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REVIEW ARTICLE

Management of Adult Diabetic Patients Undergoing Surgery

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Abstract: ***Diabetes seriously interferes with surgical procedures and in turn surgery also seriously interferes with diabetic control. Metabolic perturbations observed as release of stress hormones added up with marked insulin resistance lead to altered glucose homeostasis resulting in severe hyperglycemia. Associated comorbid states further fuel this prevailing volatile state. Added to this misery is lack of definite guidelines regarding acceptable glycemic range in perioperative period. Also relation of glycemic state to wound healing and various insulin regimen is not established so far. A very clear, logical, calculated and planned strategy remains the need of the time to sail through this difficult and unpredictable situation. The management goal is to optimize metabolic control through close monitoring, adequate fluid and calorie repletion, judicious use of insulin to maintain desirable glycemic state and avoidance of hypoglycemia.***

Introduction

Diabetes is associated with increased requirement for surgical procedures and is likely to be associated with longer hospital stay and increased perioperative mortality. [1,2]The higher number of adverse outcomes is due to a raised incidence of comorbid conditions which include heart disease, hypertension and renal failure in the diabetic patients. Surgical procedures can result in metabolic perturbations that alter glucose homeostasis and lead to persistent hyperglycemia. Instability resulting from these alterations leads to life threatening complications. [3,4] Undiagnosed diabetes is also associated with poorer surgical outcomes.

Stress Response and Glucoregulation

Stress response to surgery is the root cause of concern in diabetes. Invariant feature of metabolic stress response include release of catabolic hormones epinephrine, norepinephrine, cortisol, glucagon and growth hormone. [5,6]On the other hand, traumatic injury, tissue injury due to surgery, inflammatory states like infection and anesthesia also lead to metabolic stress response. All these states will result in decrease tissue responsiveness to insulin i.e. decrease in insulin sensitivity and increase in insulin requirement (insulin resistance state). [9-11]

ANTI INSULIN EFFECTS OF SURGICAL STRESS

In addition to insulin resistance induced by circulating stress hormones, surgical stress also results in deleterious effect on pancreatic β-cell function leading to inhibition of insulin secretion and fall in level of plasma insulin. Insulin secretory response to glucose also become impaired during surgery. (Mechanism of stress induced β- cell dysfunction remains unclear.)

Anabolic Actions of Insulin are Reversed

Insulin mediated stimulation of glucose uptake and glycogen storage, aminoacid uptake and protein synthesis by skeletal muscles and fatty acid synthesis in liver are reversed.

Anticatabolic Actions of Insulin are Attenuated

These actions include inhibition of hepatic glycogen breakdown, inhibition of gluconeogenesis, inhibition of lipolysis, inhibition of fatty acid oxidation and ketone body formation and inhibition of proteolysis and amino acid oxidation. Along with these inhibition of insulin secretion and insulin action due to stress leads to perioperative milieu towards hyper-catabolism.

Direct Catabolic Effects of Counter Regulatory (Stress) Hormones

Neuroendocrine response resulting in secretion of counter regulatory hormones happens due to the stress of general anesthesia and surgery. These hormones stimulate gluconeogenesis, glycogenolysis, inhibits glucose utilization by peripheral tissues and inhibit insulin secretion. [12,13]Glucagon causes increased hepatic glucose production and ketogenesis. Corticosteroids lead to increase hepatic glucose production and induction of lipolysis. [14]Growth hormone potentiates the catabolic effects of catecholamines and glucagon. The products of lipolysis and proteolysis become substrates for gluconeogenesis in liver. All these effects occurring due to stress response and consequent altered glucoregulation predisposed to severe hyperglycemia which is a risk factor for endothelial dysfunction, post-operative sepsis, impaired wound healing, cerebral ischemia and acute metabolic complications which include diabetic ketoacidosis and hyperglycemic hyperosmolar state. [15-17]

Approach to Management

All the patients with type-1 diabetes undergoing minor or major surgery and patients with type 2 diabetes undergoing major surgery are appropriate candidates for intensive perioperative diabetes management.

Management Aims for Diabetics Undergoing Surgery[18]

- No excess mortality
- No increase in post-operative complications
- No infections
- Normal wound healing
- No increase in the duration of hospitalization
- No hypoglycemia
- No DKA/HHS

Pre-Operative Evaluation and Preparation

Goals are set to stratify perioperative risk, to ensure optimal management of concurrent illnesses (CHF, Hypertension) and perform screening for specific anesthesia related problems.

Evaluate for:

- Cardiovascular diseases
- Renal function
- Stiff joint syndrome
- Autonomic neuropathy
- Aspiration risk and
- Acute diabetic emergencies

Cardiovascular Evaluation

Diabetics are always at risk of CAD/silent ischemia. Cardiac risk must be determined in all diabetic patients undergoing surgery particularly at or over 40 years of age. Evaluation should begin with a resting ECG.

CVS Risk Stratification

Goldman Cardiac Risk Index(1995):Nine independent risk factors that correlate to perioperative fatal or major nonfatal events are:[19]

1) Age over 70 years- 5 points
2) MI in the previous 6 months-10 points
3) S3 gallop or jugular venous distension-11 points
4) Important aortic stenosis-3 points
5) Rhythm other than sinus or premature atrial contractions on last preoperative EKG-7 points.

6) >5 premature ventricular contractions per minute documented at any time before operation-7 points
7) PO_2<60 or PCO_2>50mmHg;K<3.0 or HCO_3^-<20 meq/L;BUN>50 or Cr>3 mg/dl; abnormal AST, signs of chronic liver disease, or bedridden from noncardiac causes.
8) Intraperitoneal, intrathoracic, or aortic operation-3 points
9) Emergency operation- 4 points

Risk Assessment

Class 4: High riske ≥ 26 points
Class 3: Intermediate to high risk: 13-25 points
Class 2: Low to intermediate risk: 6-12 points
Class 1: Low risk: 0-5 points

Revised Cardiac Risk Index

It is based on Modified Goldman Criteria (1999), indices including type of surgery, H/O IHD , H/O heart failure, H/O cerebrovascular disease, preoperative treatment with insulin and preoperative serum creatinine >2 mg%.[20] Each risk factor is assigned one point.

1. **High-risk surgical procedures**
   - Intraperitoneal
   - Intrathoracic
   - Suprainguinal vascular

2. **History of ischemic heart disease**
   - History of myocardial infarction
   - History of positive exercise test
   - Current complain of chest pain considered secondary to myocardial ischemia
   - Use of nitrate therapy
   - ECG with pathological Q waves

3. **History of congestive heart failure**
   - History of congestive heart failure
   - Pulmonary edema
   - Paroxysmal nocturnal dyspnea
   - Bilateral rales or S3 gallop
   - Chest radiograph showing pulmonary vascular redistribution

4. **History of cerebrovascular disease**
   - History of transient ischemic attack or stroke

5. **Preoperative treatment with insulin**

6. **Preoperative serum creatinine > 2.0 mg/dL**

Risk of Major Cardiac Event

Points	Class	Risk
0	I	0.4%
1	II	0.9%
2	III	6.6%
3 or more	IV	11%

"Major cardiac event" includes myocardial infarction, pulmonary edema, ventricular fibrillation, primary cardiac arrest, and complete heart block.

This revised cardiac risk index is adopted by 2007 American College of Cardiology (ACC) and American Heart Association (AHA) which issued guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery. [21]

Guidelines recommend that this index should be used to determine whether the patient needs non-invasive testing (stress testing) before surgery or not. In diabetics, the answer is YES. But, testing is useful if it changes perioperative management. That is to be decided by anesthetist and cardiac surgeon together. Interestingly, guidelines emphasize that the literature is inconclusive regarding testing but as observed in studies, testing improves outcome. Also surgery specific risk like hemodynamic and oxygenation related alterations should be considered when assessing the need for stress testing.

Evaluation of Renal Functions

A metabolic panel is advised which includes serum creatinine, blood urea, potassium, sodium, chloride, bicarbonates and eGFR. Concurrent use of medications like renin angiotensin system inhibitors, beta-blockers, and insulin itself can alter potassium levels.

Evaluation of Joint Stiffness

This thought result from glycation of connective tissues with chronic exposure to hyperglycemia. Cervical spine, temporo-mandibular joint and arytenoid joints are involved-making endotracheal intubation difficult. In this context, **'PRAYER SIGN'** is used as a screening tool which suggest the presence of joint stiffness. To demonstrate the sign, patient is asked to join palmar surfaces of both the hands opposing each other. If patient can not completely oppose the palmar surface of hands, it is likely that glottic structures also have reduced mobility. These structural alterations may need for a small

endotracheal tube for a narrow glottis or difficult passage for airway intubation. [22]

Evaluation of Autonomic Neuropathy

Can represent as silent myocardial ischemia/infarction, cardiorespiratory arrest, increased peri-operative and peri-intubation risk, resting tachycardia, ventricular arrhythmia /prolongation of QT interval, orthostatic hypotension, poor exercise intolerance, hypoglycemic unawareness, increased risk of severe hypoglycemia and may lead to sudden death.

Diagnose Cardiovascular Autonomic Neuropathy

Heart rate variability seen in ECG tracing in response to deep breathing, valsalva maneuver, heart rate response to change in posture and measurement of systolic BP in response to standing. [23,24]

Evaluation for Gastrointestinal Autonomic Neuropathy

This autonomic neuropathy can be a risk for aspiration of gastric contents. Suggestive features in history include early satiety, prolonged postprandial fullness and presence of significant gastro-esophageal reflux.

Evaluate for Diabetic Metabolic Complications

These include Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS). Both these may manifest as the result of a surgical emergency. Metabolic corrections should be done before anesthetic intubation. I.V. insulin infusion is provided to correct hyperglycemia and clear ketones. [25]

Glycemic Regulation

1. **Diet:** If patient is well controlled on diet, then no therapeutic intervention is needed.
2. **Antidiabetic agents:** Most oral hypoglycemic agents are discontinued day prior to surgery. Evening dose can be given. Long acting sulphonylureas and metformin are discontinued 48 hours prior to surgery. Metformin is unsafe in procedures leading to renal hypo perfusion, tissue hypoxia, and lactate accumulation. However, as according to Australian Diabetes Society 2012, metformin can be given in the morning of minor surgery.
3. **Insulin:** (patient on regular insulin therapy and controlled)

Long acting insulin (ultralente, glargine, levemir, and degludec) are stopped and changed to intermediate acting insulin (NPH) 1-2 days prior to surgery.

Short acting insulin (actrapid, lispro, aspart, glulisine) is given till the evening prior to day of surgery. These are to be avoided immediately before or during surgery as bolus as this may lead to hypoglycemia.

Specific Anesthesia Related Problems

Anesthetist should be on alert for hemodynamic instability, need of rapid fluid infusion, electrolyte repletion and carrying on frequent blood glucose and electrolyte monitoring.

Ensure Optimal Management for Concurrent Illness

Optimal management of hypertension, congestive heart failure and renal failure should be achieved. Dyslipidemic state should also be corrected as it promotes atherosclerosis.

Type of Surgery planned

- **Minor surgery**
  When the procedure duration is less than 2hrs. Patient is anticipated to resume oral intake prior to discharge on the same day.
- **Major surgery**
  Procedure duration more than 2 hrs. Surgery requiring overnight admission postoperatively.

Premedication

Metoclopramide, histamine blockers (famotidine) and liquid antacids can minimize the risk of aspiration.

Benzodiazepines/opioids to be given as per schedule.

It is important to remember that diabetic should be kept as first patient in morning list for surgery because this is least disturbing to patient's usual diabetes management routine and also least disruptive to their glycemic control.

Intraoperative Management

Patient should be in the operation theatre by 9 am. Plasma glucose and ketones are checked as MUST along with general assessment using glucostrip/ketostix. This is to be kept in the mind that regional anesthesia causes

greater risk to diabetic patient with autonomic neuropathy resulting in profound hypotension. It also increases risk of infection like epidural abscess. Also, anesthetic agents though may affect regulatory hormones but at the end they do not have any impact on intraoperative/postoperative glycemic control.

Acceptable Glycemic Control Intraoperatively

- Achieving well controlled normal range of 80-110mg/dl is most needed but evidence is limited regarding achieved benefits. Many studies tried to achieve this range, but resulted in hypoglycemia and increased mortality.
- Levels higher than 180 mg/dl lead to protein glycation and osmotic diuresis, so is not acceptable.
- Levels higher than 250mg/dl lead to impaired leucocyte function resulting in impaired phagocytosis decreased bacterial killing and decreased chemotaxis leading to severe infection.

Recommendations of different Diabetic Associations, Bodies and Centers all over the globe regarding intraoperative period glycemic control are as follows:

1) Joslin Diabetes Centre Recommendations[26]

	Non-critical	Critical
Intraoperatively	90-130 mg%	110 mg%
Postoperatively	<180 mg%	<180 mg%

2) AACE/ADA Recommendations(2009) [27,28]

a) Critically ill patients

- Insulin therapy should be started at a threshold of no greater than 180 mg%.
- Once insulin therapy is started, a glucose range of 140-180 mg% is recommended.

b) Non-critically ill patients

- Premeal blood glucose <140 mg%
- Random blood glucose <180 mg%

3) Australian Diabetes Society(2012) [29]

- Perioperative blood glucose levels recommended 5-10 mmol/L(90-180 mg%)

4) British Guidelines(NHS)2011[30-32]

- Blood sugar should be maintained in the range of 6-10 mmol/L(110-180mg%) if this can be achieved safely.
- A range from 4-12 mmol/L(74-220 mg%) is acceptable.

5) WHO (2011)

- Surgical safety checklist also endorses the same view. The target blood glucose should be 6-10 mmol/L (acceptable range is 4-12 mmol/L).

HbA1c

- If maintained below 8.5% represents good glycemic control perioperatively

Why Insulin Therapy Perioperatively? [33]

- To manage hyperglycemia due to insulin resistance and excessive catabolism due to counter regulatory hormones, it is logical to keep these patients on insulin therapy perioperatively.
- Also as action of oral antidiabetic agents is unpredictable.

Minor Surgery

- Duration of surgery is short.
- Impact of the surgery on glycemic control is minimal.
- Recovery is quick.
- Resumption of the patient's usual diet and routine occurs in short span of time.
- Delay the morning dose of insulin-if procedure is completed within 1-2 hours. Patient can have a late breakfast after the usual dose of insulin/OHA is given.
- For late procedures-reduced dose of insulin in the form of intermediate/long acting insulin (N/2)
- If the blood glucose level remains elevated(>180 mg%), an insulin glucose infusion is started.
- The infusion should be stopped and usual insulin/OHA therapy resumed once oral intake is established.

Major Surgery

- Patient should have target pre-prandial value of 90-130 mg% and bedtime values of 100-140 mg%, observed by SMBG before start of surgery.
- I.V. insulin, glucose, potassium chloride infusion (GKI infusion)[34]
- 500 ml of 5% dextrose+10 units of short acting insulin+10 meq KCl. infusion rate 100ml/hr running for 5 hrs. It delivers:
  - 2U insulin
  - 2 meq of KCl and
  - 10 gm glucose per hour

- 500 ml 10% dextrose+15 U of regular insulin+10 meq of KCl given at 100ml/hr
- NHS DIABETES (U.K.) recommends 0.45% saline+5% glucose+0.15%KCl as 1st choice solution.[35]

Algorithm for adjusting content of GKI infusion:[36-38]

- Measure blood glucose levels with test strips every 2 hrly
- Adjust infusion as follows:
  a) Blood glucose (117-200 mg%)
     15 Units insulin/500ml
  b) Blood glucose (>200 mg%)
     increase insulin to 20 Units
  c) if Blood glucose less than 117 mg%
     decrease insulin to 10 Units
- Continue GKI till patient eats, then revert to usual treatment

Regimen for Glucose Potassium Insulin infusion

Blood glucose	GKI infusion rate	
	5% dextrose	10% dextrose
<80 mg%	↓ 5 U	↓ 10 U
<120 mg%	↓ 3 U	↓ 5 U
120-180 mg%	No change	No change
181-270 mg%	↓ 3U	↓ 5 U
>270 mg%	↓ 5U	↓ 10 U

Management of Hypoglycemia and Hypoglycemic Risk[39]

1) If CBG (capillary blood glucose) is 4-6 mmol/L (74-110 mg%), provide 50-100 ml of 10% dextrose as a stat i.v. bolus and repeat CBG after 15 minutes.
2) If CBG is less than 4 mmol/L, provide 80-100 ml of 20% glucose and repeat CBG after 15 minutes.

Restarting Oral Hypoglycemic Medication[40]

- Recommence oral hypoglycemic agents at preoperative dose once the patient is ready to eat and drink.
- Withhold or reduce sulphonylureas if the food intake is likely to be reduced
- Metformin should only be recommend if the eGFR is greater than 50.

Restarting Subcutaneous Insulin for patients already established on insulin

The transition from intravenous to subcutaneous insulin should take place when the next meal related subcutaneous insulin dose is due e.g. with breakfast or lunch.

Patient on Basal Bolus Insulin

There should be an overlap between insulin infusion and the first injection of fast acting insulin. The fast acting insulin should be injected subcutaneously with the meal and the i.v. fluids and insulin discontinued 30-60 minutes later.

Postoperative Care

This period is very important because glucose control during this period is unpredictable and difficult. It is a potentially dangerous time for patients with diabetes.[41]

Aims[42]

- Ensure glycemic control
  preferable 110-180 mg%
  acceptable 74-216 mg%
- Maintain fluid and electrolyte balance.
- Look for renal function/urinary ketones.
- Optimise pain control.
- Treat postoperative nausea and vomiting to promote normal feeding
- Encourage an early return to normal eating and drinking
- Facilitate return to the usual diabetes regimen either OHA's/Insulin.
- Maintain meticulous infection control.
- Discharge planning must begin as soon as the patient is able to eat normally.
- Patient must be advised for diet planning at home and supportive care.

Emergency Surgery

Approximately 5% of people with diabetes will require emergency surgery.[43]Commonly performed surgeries include laparotomy, appendicectomy, cholecystectomy, diabetes related procedures like abscess drainage and amputations. Particular care should be taken to exclude DKA. It is important to keep in mind that DKA presents with prominent abdominal symptoms and patient may undergo needless surgical exploration for a non-existent acute abdominal emergency. [44]Other suggestive problems includes gastroparesis, gastroenteropathy, intractable/

cyclical vomiting and pseudotabes syndrome.

- Patients usually have suboptimal glycemic control
- Blood specimens should be sent immediately for blood glucose, electrolytes and acid-base assessment.
- Gross derangements of volume and electrolytes (hypokalemia, hypernatremia) should be corrected.
- Correct DKA/HHS urgently.
- Start GKI regimen infusion.
- Maintain blood glucose in range of 120-180 mg%.
- Serum potassium should be checked frequently (every 2-4 hrs).
- Potassium supplementation to ensure patient remains eukalemic throughout surgery and post operatively.

Conclusion

- With scores of studies and meta-analysis carried out in this field, there is no definite guideline yet available to define most acceptable range of glycemic state perioperatively.
- This relationship between glycemic control and outcomes including wound healing is far from clarified and requires further research.
- Evidence is also required in clarifying the roles of various insulin regimens in the surgical setting.
- The diligent application of an accepted and efficacious system will result in reasonably good glycemic control, minimize avoidable disasters, and acceptable patterns of mortality and morbidity.
- Management of diabetes during surgery requires perfection in organization, cooperation and communication.
- The aim of management remains to return the patient back to routine care with minimum disruption to quality of life.

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"We know what we are, but know not what we may be."
— William Shakespeare