REVIEW

MANAGEMENT OF DIABETES MELLITUS DURING NON-METABOLIC EMERGENCY SITUATIONS

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Any acute illness superimposed on diabetes mellitus invariably leads to worsened glycemic control. This is mediated by a dramatic increase in the release of catecholamines, which lead to decrease in insulin production and tissue sensitivity to insulin. Catecholamines also increase lipolysis, thereby increasing free fatty acid (FFA) metabolism. FFA has recently been found to be one of the major factors in causation of insulin resistance (1). To complicate the situation further counter-regulatory hormones like cortisol, glucagon and growth hormone are released which further enhance the hyperglycemia. Any associated inflammatory process is associated with the production of cytokines and interleukines. One of these factors, TNFα especially aggravates insulin resistance through inhibitory effect on insulin signaling and GLUT – 4 translocation. This then has a cascading effect, which induces a series of metabolic, inflammatory, and endothelial responses. Hyperglycemia (even of acute onset) generates the formation of free radicals (reactive oxygen species –ROS). Under inflammatory conditions, inducible nitric oxide synthase (NOS) is activated and large quantities of nitric oxide (NO) are formed. This large quantities of NO instead of having its usual beneficial effect (vasodilatation) on the vasculature, acts as a toxin and causes mitochondrial membrane depolarization and induction of programmed cell death or apoptosis (2). This is further linked to changes such as vasoconstriction, proliferation and thrombosis of the vasculature associated with blood cell adhesion, infiltration and lipid accumulation in the vascular wall.

Furthermore, there is glycoperoxidation and nitrotyrosylation of proteins, collagen and enzymes, all processes detrimental to healing and worsening of the prognosis (3).

In this review, we shall be discussing the management of the following emergencies superimposed on the diabetic state.

1. Acute myocardial infarction.
2. Cerebro-vascular accident.
3. Surgery (emergency/planned).

INSULIN THERAPY IN EMERGENCIES

A unified simple approach to insulin therapy in all emergencies under discussion is essential. Such standardized approach prevents serious mistakes in a hospitalized patient at the hands of health care professionals. This approach is based on a few important principles that are outlined here (4,5).

1. A bolus of insulin has an evanescent effect on blood glucose, because the half-life of insulin is only about four minutes.

2. A continuous IV infusion is the most optimal method to deliver insulin. The therapeutic concentration of insulin in circulation is about 100 μU/ml. In order to achieve this rapidly, it is advisable to use a very small bolus IV (6-12 units) followed by a continuous IV infusion. This meets both the objectives desired; rapid attainment of blood insulin levels and a steady maintenance of the same.

3. In type 1 diabetes mellitus, when IV insulin infusion is used, a state of sudden DKA can develop if the infusion is interrupted. This is because the IV insulin is being delivered on a minute-to-minute basis and cessation of infusion produces total insulinopenia in a short time. In such situations, a subcutaneous (SC) or intramuscular (IM) insulin injection must precede the drug interruption by about 30 minutes.

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4. Insulin is adsorbed to glassware as well as plastic ware. The amount of insulin adsorbed is maximum with the soft plastic ware, moderate with hard plastics, and minimum with glassware. The adsorption may wary from 15-60%, but is usually around 30%. In order to minimize this unpredictable loss of insulin, various measures have been suggested; e.g. running about 50 ml of infusate rapidly through the tubing to saturate the adsorption sites or adding a small amount of protein to the infusate. We add 2 ml of patient's serum to the IV fluids before adding insulin. This insures near complete delivery of the insulin added to the infusate.

5. Use of sliding scale in the form of IV boluses or SC insulin is to be deprecated for various reasons. The therapeutic decisions while using a sliding scale are basically wrong because in this situation, an action (like higher insulin dose) follows the problem (high blood glucose). If at all used, it should be restricted to one or two days and as soon as possible, a fixed dose of insulin be prescribed either for IV infusion or SC injection. This should be revised on a daily basis, depending upon the response. This results into modifications in the appropriate insulin dose, e.g. an increase in pre-breakfast dose of regular insulin for a pre-lunch hyperglycemia. In sliding scale, invariably pre-lunch dose will be increased, which is obviously erroneous. A plan where a fixed basic dose is prescribed with further on the spot alterations to take care of very low
(< 100 mg/dl) or very high (> 250 mg/dl) blood glucose is acceptable in the interim period, while the final dose is evolved.

6. In all emergencies, continuous basal supply of insulin or a basal – bolus plan should be undertaken. When patient is on a continuous dextrose infusion, a constant basal insulin supply is in order. When he also starts his meals, boluses (IV regular insulin) should be provided. When eating per os, the basal – bolus plan is converted to SC multiple dose insulin injections. In this situation, the total basal and bolus insulin requirements often work out to be in equal ratio. A small amount of basal insulin (NPH or Lente) is needed at breakfast and lunch, while a much larger amount is needed at pre-dinner time or at bedtime.

7. The IV insulin infusion can be set up by two different methods. In surgeries of moderate severity, where there is no fluid restriction, insulin can be added to dextrose or dextrose –saline bottles. There is a possibility of insulin loss; hence, a larger dose is added. The total pre-operative insulin requirements should be divided into 4-5 parts and each part be added to a bottle of dextrose or dextrose saline. The IV fluids should be spread over the entire 24-hour period.

   In all emergencies, like myocardial infarction, stroke or major surgeries, it is advisable to set up a concentrated solution of insulin in saline (2 ml of patient's serum added to infusate before addition of insulin). The concentration used is varied from 0.5-2.0 U/ml of solution. The concentration of insulin is determined on the basis of patient's previous insulin requirement; those with low requirements are treated with 0.5 U/ml solution and those with higher requirements are treated with 1.5-2.0 U/ml solution. Most frequent dose used is 1.0 U/ml. We usually keep the scale of infusion rates the same for all patients; e.g. for blood glucose <100 mg/dl, no infusion, for 100-150 mg/dl, 1 ml/hour; 200-250 mg/dl, 2ml/hour, 250-300 mg/dl, 4ml/hour and for >300 mg/dl, 8 ml/hour. It is important to give a small dose of subcutaneous (SC) insulin (NPH type) at 8am and 8pm in type 1 diabetics because the infusion may be interrupted when blood glucose is <100 mg/dl or it may be interrupted for other reasons, thus resulting in acute insulin- withdrawal DKA.

8. With the availability of Lispro insulin, its use has been considered in the peri-operative period. When using IV insulin, either as bolus or through continuous infusion, there is obviously no difference in the actions of regular human insulin versus Lispro insulin. However, for SC administration in postoperative period,

Lispro insulin may have an edge because the food intake may be variable and hence insulin injection just before or after a meal will permit greater flexibility. In the hospital setting, regular insulin is often injected a few minutes before or even after a meal, in spite of clear instructions to administer it 30-45 minutes before a meal. Therefore, Lispro may offer a better prandial glucose regulation. However, it must be appreciated that glycemic control may deteriorate with the use of Lispro insulin in the inter-prandial period unless a small dose of NPH/Lente insulin is incorporated with each dose of Lispro insulin.

ACUTE MYOCARDIAL INFARCTION

It has been well established that diabetes mellitus is a potent independent risk factor for cardiovascular diseases (CVD). The Framingham study showed that the risk of CVD was twice the normal for men, and three times the normal for women after adjustment for other risk factors (dyslipidemia, hypertension and smoking) (6). NHANES 1 showed that the diabetic population was twice as likely to develop CVD compared to non-diabetics, with 75% excess mortality in men (7). The Hoorn Study (8) and Honolulu heart study (9) have even shown a direct link of postprandial glucose rise with risk of CVD and CVD-linked mortality. The prevalence of many manifestations of coronary artery disease (CAD) [angina, myocardial infarction (MI) and sudden death] is increased in patients with type 1 and type 2 diabetes mellitus. These manifestations are more marked in women than men and CAD may be present at diagnosis of diabetes before other macro-or microvascular complications are evident (7). Diabetics usually have more diffuse disease, with a higher degree of coronary atherosclerosis, with more triple vessel disease and fewer normal vessels. Thus more severe coronary artery disease may not lead to increased incidence of anginal symptoms, because ischemia is often silent in diabetics and is only discovered on exercise testing or nuclear imaging. In general, patients taking insulin or with signs of organ damage (e.g. retinopathy, nephropathy) are at a greater risk of silent ischemia. Diabetic autonomic neuropathy may be one of the factors involved. Diabetic patients with silent ischemia may have a worse prognosis than non- diabetics (7).

In acute MI, hyperglycemia is known to accentuate myocardial damage because of less efficient salvage. Thus in a diabetic with MI, not only is the zone of infarction larger, but also areas of surrounding myocardium are unable to maintain adequate function because of poor metabolic control. This is attributable to :

- Metabolism of FFA is high in the myocardium following MI. Excessive generation of reactive oxygen species regularly uses up all available scavenger molecules following which the potential of free radicals to produce further damage is enhanced.
- Diminished supply of glucose to the myocardium, which is carbohydrate dependent, may contribute to high initial mortality.
- Impaired platelet or fibrinolytic activity contributes to the mortality and high rate of early recurrences.

Management

So far only a few studies, the most notable of which being the DIGAMI study (prospective trial) (10), have unequivocally shown the benefit of tight glucose control in reducing mortality in diabetics with acute myocardial infarction. In this study, 620 diabetic patients were randomized to either receive standard treatment (n=314) or an intensive treatment (n=306) with glucose-potassium-insulin (GKI) infusion targeted to achieve a tight control of glycemic levels. The insulin treatment was then continued long term. Data showed that the intensive treatment group had a lower one-year mortality (8.6 vs. 18.01%; p=0.02) and that this beneficial effect was most pronounced among a predefined group (n=272) who had previously not been on insulin and were at a lower cardiovascular risk (RR=0.49; p=0.004). This beneficial effect was even noticeable five years following acute myocardial infarction.

What this study has highlighted is that control of hyperglycemia during the acute phase, not only has immediate benefits, but these benefits persist thereafter. Also, patients who had relatively milder diabetes (not on insulin), benefit relatively more than those who were previously on insulin.

GLUCOSE-POTASSIUM-INSULIN DRIP

Usually GKI drip is instituted by using an infusion pump. The infusate consists of 500ml of 10%

dextrose with 16 units human soluble insulin and 20meq of potassium chloride (10ml of IV KCl solution). It is usually started with a fixed rate of 100ml per hour through a peripheral vein. Blood glucose is monitored throughout at two-hour intervals, with the aim of keeping blood glucose values between 80-130mg/dl. Initially, blood glucose should be done after one hour to determine the rate of fall of blood glucose. The insulin in the infusate is reduced by 4 units if blood glucose values are less than 80mg/dl or increased by 4 units if blood glucose values are more than 130mg/dl. Whenever GKI infusion is altered, blood glucose values are determined more frequently to keep them in the predetermined range. If blood glucose values are < 70mg/dl, GKI infusion should be stopped and blood glucose monitored every 30 minutes. Once it has again gone beyond 80mg/dl, GKI infusion should be restarted.

In view of variable insulin sensitivity in diabetics, we often disassociate glucose plus potassium drip from insulin drip. Thus, the glucose plus potassium drip is administered through one line at the rate of 100 ml/hour while insulin is administered as 0.5-2.0 U/ml infusate at a variable rate as described above, through another line.

GKI infusion is maintained for a minimum period of 24 hours following hospitalization. Then depending on the patient's condition insulin therapy (subcutaneous) can be initiated or GKI continued for some more time. If patient has pump failure (Killip Class II or more), it is preferable to continue GKI for a longer duration. Studies have demonstrated significant benefit of GKI in respiratory and left ventricular failure after cardiopulmonary bypass or aortocoronary bypass surgery (11) and in thrombolysis after myocardial infarction (12). Systemic effects of GKI are summarized in Table 1.

Table 1: Systemic Effects of GKI

Metabolic	
Glucose utilization	↑
Insulin	↑
Lactate	↑
NEFA	↓
Hemodynamic	
Cardiac output	↑
Systemic vascular resistance	↓
Skeletal muscle blood flow	↑
Renal blood flow	↓

Epidemiological studies have consistently shown that diabetes mellitus increases the risk of stoke by approximately 2-3 fold (13,14). The prevalence of previously diagnosed diabetes mellitus patients with acute stroke varies from 8-12% (15,16) and an additional 5-28% (16,17) may have unrecognized diabetes mellitus or impaired glucose tolerance. In addition, 10-20% patients may have hyperglycemia at presentation with a normal glycosylated hemoglobin (HbA_{1c}) concentration (18,19), as a consequence of the early hormonal response to cerebral ischemia (20,21). Therefore, approximately between 20-50% of acute stoke patients have been shown to have hyperglycemia at the time of presentation (15,16). Animal studies are equivocal as to the effect hyperglycemia has on the infarct size (22-24), but most, though not all clinical studies (15,25) in humans have shown a significant relationship between hyperglycemia and poor outcome after stroke in terms of mortality and neurological recovery (16,17). Some studies have suggested that the detrimental effect of hyperglycemia in acute stroke is more pronounced in patients with diabetes mellitus and that hyperglycemia may actually be beneficial in acute stroke patients without diabetes mellitus, depending on the presence or absence of collateral blood supply to the ischemic area of cerebral tissue (26). Until recently, most authorities described hyperglycemia in stroke as a secondary phenomenon resulting from either the stress response to cerebral ischemia or underlying abnormal carbohydrate metabolism (IGT). It has been argued that those with stress hyperglycemia have a poor prognosis conferred by the severity of the initial lesion, whereas those with diabetes mellitus have a poor prognosis because of the natural history of stroke in diabetic patients, and therefore active intervention to normalize mild to moderate elevation of blood glucose is not desirable (21,27). However, hyperglycemic coma is known to be a risk factor for poor outcome following stroke, irrespective of the diabetic status, although a definitive statement cannot be made in the absence of randomized controlled trial data.

The GST trial (28) was undertaken to determine the effect of tight glycemic control on the morbidity and mortality outcomes following acute stroke. Till final data is available, GKI infusion for the management of acute stroke cannot be recommended as established therapy, though it may be inferred from parallel studies like the

DIGAMI study for acute myocardial infarction, that it may be beneficial.

In patients of stroke, problems of water and sodium metabolism are likely to occur because of several reasons. Patients' thirst mechanism may be inoperative because of mental obtudation. In addition, use of diuretics and corticosteroids will have profound and well-known effects on the state of hydration and serum sodium levels. Hence, insulin administration either in a low volume, high concentration IV fluid bottle should be in consonance with the water and sodium requirements. Possibility of development of a hyperosmolar state or DKA is a real one and must be forestalled.

PERIOPERATIVE MANAGEMENT

The morbidity and mortality rates during peri-operative period are greater in diabetics compared to non-diabetics of comparable age for a multitude of reasons. Macrovascular disease including CAD, is extremely common in both type 1 and type 2 diabetes mellitus (29). In addition, a high percentage of patients (especially those more than 50 years of age) have impaired renal function and are prone to fluid and electrolyte imbalance, dehydration and obtundation (30,31). During the post-operative period the diabetic has a higher incidence of infection at the operative site as well as a greater potential of urinary tract infection, pneumonia and other systemic infections (32,33). Wound healing may be impaired in the presence of persistent hyperglycemia (>240 mg/dl) as a result of modified fibroblast function (34,35). This defect along with infection may result in wound dehiscence (especially after CABG), which frequently leads to a difficult and protracted hospitalization and frequent readmissions (36-38). Morbidity is especially high following renal transplant and CABG (33,36). Consequently, the diabetic patient spends 30-50% more time in the hospital than his non-diabetic counterpart following major surgery, even if the surgery proceeds without incident (37).

The stress and trauma associated with surgery and anesthesia causes a protracted catabolic response (Table 2). These events are stress mediated and are consequent to an increased production of counter-regulatory hormones, glucagon, cortisol and catecholamines (38,39). The associated insulin deficiency/resistance results in a decrease in both the anabolic and anti-catabolic effects of insulin (40,41). The magnitude of the catabolic response depends upon the severity of the underlying disorder, the duration of surgery and the type of diabetes (complicated/uncomplicated). The cumulative metabolic alterations that result in hyperglycemia are due to increased glucose production and decreased disposal, mild (type 2) and moderate (type 1) ketosis caused by lipolysis, ketogenesis and protein catabolism. Thus, patients will rarely have hypoglycemic episodes unless treated with excessive insulin or unless they are affected by an erratic or unpredictable absorption of an intermediate acting insulin from subcutaneous administration before the procedure. Additionally, dehydration induced by osmotic diuresis is associated with considerable hemodynamic alterations. Should this state be complicated by ketoacidosis, progressive obtundation will develop. It is important to note that serious ketosis may also develop in patients with type 2 diabetes under severe stress (37). It is also important to emphasize that in contrast to general anesthesia, epidural anesthesia has minimal effect on glucose metabolism (42). Thus, insulin secretion, action and dosage requirements in the diabetic treated with spinal anesthesia are similar to those for normal patients.

Table 2: Endocrine and Metabolic Response to Surgery in Diabetic Patients.

Endocrine

- Increased secretion of counter regulatory hormones:
  - Catecholamines; glucagon; cortisol; growth hormone
  - Decreased insulin secretion (Loss of anti-catabolic effect)
  - Decreased insulin action (insulin resistance)

Metabolic

- Hyperglycemia
- Decreased glucose disposal (utilization)
- Increased glucose production (secondary to glycogenolysis and neoglucogenesis)
- Increased protein catabolism
- Increased lipolysis and ketogenesis (variable)
- Increased metabolic rate and catabolism

Consequences (immediate and long term)

- Dehydration and hemodynamic instability (osmotic diuresis)
- Negative nitrogen balance
  - Loss of lean body mass
  - Impaired wound healing
  - Reduced resistance to infection
- Loss of adipose tissue and energy reserve (lipolysis)
- Deficiency of essential amino acids, vitamins and minerals.

The traditional peri-operative management has changed little despite modern advances in medical technology and a better understanding of insulin and glucose pharmacokinetics. Most recent reports have encouraged the practitioner to re-evaluate this area of critical care and consider the usage of novel regimes based on the metabolic response to surgical stress and the known pathophysiological differences between type 1 and type 2 diabetes mellitus (29,37). These newer regimens use controlled insulin glucose infusion (intravenous regimes), in contrast to traditional regimes, which involves the administration of 30-50% of usual insulin dose subcutaneously on the morning of surgery. This is usually combined with an intravenous infusion of 5% dextrose at the rate of 100ml/hour. There are major disadvantages with this approach (42-45). Insulin absorption is variable and unpredictable and extremes in blood glucose levels frequently occur. Once administered (NPH or Lente) the effect of insulin cannot be modified and thus should the operation be delayed until the afternoon, severe hypoglycemia may result. Postoperative care becomes very demanding and confusing for the associated nurses. Supplemental schedules for regular insulin (subcutaneous) based on delayed laboratory reports or worst still based on urine glucose, are frequently used. This type of care is retrospective and generally results in a roller coaster like blood glucose profile (37). Therefore regimes consisting of continuous regular insulin infusion combined with a rapid bedside blood glucose monitoring system are generally gaining acceptance for peri-operative blood glucose control and are replacing the traditional methods.

Preoperative Evaluation

The aim of therapy is to avoid excess morbidity and mortality. An appropriate pre-operative evaluation is important in this regard (Table-3). Clinical evaluation should be performed well in advance of surgery and the type of diabetes along with the associated complications must be meticulously identified. Type 2 diabetics have both insulin resistance as well as diminished insulin secretion peri-operatively and thus their insulin requirements are greater than anticipated. Type 1 diabetics need more frequent administration (MSI regime) or intravenous infusion. Importantly, the algorithm for withholding or stopping insulin should not be set too high and insulin should not be withheld unless blood glucose levels dip below 100 mg/dl. Very frequently, type 1 patients may develop ketoacidosis peri-operatively because of the practice of withholding insulin unless blood glucose values exceed 180-240 mg/dl.

Table 3: Preoperative Evaluation of Diabetic Patients

Identify Type of Diabetes Mellitus

Type 1; Type 2; Other.

Determine Preceding Glycemic Control

HbA_{1c}; Blood glucose records; Self-monitoring blood glucose levels.

Ascertain Associated Diabetic Complications

Nephropathy – Fluid and electrolyte balance; hypertension; drug dosage.

Neuropathy -

- Cardiovascular – arrhythmias; postural hypotension
- Gastrointestinal – gastroparesis; postoperative nausea and vomiting
- Bladder – urinary retention

Proliferative Retinopathy–vitreous hemorrhage (especially with anticoagulation)

Assess Cardiovascular System

Coronary artery disease
Hypertension
Congestive heart failure

History and record of previous glycemic control has a direct bearing on the surgical outcome. Previous poor glycemic control as evidenced by HbA_{1c} of more than 9% or fasting blood glucose (FBG) of more than 180 mg/dl is associated with abnormalities in fluid and electrolyte balance, increased risk of infections and delayed wound healing (37). Practically speaking, physicians rarely have the luxury of time to implement ideal glycemic control owing to the fact that they are often called upon to see the patient just prior to surgery. However, for elective surgery, prior outpatient evaluation and metabolic control is recommended. Fortunately, with the availability of insulin glucose infusions regimes, which have been detailed above, glycemic control can be improved within a few hours in emergency medical situations. Notwithstanding the above, prior day admissions are still recommended for poorly controlled diabetics and for those

undergoing major elective surgery such as CABG or renal transplant.

It is also important to convert type 2 diabetic patients who are on long acting OHA's such as glibenclamide to shorter acting agents such as glipizide or repaglinide and patients on insulin from long acting agents such as ultralente and glargine to intermediate acting insulin (NPH/lente) or short acting regular insulin several days before hospital admission. Generally the usual diabetes medication (OHA or insulin) is given the evening before surgery and the dosage omitted on the day of the surgery (37).

Preoperative assessment must include a review of complications such as neuropathy (especially autonomic), hypertension and coronary artery disease (CAD). Nephropathy complicates fluid management, alters insulin pharmacokinetics (sustained effect) and necessitates a careful selection of antibiotics to prevent nephrotoxicity. Use of radio contrast dyes in such patients may be hazardous. Autonomic neuropathy is linked to a high incidence of arrhythmias (29). It may also lead to post-operative urinary retention and delayed post-operative refeeding as a result of gastroparesis. Hypertension and CAD are the major causes of surgical mortality in 30% of diabetic patients (29).

Per-operative Management

Indications for Insulin

All patients taking insulin, whether type 1 or type 2 diabetes, should receive insulin during surgery (Table 4). In addition, most patients with type 2 diabetes should be given insulin during the peri-operative period. This is indicated for all patients whose HbA_{1c} is > 9% and FBG is > 180 mg/dl. A small subset of type 2 diabetic patients with good control (HbA_{1c} 7-9%; FBG <180mg/dl) on diet and OHA may not require an intensive approach. However, such patients will need close peri-operative monitoring with frequent blood glucose analysis. This approach is acceptable for a - surgical procedure not invading a body cavity and when the procedure is relatively simple and short (less than 2 hours). The latter group may be treated with regular insulin given SC every 4-6 hours, based on an appropriate blood glucose algorithm.

Table 4: Indications of Insulin Therapy During Major Surgery

ABSOLUTE

- All type 1 and insulin taking type 2 diabetics
- Type 2 diabetics on oral hypoglycemics (OHA) but with poor glycemic control (HbA_{1c}>9.0%; Fasting Blood glucose (FBG) >180 mg/dl)

RELATIVE (Sometimes)

- Type 2 diabetic treated by diet or OHA with good or fair control
- Average FBG <180 mg/dl
- HbA_{1c}<9.0%
- Surgery duration < 2 hours
- Body cavity not invaded
- Spinal/epidural anesthesia
- Food intake anticipated soon after surgery

Estimating Insulin Requirements

There is no absolute method of correctly predicting insulin need for a given patient. However, a few basic principles need emphasis. In the post absorptive state (6-14 hours after a meal), the normal blood glucose level is maintained between 80-110 mg/dl, because of a linkage between hepatic glucose production (HGP) and the peripheral glucose disposal rate (GDR). The range of post-absorptive HGP is 5-10g/hr; the average is 2.0mg/kg/min, which is equivalent of 8.4g/hr in a 70kg person. HGP is regulated by various factors, but predominantly is influenced by insulin and glucagon levels (37). Under basal conditions the beta cells secrete 0.5-1.0 U/hr of insulin (12-24 U/day), which maintains peripheral insulin concentration at approximately 6-12 mU/ml (37). Glucagon appears to play a major role in sustaining HGP and the net effect on HGP reflects the balance between insulin and glucagon. In stress situations such as surgery, other hormones such as catecholamines, cortisol and growth hormone come into play and will stimulate HGP and decrease the insulin mediated suppressive effect, resulting in greater insulin needs. Further, these counter regulatory hormones also reduce GDR, all causing a rise in blood glucose levels. 1U of insulin reduces blood glucose by about 50mg/dl. Most algorithms are based on this principle. However, stress modifies insulin requirements and disposal and these algorithms remains only a guide at its very best (Table 5).

Table 5: Guidelines for Estimation of Insulin Dosage.

- For insulin treated diabetics (type 1 or 2) on >50 U/day, suggested dose is 36U/day (1.5 U/hour – Blood glucose 141-180 mg/dl)
- For patients on diet, OHA or insulin <50/day, suggested dose is 24U/day (1.0 U/hour – Blood glucose 141-180 mg/dl)
- Further dose adjustments as follows:

o Conditions associated with insulin resistance
  - Poor glycemic control, HbA_{1c}>9.0%: Selected dose x 1.5
  - Obesity > Class 1; hepatic disease: Selected dose x 1.5
  - Severe infection; Steroid therapy: Selected dose x 2

o Type of Surgery
  - General surgery: Selected dose
  - Renal Transplant: Selected dose x 2
  - CABG: Selected dose x 3-5

Clinical experience has shown that most operative patients can be maintained between 120-180 mg/dl blood glucose range with a regular infusion rate of 1-2 U/hr (29,37). This applies to most surgical situations except coronary artery bypass graft (CABG) and renal transplant, where the insulin requirements may be enhanced dramatically due to use of sympathomimetic drugs, pump priming with glucose enriched solutions and hypothermia in patients undergoing CABG.

Insulin Regimen

Continuous insulin infusion is the most rational approach and has been discussed. It should be started the night before for early morning procedures and also for those with poor metabolic control. Otherwise, the patient takes the usual evening dose of insulin or OHA. Importantly, in all patients requiring insulin, the insulin infusion must be started 2-3 hours prior to surgery in order to titrate blood glucose to the appropriate value. Blood glucose values should be monitored frequently and at least hourly during surgery by the anesthetist.

The preferred method is to use a separate insulin infusion (pump or drip) and a 5% dextrose or dextrose saline solution, which allows for independent adjustment of rates (Table 6). The other method is to combine both, but this method lacks flexibility (Table 7). Frequent blood glucose monitoring is the keystone to success and close collaboration is needed between the physician, surgeon, anesthetist and the nursing staff. The infusion is continued till oral feeding is permitted. Infusions can ensure excellent glycemic control for brief (12 hours) to prolonged (more than 72 hours) postoperative period.

Table 6: Guidelines for Peri-operative Diabetes Management with an Insulin Drip.

- Insulin: regular (human) or Lispro 100 units in 100ml of normal saline (1U/1ml). Flush 50ml through line before connecting to patient or add 2ml of patient's serum before insulin is added. Piggyback insulin line to the fluid infusion line.
- Fluids containing 5% dextrose at the rate of 100ml/hour. Potassium supplementation at 20meq/L optional.
- Monitor blood glucose hourly intra-operatively.

Blood Glucose (mg/dl)	Insulin U/hour
< 80	Nil
81-100	0.5
101-140	1.0
141-180	1.5
181-220	2.0
221-260	2.5
261-300	3.0
301-340	4.0
>341	5.0

- Blood glucose less than 80mg/dl: stop insulin and administer intravenous 50% dextrose 25ml bolus. Once blood glucose> 80mg/dl restart insulin infusion. May be necessary to modify the algorithm.
- Increased insulin needs: obesity, sepsis, steroid therapy, renal transplant, CABG.
- Decrease insulin needs: patients treated with diet and/or OHA or < 50U insulin/day, endocrinal deficiencies.

Table 7: Guidelines for Peri-operative Diabetes Management with an Insulin-Glucose Infusion.

- **Diet, OHA or Insulin (Less than 50U/day)**
  - Fasting blood glucose (FBG) 120-180mg/dl: add 10U regular human insulin (Lispro) to 1000ml 5% dextrose plus 20mEq KCl
  - Blood glucose (BG) >180 mg/dl: increase insulin by 5U.
  - BG<120mg/dl: decrease insulin by 5U.
  - Check BG hourly.
  - Infuse at 100ml/hr (1.0 U/hr).

Insulin >50U/day

- FBG 120-180mg/dl: add 15U regular human insulin (Lispro) to 1000ml 5% dextrose plus 20mEq KCl
- BG>180 mg/dl: increase insulin by 5U.
- BG<120 mg/dl: decrease insulin by 5U.
- Check BG hourly.
- Infuse at 100ml/hr (1.0 U/hr).
- Blood glucose less than 80mg/dl: stop insulin and administer intravenous 50% dextrose 25ml bolus. Once blood glucose> 80mg/dl restart insulin infusion. May be necessary to modify the algorithm.
- Increased insulin needs: obesity, sepsis, steroid therapy, renal transplant, CABG.

Adequate glucose to prevent hypoglycemia, severe catabolism and to provide for basal energy needs should be administered peri-operatively in the diabetic patient. Maintenance fluids contain 5% dextrose administered at the rate of 100 ml/hr (1.2 mg/kg/min for 70 kg man). However, this infusion rate may not be sufficient to suppress glycerol, free fatty acid mobilization and development of negative nitrogen balance (46,47). Thus this has to be supplemented often with additional glucose (10% dextrose drip). Similarly additional insulin may be required in obesity, CABG and renal transplant.

Careful monitoring of potassium levels is needed during insulin glucose infusion. Often GKI is used instead or maintenance fluid should contain 20meq/L of potassium for patients with normal potassium values, to be modified according to peri-operative variations.

Postoperative Care

There are two critical phases in the peri-operative care. First is the initial catabolic phase, which extends from the pre-operative period into the immediate postoperative period. The second is the transitional phase, in which the patient moves from taking nil per os to a regular diet (Table 8). Once oral refeeding has begun, blood glucose values may spike abruptly and remain unstable for some time thereafter. However, the continuous insulin infusion is excellent in this situation and can control blood glucose adequately.

Table 8: Post-Operative Management of Patients with Diabetes Mellitus.

- Continue the peri-operative insulin infusion until food is tolerated.
- Overlap (30min) the initial subcutaneous dose of regular insulin before stopping infusion, especially in type 1 diabetes.
- Type 2 diabetics previously treated with diet and/or OHA: prescribe usual medication if blood glucose (BG) <180mg/dl. Higher BG may require regular insulin every six hours (pre-meal).
- Insulin treated diabetics: prescribe usual regimen or use prior 24-48 hour-insulin dosage to develop a new basic dose regimen. The dose selected should be 80-100% of previous day's total dose. Higher doses may be required during persistent stress, infection, pain, steroids or total parenteral nutrition.
- Selected basic dose may be given premeal (breakfast 25%, lunch 25%, dinner 25%), as regular insulin and NPH/Lente given at bedtime (25%). Aim to keep BG between 120-220mg/dl.

Premeal BG (mg/dl)	Basic dose (regular insulin)
<80	4U less
81-120	3U less
121-180	basic dose (no adjustment)
181-240	2U more
241-300	3U more
>300	4U more

- Modify the basic dose regularly according to the sliding scale needs. Additional doses of regular insulin may be needed at other times.
- Establish the most suitable insulin regimen or the patient's previous regimen before patient's discharge.

During the re-introduction of foods, it is preferable to continue low maintenance rate of insulin infusion, supplementing it with small doses of regular (SC) insulin preprandially. Once, food tolerance is established, the infusion is stopped and the insulin treated diabetic may return to the previous dosage or a MSI regime.

Patients are continued on the treatment plan until the postoperative complications have stabilized and their glycemic control is satisfactory. Subsequently, they can return to their pre-surgery insulin or oral regimes. Even type 2 diabetics who were adequately controlled with diet and OHA prior to surgery, may require several days of MSI to regain glycemic control.

Peri-operative management in the setting of ketoacidosis requires an aggressive approach to correct fluid and electrolyte imbalance, reverse acid base disturbances and optimize glycemic control. In the presence of ketoacidosis, surgery should be delayed for 4-6 hours whenever possible, while the patient is being given standard therapy. Separate insulin and fluid infusion systems are excellent for this. In ketoacidosis the insulin requirements are higher and a bolus insulin (10 units) may be administered prior to starting infusion. Once blood glucose values approach 250 mg/dl, 5% dextrose should be introduced into the rehydration fluids. Potassium replacement is crucial, along with assessment of acid base balance, renal function and electrolytes.

A well-coordinated plan for peri-operative care of the diabetic patient is a dynamic process and requires a team effort. Frequent interaction between physician, surgeon, anesthetist and nursing staff is essential for a successful recovery.

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