A systematic review of management strategies for diabetic patients and the pathophysiology of hyperglycemia perioperatively.

Al-Awa Marie-Isabelle[1], Dr. Al-Harizi Randa[2]

[1.] MBBS, Ibn Sina Medical College, Jeddah, KSA
[2.] Professor of Internal Medicine, Ibn Sina Medical College, Jeddah, KSA
alawamarie@gmail.com; randaalharizi@yahoo.com

Abstract: With the increasing number of diabetes mellitus worldwide and knowing that a quarter of patients might need surgery at least once in their life, it is important to know how to decrease morbidity and mortality perioperatively. 66% of infections account as diabetic patients' postoperative complications and nearly one quarter of perioperative deaths. Our aim through this review is to understand the importance of correct glycemic control. It has been proved that tight glycemic control was worse than "less tight" control. Perioperative morbidity and mortality could be prevented with less glycemic variability due to correct titration to each individual's need. Correct glycemic control perioperatively depends on each case. Stress hyperglycemia remains a challenge to all, added to the effects of volatile anesthetic agents that produce hyperglycemia by inhibiting insulin release. Intensive insulin therapy (80-110 mg/dL) for critically ill surgical patients appears to be beneficial but requires frequent measurement of glucose to avoid hypoglycemia. Other studies have however, proved that tight glycemic control has been shouldn't be the method of choice in critically ill surgical patients. Surgical patients benefit from maintaining serum glucose concentrations <200 mg/dL. Further studies are yet needed to determine the appropriate target range and the influence of nutritional provision and other factors on outcome. Tight glucose control appears to be more beneficial in patients without diabetes than in those with known diabetes. It also may be more beneficial in improving outcomes in surgical rather than nonsurgical ICU patients, and in decreasing sepsis rather than mortality.
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Introduction:

The International Diabetes Federation estimated that in 2013, 381 million people had diabetes mellitus.[1] This number is estimated to be almost doubled by 2030.[2] Saudi Arabia is in the top 10 of highest prevalence of Diabetes worldwide with 23,9% of diabetics among its population. [3] This number is yet constantly growing due to the increase of obesity and unhealthy lifestyle. Chronic complications of the disease resulting in microangiopathy (retinopathy, nephropathy, and neuropathy) and macroangiopathy (atherosclerosis) directly increase the need for surgical intervention and the occurrence of surgical complications due to infections and vasculopathies [5-6-7-8]. Statistics have showed that, an estimate of 25% of diabetics might need surgery. Mortality rates have been estimated to be up to 5 times greater than in non-diabetic patients, often resulting due to end-organ damage caused by the disease and uncontrolled blood glucose concentrations. [4]

Despite earlier researches, which suggested decreased morbidity and mortality with "tight" glucose control, later investigations found no benefit when hyperglycemia was aggressively treated with insulin.[27] Because of these conflicting data, the optimal glucose range has not been defined. Studies have also identified the possible downside of tight glycemic control because of the increased incidence of severe hypoglycemia. The risk of increased glucose variability should be recognized as well, as it is associated with increased risk for worse outcomes. Diabetic patients experience chronic hyperglycemia and often require more intensive perioperative glucose control. When diabetic patients are evaluated preoperatively, appropriate management of oral hypoglycemic agents is necessary, as several of these agents need special consideration. Currently, recommendations for perioperative glucose management vary, but, most suggest that tight glucose control may not be beneficial, while mild hyperglycemia appears to be well tolerated.

Effects of uncontrolled diabetes mellitus:

Uncontrolled DM is our biggest fear as health practitioners. The complications that it leads to are disastrous and make our job much harder. Diabetes is characterized by a hyperglycemic state and insulin resistance. In many situations in hospitalized patients that are chronically ill or that have experienced a

major trauma or undergoing surgery, patients may develop what we call a hypermetabolic stress response. It involves an increase in endogenous hepatic glucose production and insulin-stimulated peripheral glucose uptake reduction. Also referred as "stress hyperglycemia", it was initially considered as a beneficial adaptation in diabetics and non-diabetics, as an additional supply of glucose was available. Yet, many data show that acute severe hyperglycemia leads to multiple immediate serious adverse outcomes.

The severity of hyperglycemic response in patients undergoing major surgery may be affected by an individual's ability to control glucose [9] and extent of surgery.[10]

Therefore, glucose intolerant or diabetic patients, with a more invasive procedure, would develop more severe hyperglycemia. This is mainly due to glucagon, epinephrine, cortisol, growth hormone, and norepinephrine increase gluconeogenesis and glycogenolysis. [24] Gluconeogenesis and plasma glucagon are thought to be increased by Tumor necrosis factor-alpha.[25] Concerning insulin production, it is also increased, but critical illness and sepsis impair the insulin signaling pathway. This leads to a decrease in glucose transporter (Glut)-4 mediated glucose uptake, which in turn leads to insulin resistance.[26]

In surgical patients, perioperative hyperglycemia increases the risk of morbidity and mortality postoperatively. [11-12] Numerous adverse cellular and biochemical events occur such as abnormal monocytes and polymorphonuclear neutrophil function, decreased intracellular bactericidal activity, and glycosylation of immunoglobulins[13-14]. Hyperglycemia activates blood coagulation, circulation prothrombin and D-dimers are increased leading to platelet aggregation and thrombosis[15]. It inhibits complement opsonization by competing with microorganisms to their attachment through complement glycation.[16-17-18]

Inflammation and proinflammatory cytokines is also induced by hyperglycemia. Added to that, intrinsic myocardial protective mechanisms, such as ischemic preconditioning is absent due to hyperglycemia.[19] This means that it abolishes effective glycolysis and mitochondrial respiration and increases cell apoptosis.[20] It is caused by an uncontrolled influx of high level of glucose into cells, leading to a vicious cycle of up-regulation of Glut-1 transporters.[21] This increases the production of reactive oxygen species, which then creates a cascade of cellular effects, increasing polyol pathway influx, advanced glycation end products, NFκB, and hexosamine pathway. [22] These downstream consequences lead to blood-flow disturbances, increased vascular permeability, angiogenesis, capillary occlusion, and pro-inflammatory gene expression.[23]

Preoperative Management:

Knowing that patients with DM are treated with different regimens and are scheduled for surgery at varying times of the day, there is no established consensus for optimal perioperative management.[29-30-31-32-33]

However, to minimize glycemic variability due to stress hyperglycemia being subjected to tight glucose control with the risk of hypoglycemia occurring, it is important that patients' general doctor, internist, or endocrinologist, anesthetist, surgeon and dietician, be aware of any modifications done for an optimal glycemic control.

On an other hand, during fasting state or during inadequate oral intake patients are more at risk of developing hypoglycemia. Thus, a thorough understanding of the glucose management issues in diabetic patients beginning in the preoperative period is necessary. Diabetic regimens include insulin but also oral hypoglycemic drugs, such as sulfonylureas and meglitinide agents. Regimens that potentially produce hypoglycemia during fasting or low intake , perioperatively. The long half-life of many of these drugs make titration in the rapidly changing clinical parameters difficult to titrate.

Concerning oral hypoglycemic insulin secreting agents (sulfonylureas, meglitinides), they are held 24 hours prior to surgery. The major risks with these agents are that they have the potential to induce hypoglycemia and cardiac ischemia. In order to stimulate insulin secretion from the pancreas they bind to the ATP-dependent potassium (K_{ATP}) channel in the pancreatic ß-cells, leading to closure of these channels. Pancreatic β-cells are very responsive to glucose concentrations and insulin release is augmented. However, in addition to closure of the pancreatic K_{ATP} channel, cardiac K_{ATP} channels are also affected by these agents. Closure of the cardiac K_{ATP} channel may increase risk for myocardial ischemic injury by blocking ischemic preconditioning, mentioned above. [27] Indeed, sulfonylurea use was associated with in-hospital mortality in patients undergoing percutaneous coronary intervention following myocardial infarction [34]. Further, ischemic preconditioning was blocked by glyburide in non-diabetic patients undergoing angioplasty [35].

A commonly used for oral hypoglycemic treatment of type II diabetes mellitus, known as Metformin, is also stopped 24 hours prior to surgery. Metformin lowers blood glucose levels by decreasing

hepatic glucose production and intestinal glucose absorption, and increasing peripheral glucose uptake and utilization [36]. Concern has been raised due to its chemical similarities with its predecessor, Phenformin, which was associated with high risk of lactic acidosis and approximately 50% mortality [36]. Perioperative Metformin-associated lactic acidosis has been reported [37-38]. In addition, because of predisposing conditions, such as, congestive heart failure, renal impairement, hypoxemia, hypovolemia surgical patients are already at increased risk for lactic acidosis. Yet, a study showed that there was no increase in risk of adverse effects with perioperative administration of Metformin [39]. Metformin may be restarted following surgery after adequate oral intake has resumed and avoided in patients with renal insufficiency, hepatic impairment, or heart failure because of the increased risk of metabolic acidosis.[27] (see table 1)

Table 1: Considerations for Oral Agents

Class of Oral Agent	Example	Considerations
Alpha-glucosidase inhibitors	Acarbose	Inhibit enzymes that metabolize carbohydrates; no benefit if NPO
Secretagogues (eg, sulfonylureas, meglitinides)	Glyburide, glimepiride	Hypoglycemia, prolonged action, may be unpredictable, difficult to titrate
Biguanides	Metformin	Risk of lactic acidosis; use cautiously in the presence of renal or hepatic insufficiency, chronic heart failure (CHF); may be found in combination medications
Thiazolidinediones	Rosiglitazone	Increased intravascular volume (CHF), slow onset of effect, difficult to titrate
Dipeptidyl peptidase-4 (DPP-4) inhibitor	Sitagliptin	Slows inactivation of incretin hormones to enhance physiologic glucose control; dosage reduction required for renal insufficiency

Preoperative blood glucose should be maintained between 150-180 mg/dL or less. An elevated HbA1c measured immediately before surgery may predict postoperative diabetic-related complications. The value of HbA1c of less than 6% is ideal before elective surgery.

Oral hypoglycemic agents are restarted once the patient is back to normal adequate feeding. Until then, short or intermediate acting insulin is administered to treat hyperglycemia. Its ability to being titrated to rapidly changing glucose levels is the preferred glycemic control method postoperatively. [27]

Insulin dependent patients are advised to reduce their bedtime dose of insulin the night before surgery to prevent hypoglycemia while nil per os (NPO) [4] In other recent guidelines, clinicians advice that longer-acting insulins (e.g. Ultra-lente, Lantus, Levemir) should be reduced to half of the usual dose the morning of surgery. Patients using 70/30 or 75/25 (pre-mixed) insulin should replace this dose with NPH on the morning of surgery. The NPH dose should be half of the mixed insulin dose. Patients with type I diabetes who maintain glucose control with an insulin pump may need continuation of a basal insulin rate with their insulin pump the morning of surgery. [27]

Target blood glucose levels:

Target blood glucose concentrations were modified to somewhat higher values in the last years, with the expectation of decreasing the risk of hypoglycemia, which is itself a marker of poor outcome in critically and non-critically ill patients. In the intensive care unit (ICU), the threshold to start treatment is a blood glucose (BG) equal to or less than 180 mg/dL. I.V. insulin is the treatment of choice in critically ill patients because of its rapid onset and offset of action. Once I.V. insulin is started, the BG should be maintained between 140 and 180 mg/ dL; a lower BG target (110-140 mg/dL) may be appropriate in some selected patients. Targets of less than 110 mg/dL or more than 180 mg/dL are no longer recommended. In non-critically ill patients, fasting BG targets are less than140 mg/dL. Random BGs of less than 180 mg/dL are recommended. Scheduled subcutaneous insulin is the treatment of choice for hyperglycemia in non-critically ill patient and use of sliding-scale insulin is strongly discouraged. To avoid hypoglycemia, insulin regimens should be reassessed if BG falls to less than 100 mg/dL. [40]

A number of clinical trials have involved various patient populations and examined the

implications of perioperative hyperglycemia. Based on results, the American Diabetes Association made recommendations for managing blood glucose levels in hospitalized patients with DM. (see table 2) We understand that surgical patients benefit from maintaining serum glucose concentrations <200 mg/dL. In other studies, intensive insulin therapy (80-110 mg/dL) for critically ill surgical patients appears to be beneficial but requires frequent measurement of glucose to avoid hypoglycemia. Further studies are yet needed to determine the appropriate target range and the influence of nutritional provision and other factors on outcome.[41]. Tight glucose control appears to be more beneficial in patients without diabetes than in those with known diabetes. It also may be more beneficial in improving outcomes in surgical rather than nonsurgical ICU patients, and in decreasing sepsis rather than mortality.[42].

These conclusions made recently, do not mean that tight glycemic control should be abandoned in practice, it is important that further researches are carried out according to appropriate glycemic control matched to appropriate population. [42]

Table 2: Recommendations of the American Diabetes Association to manage blood glucose level.

Patient Population	Blood Glucose Target	Rationale
General medical/surgical*	Fasting: 90-126 mg/dL Random: < 200 mg/dL	Decreased mortality, shorter length of stay, lower infection rates
Cardiac surgery*	< 150 mg/dL	Reduced mortality, reduced risk of sternal wound infections
Critically ill†	< 150 mg/dL	Beneficial effect on short-term mortality, morbidity; length of stay
Acute neurologic disorders‡	80-140 mg/dL	Lack of data, consensus on specific target; consensus for controlling hyperglycemia
*American Diabetes Association. †Society Critical Care Medicine. ‡American Heart Association/American Stroke Association.		

Intraoperative glycemic control:

Stress hyperglycemia develops during surgery in both diabetic as well as non-diabetic patients. Other factors may also contribute to hyperglycemia during the perioperative period, including administration of dextrose-containing I.V fluids, hypothermia [43], increased lactic acid, and decreased exogenous insulin activity [44]. Administration of heparin [45] and glucose-containing cardioplegic solutions [46] contribute to hyperglycemia, in patients undergoing cardiac surgery.

In a study conducted in 2008, by Zuurbier et al, the effects of anesthetic agents were studied on anaesthetized and non-anesthetized (control) rats. It consisted on determining and comparing levels of plasma glucose and insulin under the effects of pentobarbital (PENTO), isoflurane (ISO), sevoflurane (SEVO), ketamine-medetomidine-atropine (KMA), and sufentanil-propofol-morphine (SPM) and their effects on the cardiac cellular localization of hexokinase (HK). The role of mitochondrial and sarcolemmal K(ATP)-channels and alpha2-adrenergic receptor in ISO-induced hyperglycemia was also evaluated. Results proved that, “mean arterial blood pressure was similar among the different anesthetic strategies. PENTO (5.3 +/- 0.2 mM) and SPM (5.1 +/- 0.2 mM) had no significant effect on plasma glucose when compared with control (5.6 +/- 0.1 mM). All other anesthetics induced hyperglycemia: 7.4 +/- 0.2 mM (SEVO), 9.9 +/- 0.3 mM (ISO), and 14.8 +/- 1.0 mM (KMA). Insulin concentrations were increased with PENTO (2.13 +/- 0.13 ng/mL) when compared with control (0.59 +/- 0.22 ng/mL), but were unaffected by the other anesthetics. Inhibition of the mitochondrial K(ATP) channel (5-hydroxydecanoate acid) or the alpha(2)-adrenergic receptor (yohimbine) did not prevent ISO-induced hyperglycemia. Only the nonspecific K(ATP) channel inhibitor glibenclamide was able to prevent hyperglycemia by ISO. Cytoslic HK relative to total HK increased in the following sequence: control (35.5% +/- 2.1%), SEVO (35.5% +/- 2.7%), ISO (36.6% +/- 1.7%), PENTO (41.2% +/- 2.0%; P = 0.082 versus control), SPM (43.0% +/- 1.8%; P = 0.039 versus control), and KMA (46.6 +/-

2.3%; P = 0.002 versus control).” [49] We may understand through that, volatile anesthetics and KMA induce hyperglycemia, which can be partly explained, by impaired glucose-induced insulin release. The data indicate that the inhibition of insulin release by ISO is mediated by sarcolemmal K(ATP) channel activation. The use of PENTO and SPM is not associated with hyperglycemia. SPM and KMA reduce the anti-apoptotic association of HK with mitochondria. [49]

As several earlier results found that hyperglycemia was associated with postoperative outcomes, some report that intraoperative hyperglycemia, defined as the measurement of four consecutive blood concentrations greater than 200 mg/dL, was associated with much higher risk of mortality, as well as increased risk for cardiovascular, respiratory, renal and neurologic morbidity [47]. Another research by, Duncan and colleagues found that, although severe intraoperative hyperglycemia (average BG >200 mg/dL) was associated with high risk of morbidity and mortality, BG closest to normoglycemia (140 mg/dL or less) were also associated with increased mortality and morbidity [12]. The lowest risks of adverse outcome were in fact found with a BG level ranging between 141 and 170 mg/dL. These results suggested that mild hyperglycemia was well tolerated and “tight” glucose control during cardiac surgery was not associated with improved outcomes. Actually, lowest glucose concentrations during the intraoperative period were associated with an increased risk of complications. However, during postoperative period, the risk of adverse outcomes consistently decreased with decreasing glucose concentrations.[27]

Another comparison, I would like to mention was a review on outcomes of use of lactated Ringer’s versus Normal Saline infusions during surgery and after surgery on blood glucose. Knowing that hyperglycemia is associated with poor postoperative outcomes after carotid endarterectomy. This retrospective study examined the effect of lactated Ringer's compared to normal saline solutions on intraoperative glycemic control in diabetic patients undergoing carotid endarterectomy. They have concluded that lactated Ringer's solution does not appear to cause a major change in the mean blood glucose levels in diabetic patients undergoing carotid endarterectomy compared to patients receiving normal saline, yet they think that randomized controlled trials are needed to further determine whether lactated Ringer's solution adversely affects glucose control in diabetic surgical patients.[48]

Conclusion:

Diabetes today is a challenge that all countries worldwide are facing. To attain best health care our aim is to manage hyperglycemia perioperatively, in order to prevent any further complications. Until now, no recipe has been given, each and every patient is unique and should be treated uniquely according to his condition. With this review, we have understood the different reasons behind hyperglycemia in surgical patients, the target values of each category of patients, how and when to correctly control blood sugar as anesthetists. Knowing that volatile anesthetics and KMA induce hyperglycemia, which can be partly explained, by impaired glucose-induced insulin release, hyperglycemia increases in patients. In conclusion, surgical patients benefit from maintaining serum glucose concentrations <200 mg/dL. In other studies, intensive insulin therapy (80-110 mg/dL) for critically ill surgical patients appears to be beneficial but requires frequent measurement of glucose to avoid hypoglycemia. Further studies are yet needed to determine the appropriate target range and the influence of nutritional provision and other factors on outcome. Tight glucose control appears to be more beneficial in patients without diabetes than in those with known diabetes. It also may be more beneficial in improving outcomes in surgical rather than nonsurgical ICU patients, and in decreasing sepsis rather than mortality.

Still, researches should be further carried out, in order to minimize morbidity and mortality of rapid glucose variability. A proper lifelong multisystem follow-up before, during and after hospital stay of each patient is the key to reducing further morbidity and preventing early mortality. The variability of oral hypoglycemic regimens and insulin dosing may not be easy to tailor to each individual, matching nutrition, activity, body requirements and health status. With new researches showing a promising project such as the closed-loop insulin infusion also known as the artificial pancreas, patients, patients’ families and caregivers, hope that this new invention could easily surpass its predecessor treatments while being reliable and accessible to all.

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