inhibit intestinal absorption of glucose and
fructose, and thiazolidindiones enhance peripheral gluco-
se uptake, principally into muscle and fat tissue.17,18 In-
cretin agonists are newer class of OH, expected to make a
revolutionary progress in treatment of DM. Incretins are
intestinal gut hormones. Their secretion is meal stimu-
lated and they have a short half-life (2 minutes), being en-
zymatically cleaved by dipeptidyl peptidase (DPP4). Two
incretins have been syntetised by now for use in treatment
of DM: GLP1 (glucagone like peptide, exende; liraglu-
tide) and GIP (glucose dependent insulinotropic peptide).
They act through stimulation of insulin secretion as a re-
sponse to oral intake of glucose, inhibition of glucagone
secretion and delaying gastric empting.19 DPP4 (Sitaglipi-
tin, Vildagliptin) are newer class of OH which have a long
half-life and can be taken once daily (as a monotherapy or
in a combination with other OH). Their mechanism of ac-
tion resides on inhibition of enzyme DPP4, which pro-
longs action of incretins. They also improve function of
pancreatic β-cells.20

From the aspect of preoperative evaluation, and decision
making about changes of antidiabetic therapeutic regimen,
and the time to start soma and its duration of action the
first time, it is important to be familiar with side effects and con-
traindications for use of OH. (Table 2)14,21

Evaluation of chronic complications of DM

Preoperative evaluation of diabetic patient includes tho-
rough search for any diabetes associated chronic compli-
cations (angiopathy, peripheral neuropathy, nephropathy,
retinopathy) as they increase risk for postoperative mor-
bidity and mortality. Surgery itself can exacerbate DM or
elicit acute complications of the disease.22

Cardiovascular diseases such as coronary artery disease,
peripheral vascular disease, hypertension and cerebrovas-
cular disease are common in diabetic patients. That’s why
diabetics are under risk for myocardial ischemia during
perioperative period. It is usually necessary to perform so-

<table>
<thead>
<tr>
<th>OH</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Hypoglycemia (chlorpropamide-long half-life)</td>
</tr>
<tr>
<td>Biguinides</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Metabolized completely by the liver (avoid in liver disease; suitable in renal failure)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>CVS complications (aggravate peripheral edemas); CI:NYHA III and IV, attention HYHA II!</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Worsening of renal function; transaminases (CI: renal and hepatic diseases, inflammatory and obstructive bowel disease)</td>
</tr>
<tr>
<td>Incretin agonist</td>
<td>Pancreatitis, nausea, vomiting</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Concentration of gastrin-releasing peptide, substance P, neuropeptide (hypertension, immunological reactions, neurogenic inflammation)</td>
</tr>
</tbody>
</table>

Abbreviations: CVS-cardiovascular system; CI-contraindication
me additional cardiovascular assessment, including ergometric tests, stress-ecocardiography, etc.10

Diabetic nephropathy is specially important for anesthesiologists since majority of drugs used during anesthesia are being excreted by the kidney. Presence (and degree) of albuminuria in 24-hour urine are diagnostic for severe diabetic nephropathy. Therefore, particular attention should be given to renal function evaluation and urine albumin, serum creatinine level and BUN should be assessed in all diabetic patients.12

Peripheral neuropathy has to be meticulously evaluated, since it can have impact on outcome, particularly when regional anesthesia is planned. Recent investigations revealed higher susceptibility of peripheral nerves to trauma and toxic effects of local anesthetics in diabetic patients.12,22

Diabetic autonomic neuropathy (DAN) is a common feature of diabetes, present in more than 50% of patients with type 1 DM, and 20% with type 2 DM. It can be asymptomatic or accompanied by diarrhea, sweating or postural hypotension. DAN results in gastroparesis and a delay in gastric emptying enhancing the risk for regurgitation and acid aspiration during the induction of anaesthesia. It is usually underestimated, and not a subject of routine preoperative evaluation, but it has been shown that patients with loss of heart rate resulting from DAN, are at risk for ventricular arrhythmias and sudden postoperative death. DAN also causes unexpected perioperative bradycardia and hypotension, specially in cardiosurgery.12,22

Airway evaluation

Difficulties with tracheal intubation are an established risk in diabetics due to limited mobility of upper cervical spine. All diabetic patients require a thorough airway evaluation, specially in the fields of surgery with higher incidence of difficult intubation (such as thyroid surgery). Patients with type 1 DM can develop "stiff joint syndrome" (SJS), disabling neck extension and resulting in poor or impossible visualisation of glotis during direct laryngoscopy. SJS must be diagnosed preoperatively performing the "prayer sign". The patient is asked to put his hands in the position for prayer, and if stiffed interphalangeal joints keep fingers from crossing and prevents palmar sides of fists to touch, the test is positive and predicts difficult intubation.22,23

PREOPERATIVE MANAGEMENT OF PATIENTS WITH DM

The immediate aims of perioperative management in diabetic patients are to avoid: hypoglycemia (<3.8 mmol/l) as well as excessive hyperglycemia (> 12mmol/l), loss of electrolytes (potassium, magnesium, phosphate) and to prevent lipolysis, proteolysis and ketogenesis.22,23

There are several questions that can be raised regarding those perioperative goals: What are the target BG values that provide uneventful perioperative course and lead to favorable outcome of surgery? Which BG levels require postponing of surgery? What therapeutic regimens are available for achieving target BG levels?

There was a fear, in the past decades, that unrecognized hypoglycemia during general anesthesia represents the major risk for postoperative outcome in diabetic patients, which led to the concept of "permissive hyperglycemia". High BG levels of 12 mmol/l (and even 14 mmol/l in patients with bad metabolic control) were tolerated.

In order to prevent and minimize adverse effects of both, hypo- and hyperglycemia, it is important to establish the target BG level in the perioperative period. Unfortunately, there has been considerable controversy over the safety of different BG levels. There are authors indicating the need for tight glycemic control (4.4-5.6 mmol/l), while the others suggest that BG should be kept in the range of 6.1-11.1 mmol/l. On the other hand, in vitro studies reveal that adverse effects of hyperglycemia can be seen at the levels of 9-10 mmol/l.24,25,26

It has been shown that traumatized type 1 diabetics may develop ketoacidosis at BG levels over 10mmol/L (even at 10.1mmol/l!), and with no clinical signs. In that case, urine ketons are diagnostic for ketoacidosis.27,28

American College of Endocrinology (ACE) recommended that BG should be in the range of 6-10 mmol/l in order to prevent effects of hypo- and hyperglycemia. The same association’s statement is that significant variations in BG levels resulting from attempts to achieve tight glycemic control (<6.1mmol/l) make more damage than the BG level itself.28,29

Most of the authors agree that scheduled surgery should not be postponed if BG level on the morning of surgery is <11.1mmol/l. If it is between 11.1-19.5 mmol/l, insulin should be provided, and surgeon and anesthesiologist should discuss whether to delay or proceed with surgery. If BG is >20mmol/l, scheduled surgery is postponed until BG control is improved.

PERIOPERATIVE DIABETES THERAPY

There are different regimens for treating diabetic patients undergoing surgical procedures. Practical approach to diabetic patient is influenced with the type of diabetes, antecedent diabetic therapy (insulin, OH, combination of insulin and OH, diet), level of metabolic control, treatment of comorbidities and type and length of surgical procedure.30

Patients treated with diet only, generally, do not require any therapy during the perioperative period. According to BG levels, small amounts of short-acting insulin may be given with frequent BG monitoring (every 2-4 hrs).13,22,30

Perioperative management of diabetic patients treated with OH depends on type of preoperative OH, type and length of surgery and expected resuming of oral intake. In the case of minor surgery, short-acting OH should be continued till the day of surgery (including the morning of surgery). Long acting OH should be held two days prior to surgery and replaced with short acting OH or short-acting insulin. That regimen should be kept until patient resumes eating. If oral intake is discontinued for a longer period, some basal insulin should be provided. It’s not
that clear how to manage type 2 diabetics undergoing surgery with moderate surgical stress (neither minor nor major). It has been noticed that insulin infusions in those patients cause significant metabolic derangements and that it better to administer insulin and glucose according to frequent glucose monitoring.\textsuperscript{12,22,30}

General rules for perioperative management of insulin treated diabetics (all type 1 and some of type 2 DM) suggest discontinuation of long acting insulin 1-2 days before surgery. It should be replaced with intermediate-acting mixed with short-acting insulin twice daily or short-acting insulin before every meal. If the procedure is not long or complex, subcutaneous insulin can be continued. Long or complex procedures require intravenous insulin infusions. Complex procedures, such as cardiovascular, renal transplant, neurosurgery or abdominal surgery, are long surgery, characterized with significant hemodynamic fluctuations or associated with variable tissue perfusion, disabling predictable absorption of subcutaneously administered insulin.\textsuperscript{13}

Insulins for intravenous administration are either rapid acting or short acting, and they can be administered in two ways: as small IV boluses (4-6-8U) or IV infusions. The latter can be prepared as GIK infusion, containing glucose, insulin and potassium in the same bottle or variable rate infusion, where insulin and glucose are administered from separate bags in the same vein ("piggyback technique"). Variable rate infusions are preferred method of IV insulin administration, since it allows easy adjustments of both infusions. They are usually prepared to contain 1U of insulin/1ml, by mixing 100U of short-acting insulin in 100ml of normal saline.\textsuperscript{22}

Basal insulins (intermediate or long-acting) are for subcutaneous use only.

Insulin infusions are generally safe and readily titrated because the half life of short-acting insulin is 5 minutes and biological duration of action is less than 20 minutes. The optimal protocol hasn’t been established yet, but they are usually started at 0,5-1 U/h (0,2-1,5), with concomitant infusion of 5% dextrose (100ml/h). There are several algorithms for administration of insulin infusions, where the infusion rate (and so the insulin dosage) adjusts to the observed BG level. Smaller doses of insulin are needed for well controlled diabetics, while patients undergoing extensive surgery, those treated with steroids and diabetics with TDD of insulin > 80U require higher doses of insulin for achieving targeted BG levels. Insulin infusions are started on the morning of surgery (or the evening before surgery) and should be continued until 2 hours after the first meal.\textsuperscript{22}

Insulin infusion administration can be associated with the occurrence of hypoglycemia (BG < 60mg/dl), which has to be treated promptly, because of potentially deleterious effects on organs using glucose as the main metabolic substrate. Management of hypoglycemia during insulin infusion should be based on this strategy:\textsuperscript{22}

1. Stop insulin infusion
2. Give 50% dextrose IV (25ml if patient is awake or 50ml if patient is under general anesthesia)
3. Recheck BG every 20 minutes
4. Give 50% dextrose again in 25 minutes, if BG is still < 3,3mmol/l
5. Continue insulin infusion once BG is >3,8mmol/l

When diabetic patients resume eating, their therapy should involve insulin divided into basal, prandial and correction insulin. Basal insulin (0,2-0,3 U/kg/d) should be provided in the form of long-acting insulin once daily or twice daily intermediate insulin. Prandial insulin (0,05-0,1U/kg) is usually given in the form of short-acting or rapid-acting insulin before meal, serving to prevent post-prandial spikes of BG. Correction insulin, in the form of short-acting insulin should be administered if BG is >8mmol/l (1-4U for each increment of 3mmol/l based on suspected insulin sensitivity).\textsuperscript{13,22,30}

Frequent BG monitoring with adjustments of insulin therapy according to observed glucose level, is essential in the perioperative period. Major surgery and poorly controlled diabetes require BG measurement every hour. When BG achieves target range, BG monitoring can be continued every 2 hours, and later every 4 hours. More reliable results are obtained from venous samples than from capillary blood. It should be emphasized that results of BG measurements are influenced by a variety of factors, such as: hypoperfusion, anemia, hyperbilirubinemia and hyperuricemia, manitol or dextrane administration, as well as treatment with dopamine and paracetamol.\textsuperscript{31}

CONCLUSION

Preoperative evaluation and perioperative management of diabetic patients are not based on sufficient number of randomized studies, and little data is available to allow specifying the optimal strategy, guidelines or protocols. The approach to these patients is based on comprehension of diabetes patophysiology, physiological effects of insulin and intensive BG monitoring. Attempts to keep BG in tight, physiological range, might be inappropriate for diabetic patients during perioperative period.

SUMMARY

PREOPERATIVNA PRIPREMA BOLESNIKA SA DIJABETESOM MELITUSOM

U radu je ukazano na značaj prisustva dijabetesa melitus a kao komorbiditeta kod bolesnika koji se podvrgavaju hirurškom lečenju iz različitih indikacija. Prikazani su rezultati brojnih studija koje potvrđuju da je lošiji ishod hirurškog lečenja kod bolesnika sa loše regulisanim dijabetesom. Razmatrani su elementi preoperativne evaluacije i pripreme ovih bolesnika (prethodni režimi lečenja, dugo-ročna metabolička kontrola, prisustvo mikro i makrovaskularnih komplikacija itd). U skladu sa preporukama, definisani su ciljevi preoperativne pripreme, kao i režimi za njihovo postizanje. Takodje su razmatrani i intraoperativni i neposredno postoperativni režimikontrole glikemije.

Ključne reči: preoperativna priprema, dijabetes mellitus, hirurgija, anestezija
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