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CONSENSUS GUIDELINE

Indian Consensus Guideline for Insulin Use in Hospitalized Patients

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***Abstract:** In India, every sixth patient admitted to hospital has diabetes, however, there is no existing guideline for management of hyperglycemia in hospitalized patients. A guideline has been specifically created for the Indian population with the help of experts in order to improve the management of hyperglycemia in the in-patient setting. The aim of this guideline is to identify reasonable, achievable, and safe glycemic targets in hospitalized patients. Hyperglycemia is a major concern in hospitalized patients due to its association with increased mortality, inpatient complications and negative economic impact. Acute hyperglycemia has been reported in both critical and non-critical care settings. In critically ill patients, insulin therapy should be started when blood glucose level is ≥180 mg/dL. However in non-critically ill patients, insulin therapy is warranted only when blood glucose values reach a threshold of ≥140 mg/dL. In patients undergoing cardiac surgery, hyperglycemia can be managed with an intravenous infusion of short acting insulin titrated to target blood glucose of 110-140 mg/dL. Insulin therapy should be initiated in pregnant patients if 1 h postprandial blood glucose is >140 mg/dL and/or 2 h blood glucose >120 mg/dL in order to maintain a mean blood glucose level ~105–110 mg/dL for a good fetal outcome. A 20% increase in total daily insulin dose is recommended for patients taking glucocorticoid therapy. Intravenous insulin is preferred to check hyperglycemia in patients on parenteral nutrition while SC insulin should be preferred in those on enteral nutrition. The above recommendations have to be followed for insulin use in hospitalized patients.*

Introduction

Diabetes mellitus (DM) is a major endocrine epidemic of modern times. India accounts for 16%-17% of the world's total diabetics, which corresponds to almost 43 million patients. Most of the published data on DM focuses on outdoor patient morbidity without examining the impact of this disease on the health of critically ill patients.[1] Conservative estimates of the incidence of diabetes in adult hospitalized patients across western countries range from 12% to 26%.[2]Although such data is not available from

India, it has been reported that every sixth patient admitted to hospital has diabetes.[3] Hyperglycemia in the hospitalized patient has gained attention due to the association with increased mortality, inpatient complications and negative economic impact. Patients with diabetes are more likely to be hospitalized and have longer durations of hospital stay than those without diabetes. About 22% of all hospital inpatient days were experienced by people with diabetes posing huge economic burden.[4]

Prolonged hospitalization and poor outcome is a common phenomenon amongst patients with diabetes mellitus.[3] Hyperglycemia, though frequent amongst critically ill patients, has not gained much importance.[5] Various cohort studies and RCTs have suggested that intensive glucose control can improve outcomes in such patients.[4] Intensive insulin therapy in critically ill hyperglycemic patients (prolonged stay of more than 5 days) is not only associated with marked reduction in mortality varying from 40% to 50%, but also lowers the morbidity from acute renal failure, hepatic dysfunction, nosocomial infection, neuromuscular weakness, polyneuropathy of critical illness and severe anemia.[1]

Methodology

The development of diabetes guidelines followed a series of stages. The process started with the formation of a core committee comprising of health-care professionals/clinicians/researchers having wide expertise in treating diabetes across varied group of patients *viz* pediatrics, youth, elderly and pregnant population. The committee members were chosen from different geographical areas of the country for better purview of the regional disparities prevailing amidst diabetes care. The core committee met, discussed and decided that five guidelines would be framed for diabetes management in India. A separate committee was formed for each of the guideline. Each guideline committee consisted of 6-7 members and one chairperson.

Experienced individuals with thorough knowledge of the subject were assigned to prepare the draft version of the guidelines. The guideline preparation started with extensive literature search and studies pertaining to the topics were identified. In general the recommendations are based on international and Indian evidences and guidelines, published over the last few years. Extensive literature search was performed from electronic databases, primarily MEDLINE, Cochrane etc. Evidences included randomized or non randomized clinical trials, meta-analyses, evidence based reviews, case studies, cohort studies, epidemiological studies. Opinion of expert panel was also taken into account. The grading of evidences was done as below.

Levels of Evidence	Type of Evidence
A	Randomized controlled trials or meta-analyses or systematic reviews
B	Non-randomized controlled trial or uncontrolled randomized clinical trial
C	Observational trials or evidence based reviews or case studies
D	Opinion of expert panel

The initial draft was circulated among the core committee members. The members of core committee met to discuss the subject matter, to provide expert opinions based on their extensive experience and to review the evidences. The draft was made available at the Diabetes India website and comments from global, regional and interested experts were invited. All suggestions and opinions of the members were then incorporated into the draft guidelines.

The first compilations of guidelines for diabetes management in India were presented at a conference attended by 100-200 physicians. Each guideline was discussed at length and the recommendations were obtained from the group. A second draft of each guideline was formulated taking into consideration all recommendations and suggestions put forward in the conference. The second draft of the guideline was sent for further review to the core committee and the physicians for final inputs. The guidelines were then finalized and published.

Acute Hyperglycemia in Hospitalized Patients and Its Adverse Outcome

Acute hyperglycemia has been reported in the settings of trauma, stroke, myocardial infarction and sepsis. In a study of 100 patients admitted to a medical ICU, some degree of hyperglycemia was seen in all except four patients.[6] Acute hyperglycemia is a common feature during the early phase after acute myocardial infarction (AMI), regardless of diabetes status. The Cooperative Cardiovascular Project is the largest study to investigate the relationship between admission glucose level and mortality after AMI. It reviewed 141,680 patients aged

≥65 years with AMI, and showed that the 30-day and 1-year mortality rates linearly increased as the admission blood glucose level increased. Interestingly, higher glucose levels were associated with greater risk of mortality in patients without known diabetes compared to those with diabetes.[7]

Stress hyperglycemia historically was felt to be part of the natural course of acute illness and not treated unless symptomatic. However, it is now known that stress hyperglycemia is associated with longer hospital stays, higher rates of intensive care unit (ICU) admission, greater need for rehabilitation services at the time of discharge and higher mortality rates. A study by Umpierrez et al, based on the medical records of 2030 consecutive adult in-patients has shown that patients with new hyperglycemia had an 18-fold increase in-hospital mortality and patients with known diabetes had a 2.7-fold increase in-hospital mortality when compared to normoglycemic patients. In this study, hyperglycemia was present in 38% of patients admitted to the hospital, of whom 26% had a known history of diabetes, and 12% had no history of diabetes before the admission. The mortality rates were 10% fornon-ICU patients with new hyperglycemia and 31% for ICU patients. Such patients also had a longer length of hospital stay, a higher admission rate to an intensive care unit, and were less likely to be discharged.[8] A Prospective observational cohort study carried out in 903 patients admitted to the general medical ward of a tertiary Australian Hospital reported that patients without known history of diabetes but with HbA1c > 6% and fasting blood glucose > 100 mg/dL had mortality rate of 11.3% compared to 4.4% in those patients with HbA1c < 6% and fasting blood glucose < 100 mg/dL.[9]

In the Portland Diabetic Project, a 17-year prospective, non randomized, interventional study of 4,864 patients with diabetes who underwent an open-heart surgical procedure, an adverse relationship between hyperglycemia and outcomes was observed. Increasing blood glucose levels were found to be directly associated with increasing rates of death, deep sternal wound infections (DSWI), length of hospital stay and hospital cost. An increase in the 3-day postoperative average blood glucose had a direct relationship with the incidence of DSWI. The investigators identified an apparent inflection point at 175 mg/dL, at which the incidence of DSWI begins to increase significantly.[10] In the only Indian study carried out in an ICU setup, 497 (38.73%) patients out of 1283 admissions had hyperglycemia (blood glucose > 140 mg/dL) at one time or the other during the ICU stay. Of the total admissions, 179 (13.95%) were established cases of diabetes, while 64 (4.99%) were diagnosed as diabetes after admission.[1]

Recommendations

- Acute hyperglycemia is commonly encountered in hospitalized patients, both critical and non-critical and is associated with adverse outcomes. (Level B)
- In-hospital hyperglycemia may be defined as any blood glucose (admission or in-hospital) value > 140 mg/dL. Levels that are significantly and persistently above this level in hospitalized patients must be recognized promptly and managed judiciously. (Level A)
- All patients admitted to the hospital should be assessed for a history of diabetes. Blood glucose level of all patients should be tested on admission. (Level B)
- Patients without history of diabetes but having blood glucose >140 mg/dL should be monitored with bedside point of care (POC) testing for at least 24 to 48 h. (Level B)
- All in-patients without known diabetes but with hyperglycemia > 140 mg/dL should be assessed for HbA1c level. Patients with HbA1c > 6.5% can be identified as having diabetes, and patients with HbA1c 5.7%-6.4% can be considered as being at risk for diabetes. (Level C)
- The HbA1c level of known diabetics must be checked if it has not been checked in the past 2–3 months. (Level C)

Is Intensive Management of Hyperglycemia in Hospitalized Patient Beneficial? Conflicting Studies

Evidence supporting intensive management of hypoglycemia

The DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) study was the first clinical trial of tight glucose control in the hospital. This randomized study compared intravenous insulin followed by multiple dose insulin therapy versus standard care for patients with diabetes and acute myocardial infarction. Attentive control of blood glucose from the time of admission to the post discharge period reduced mortality at 1 year by 26%.[1112] In 2001, Van den Berghe et al, performed a major RCT in 1548 critically ill surgical patients (two thirds having undergone cardiac surgery) treated with an intensive insulin therapy infusion in a surgical ICU. Patients received either insulin to maintain glucose

between 80 and 110 mg/dL or insulin for glucose levels above 215 mg/dL to maintain glucose between 180 and 200 mg/dL. Among the patients who stayed in the ICU for five or more days, the intensive insulin group showed a significant benefit in ICU survival as well as in-hospital survival.[1314] The strongest support for intensive glycemic control in critical illness is derived from studies performed in cardiac surgery patients. The Portland Diabetes Project was a prospective, non randomized interventional study in patients with diabetes undergoing cardiac surgery. The introduction of a continuous IV insulin infusion targeting blood glucose levels of <150 mg/dl on the operative day through the first 2 postoperative days resulted in significant reductions in deep sternal wound infections and cardiac related mortality.[15]

Evidence against intensive management of hypoglycemia

Recent trials in critically ill patients have however, failed to show a significant improvement in mortality with intensive glycemic control or have even shown increased mortality risk. These RCTs have also highlighted the risk of severe hypoglycemia in such patients. The NICE-SUGAR trial was a very large (6104 patients) multicenter trial. It compared the outcomes of two strategies for patients in the medical ICU: keeping blood glucose concentrations below 120 mg/dL versus keeping them in the range of 140 to 180 mg/dL. The protocol achieved substantially lower glucose concentrations in the intensive control group, and tight control did not improve outcomes. In fact, mortality was statistically significantly higher in patients treated with tighter glucose control (27.5% vs. 24.9%).[12] In DIGAMI 2, three treatment strategies were compared: group 1, acute insulin-glucose infusion followed by insulin-based long-term glucose control; group 2, insulin-glucose infusion followed by standard glucose control; and group 3, routine metabolic management according to local practice. The study mortality (groups 1-3 combined) was 18.4% and there was no statistically significant difference between the groups. Moreover, there were no significant differences in morbidity expressed as non-fatal reinfarctions and strokes among the three groups.[16] The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latin America (CREATE-ECLA) with 20,201 patients tested the efficacy of glucose insulin- potassium infusion (GIK) in post-AMI patients and found no decrease in mortality.[17] The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study reported no decrease in mortality and higher rates of severe hypoglycemia with intensive insulin therapy in patients with severe sepsis. Additionally, hypoglycemia was identified as an independent risk factor for mortality.[18]

Diverse patient outcomes have contributed to confusion regarding specific glycemic targets and the means for achieving them in both critically ill and non-critically ill patients. In view of this, development of a guideline for improved management of hyperglycemia in inpatient settings is essential.

Objectives of the Guideline

This guideline is directed towards health care professionals, supporting staff, hospital administrators and other stakeholders, and is focused on improved management of hyperglycemia in the in-patient setting. The central theme is to identify reasonable, achievable and safe glycemic targets in hospitalized patients. Therefore, the guideline specifically emphasizes on the following aspects of patient management:

1. Initiation of appropriate insulin therapy based on clinical condition and blood glucose levels.
2. Defining blood glucose targets based on clinical condition and blood glucose levels and safety.
3. Optimizing insulin therapy and blood glucose monitoring requirements.
4. Minimizing risk and the severity of hypoglycemia.

Management of Hyperglycemia in Critically Ill Patients (Medical and Surgical)

Most of the studies outlined in the above sections have been carried out in critically ill patients in ICU settings. Several studies have found blood glucose variability to be an independent predictor of mortality in critically ill patients.[1920] A very tight glucose target (80 –110 mg/dL) has been beneficial in a predominantly surgical ICU population.[13] However, in a study of 399 patients undergoing cardiac surgical procedures, intensive insulin therapy (target blood glucose, 80–100 mg/dL) intra-operatively led to no difference in patient outcomes.[21] Attempts to achieve tight glycemic control have actually increased mortality in clinical trials and led to higher rates of hypoglycemia.[18]The AACE and ADA Consensus statement on inpatient glycemic control 2009 recommend that insulin therapy should be started in critically ill patients when blood glucose level is e”180 mg/dL.

The glycemic target of 140–180 mg/dL is considered as appropriate in such patients. There is some evidence that a tighter control in the range of 110–140 mg/dL may be beneficial in surgical patients. In medical patients, such tight control may be associated with increased risk of hypoglycemia.[4]Clinical practice guideline from the American College of Physicians 2011, recommends that intensive insulin therapy for strict control of blood glucose should not be used for critically ill medical patients with or without diabetes mellitus admitted in the ICU. Moreover, it also recommends that in ICU patients the blood glucose should be in the range of 140 -200 mg/dL.[22]No specific consensus guideline is available in India.

Recommendations

- In critically ill patients, insulin therapy should be started when blood glucose level is e”180 mg/dL.A glycemic target of 140–180 mg/dL is appropriate for such patients. (Level A)
- A tighter control in the range of 110–140 mg/dL may be beneficial in surgical patients. Blood glucose target below 110 mg/dL is not recommended. (Level B)
- Continuous intravenous (IV) insulin infusion based on standardized algorithms is the most effective method for achieving specific glycemic targets in such patients. (Level A)

Continuous IV insulin infusion (CII)

In the critical care setting, continuous IV insulin infusion has been shown to be most effective in managing hyperglycemia. It is also an appropriate therapy in situations like hyperglycemic diabetic emergencies, perioperative conditions and when patients are ‘nil by mouth’.[4] Due to the short half-life of circulating insulin, IV delivery allows rapid dosing adjustments. It is ideally administered by means of validated protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and insulin dose.

There are more than 20 published IV insulin infusion protocols in the literature. The calculation of the insulin-infusion rate in an ideal insulin infusion protocol and should take into account the current blood glucose value, the rate of change in blood-glucose levels and the specific patient’s sensitivity to insulin. In addition, a well-tolerated and effective protocol has the following cardinal features:[23]

1. It is effective and gets to the target goal quickly.
2. Maintains blood glucose within a defined target range over several hours.
3. Includes an algorithm for making temporary corrective increments or decrements in the rate of infusion.
4. It is well tolerated and results in minimal rates of hypoglycemia.
5. It provides clear and easy means to follow directions for treatment of hypoglycemia.
6. Can be easily implemented and executed by nursing staff in response to a single physician order. **(Table-1)**

Table 1 | Insulin infusion protocol-1 [3]

Blood glucose (mg/dL)	Insulin requirement
< 100	No insulin to be given
100–149	1–1.5U/hour
150–199	2U/hour
200–249	2.5 U/hour
250–299	3 U/hour
300–349	3.5 U/hour
350–399	4 U/hour

For any further increase in blood glucose, the consulting physician needs to decide the rate subjectively. If BG does not fall more than 10%, insulin can be increased to 1.5 times the normal dose. **(Table-2)**

Regular insulin or rapid-acting insulin analogs (aspart, lispro, glulisine) can be used as IV infusion. However, regular insulin may be more cost-effective. Glulisine should be used only with normal saline. Glucose (as required) and insulin should be given through separate IV routes. Serum potassium should be monitored and supplemented, if required. Insulin requirements may change in certain situations, including changes in nutrition, dialysis, medications (for example, octreotide and glucocorticoids), and the administration of medications (for example, antibiotics) in dextrose-containing solutions.

Types of Insulin

Insulin is available in rapid, short, intermediate and long-acting types that may be injected separately or mixed in the same syringe. The rapid-acting analogues, including aspart, lispro, and glulisine, allow a closer approximation of physiological insulin secretion. They are absorbed more rapidly than regular insulin leading to a more rapid onset and peak and a shorter duration of action. Their

Table-2 | Insulin infusion protocol -2 (for major surgeries): adapted from Ag U, Prusty V.[49]	
Step 1	Load insulin by adding 25U short acting insulin in 250 ml of Normal Salineto get a 0.1U/ml solution
Step 2	Flush 50 ml of insulin via infusion tubing to saturate the binding sites in the tubing
Step 3	Give bolus dose of insulin (optional), to decide the bolus dose, divide the current blood glucose by 50.
Step 4	Set the hourly infusion rate on the infusion pump; infuse 0.5U/hour in thin women (BMI < 19Kg/m^2) and 1U/hour in other patients
Step 5	Readjust the dose by checking glucose level every 1 hour to obtain target of 140-180 mg/dL. ✓ If blood glucose is > 180 mg/dL increase dose by 0.4U/hour. ✓ If blood glucose is > 300 mg/dL, increase dose by 1U/hour. ✓ If blood glucose is between 140-180 mg/dL, make no change. ✓ If blood glucose drops < 140 mg/dL reduce insulin by 0.4 U/hour
Step 6	Prevent hypoglycemia: If the blood glucose falls repeatedly below 80 mg/dL, stop infusion and give 1 ampoule of 25% Dextrose; recheck blood glucose every 15-30 min and start infusion if blood glucose rise to > 180 mg/dL
Step 7	Stopping infusion: if the insulin infusion is being completely stopped; give a dose of s.c. insulin 30 minutes before stopping infusion.

rapid onset allows them to be given just before meals, and they should not be given more than 15 minutes before meals. Human regular insulin is less expensive than the analogues. Its onset of action occurs in 30–60 minutes, requiring dosing 30 minutes before meals for best effect.[24] **(Table 3, 4, 5, 6)**

Difference between Human Insulin and Insulin Analogue

The insulin currently used in medical practice is recombinant insulin, either directly derived from the native human insulin or developed by structural modification in the amino acid sequence of the insulin molecule (known as insulin analogue). Human insulin and insulin analogues mostly differ in their pharmacokinetic parameters and propensity for adverse effects. When regular human insulin is administered subcutaneously, there is a delay before it dissociates from hexamer form to monomer and is then absorbed into the circulation. Accordingly, human insulin does not mimic the normal kinetics and dynamics of endogenous insulin. As a result, regular human insulin usually does not provide adequate control of postprandial glycemic excursions and has a propensity to cause delayed hypoglycemia.[24] These problems are significantly reduced with the use of insulin analogues and their combinations.

Table-3			
Insulin Type	**Onset**	**Peak**	**Duration of action**
Rapid acting Insulin aspart analogue Insulin glulisine analogue Insulin lispro analogue	10 – 30 minutes	30 minutes – 3 hours	3 – 5 hours
Short acting Human Regular insulin	30-60 minutes	2 – 5 hours	up to 12 hours
Intermediate-Acting Human NPH insulin	90 minutes – 4 hours	4 – 12 hours	up to 24 hours
Long acting Insulin detemir analogue Insulin glargine analogue	45 minutes -4 hours	Minimal peak	up to 24 hours

Table-4 | Premixed Insulin Combinations
70% NPH; 30% Regular
50% lispro protamine suspension; 50% lispro
70% aspart protamine suspension; 30% aspart
25% lispro; 75% lispro protamine

Table-5 | Compatibility of different insulin preparations with various IV fluids			
	5% Dextrose	Ringer solution	Normal Saline
Regular	✓	✓	✓
Aspart	✓	✓	✓
Lispro	✓	✓	✓
Glulisine	×	×	✓
Premixed	×	×	×

Table-6 | Approved intravenous insulin preparations	
Insulin type	**Vial (10 ml)**
Regular	40 U/ml
Aspart	100 U/ml
Lispro	
Glulisine	100 U/ml

Recommendation

- For continuous insulin infusion (CII) therapy in critically ill patients, regular insulin is as beneficial as insulin analogues. This is because regular insulin as well as insulin analogues when injected intravenously have short half-lives. (Level B)

Blood Glucose Monitoring

The glucometer allows samples from either capillary or venous source to be measured and consequently results in minimal needle pricks and elimination of factitious reporting.

Recommendations

- To minimize errors, the glucometer readings should always be tested and compared intermittently with laboratory glucose values which act as internal quality control standard. (Level C)
- Blood glucose testing should be performed for every patient on admission followed by at least two readings in the next 24 hours to rule out hyperglycemia. (Level B)
- Glycated hemoglobin should be obtained in patient with hyperglycemia without prior history of diabetes and with persistent hyperglycemia of uncertain etiology. (Level C)
- Capillary blood sample can be used except in situations like hypotension, hypothermia, shock, use of vasoconstrictors and vasopressors where venous samples are preferred. (Level C)
- The frequency of monitoring should be clearly indicated on the insulin administration chart. This will vary depending on the condition of the patient, insulin type, method and frequency of administration. Generally, initial blood glucose monitoring should be done on 30 min to an hourly basis. Interval of testing can be increased to 2 hourly or 4 hourly when three consecutive readings are consistently around the target. (Level C)
- Once patient starts oral feeding, postprandial blood glucose should be monitored every 4-6 hours. (Safe and Effective use of Insulin in Hospitalised Patients). (Level C)
- Continuous glucose monitoring system, which can monitor glucose levels continuously up to 72 hours, may be useful in emergency and intensive care units.[4] (Level C)

Consensus recommendations

- Oral glucose tolerance test should be conducted in those patients who are stable and can take food orally. (Level D)
- Once the patient is stable and feeds orally, the fasting and 2hr postprandial blood glucose level should be monitored. (Level D)

Management of Hypoglycemia

Hypoglycemia is a major safety concern with use of insulin and insulin secretagogues.

In most clinical situations, safe glycemic control can be achieved with appropriate use of insulin, adjusted according to results of bedside glucose monitoring. However, the risk of hypoglycemia can cause increase in the following situations:

1. Patients have stopped food intake.
2. Development of sepsis.

3. Patients who are receiving certain medications, including quinolone antibiotics and beta blockers.
4. Elderly patients with significant comorbidities.
5. Patients with or autonomic, kidney, liver, or cardiac failure.

Recommendations

- **Blood glucose between 50 mg/dL and 75 mg/dL:** Infuse 50 mL dextrose (25 g) if hypoglycemia manifests clinically. If asymptomatic, give 25 ml of the same. Check blood glucose every 15 minutes till blood glucose reaches> 100 mg/dL after the intervention and start insulin 1 hour after 1st reading of >100mg/dL, and only if the same is maintained at that level. (Level C)
- **If Blood glucose is < 50 mg/dL:** Infuse 50 mL of dextrose (25 g), Check blood glucose every 15 minutes till blood glucose reaches > 100 mg/dL after the intervention and start insulin 1 hour after 1st reading of >100mg/dL, and only if the same is maintained at that level. (Level C) (Table-7)

Table-7 | Common signs and symptoms of Hypoglycemia

Tremors
Light-headedness/dizziness
Nervousness, irritability
Confusion
Hunger
Tachycardia
Sweating
Headache
Weakness
Numbness or tingling in tongue or lips

Transition from Intravenous to Subcutaneous Insulin

Patients who receive IV insulin infusions will usually require transition to subcutaneously administered insulin when they begin eating regular meals or are transferred to lower-intensity care. Patients suitable for this transition ideally have a stable infusion rate (within ±0.5 U) and blood glucose levels in goal range for at least 4 hours before the transition.[25] Typically, 75–80% of the total daily IV infusion dose is proportionately divided into basal and prandial components. Subcutaneously administered insulin must be given 1–4 hours before discontinuation of IV insulin therapy in order to prevent hyperglycemia.[4] The overlap can be reduced to 15–30 min if rapid analogs are used.[3] **(Table-8)**

Patients could be shifted to more convenient insulin regimes, such as premixed insulin twice daily and monitored for a few days before discharge.

Table-8 | Protocol for transition from CII to SC insulin

STEP 1	Calculate the average insulin IV infusion rate in last 12 hrs to obtain the mean hourly rate and multiply it by 24 hrs to get total daily insulin requirement
STEP 2	Halve this 24 h insulin dose to obtain the long acting insulin analog dose and total daily rapid acting insulin analog dose.
STEP 3	Give the long-acting insulin analog sc monodose 2h before the first meal and discontinuation of IV insulin and IV glucose infusions
STEP 4	Split the total daily insulin of rapid acting sc insulin analog into 20% at breakfast, 40% at lunch and 40% at dinner.

Management of Hyperglycemia in Non-Critically Ill Patients (Medical and Surgical)

Evidence supporting active management of hyperglycemia

Only few randomized controlled trials have examined the effect of intensive glycemic control on outcomes in hospitalized patients outside ICU settings. Several observational studies, however, point to a strong association between hyperglycemia and poor clinical outcomes, including prolonged hospital stay, infection, disability after discharge from the hospital, and death.[4,26,27,28] The effectiveness of interventions to control hyperglycemia in non-critical patients and their potential outcomes is not well known. There are several case-control studies that demonstrate an increased risk for adverse outcomes in patients undergoing elective non-cardiac surgery who have either preoperative or postoperative hyperglycemia. Postoperative blood glucose values greater than 200 mg/dL are associated with prolonged hospital length of stay and an increased risk of postoperative complications,

including wound infections and cardiac arrhythmias[28,29] In a study, the incidence of postoperative infections in patients with glucose levels > 220 mg/dL was 2.7 times higher than in those with glucose levels below it.[29] In another study of 3184 noncardiac general surgery patients, a perioperative glucose value above 150 mg/dL was associated with increased length of stay, hospital complications, and postoperative mortality.[30] A meta-analysis conducted in 9 randomized controlled trials and 10 observational studies was recently reported by Murad et al.[31] Intensive glycemic control was associated with reduction in the risk of infection (relative risk, 0.41; 95% confidence interval, 0.21–0.77). There was a trend for increased risk of hypoglycemia (relative risk, 1.58; 95% confidence interval, 0.97–2.57) and was most common in surgical studies. There was no significant effect on death, myocardial infarction or stroke.

Guideline Perspectives

The AACE and ADA Consensus statement on inpatient glycemic control 2009 recommends that insulin therapy is warranted only when blood glucose values reach a threshold of e”140 mg/dL. To avoid hypoglycemia, consideration should be given to reassessing the insulin regimen if blood glucose levels are < 100 mg/dL. Modification of the regimen is necessary when blood glucose values are < 70 mg/dL, unless the event is easily explained by other factors, such as a missed meal or exertion.[4] The Endocrine Society Clinical Practice guideline for management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting 2012 recommends initial glucose measurement on admission by the hospital laboratory for all hospitalized patients, irrespective of the presence of pre-existing diabetes history or exposure to obvious hyperglycemic agents.[32] No specific consensus guideline is available in India at present.

Recommendations

- Scheduled subcutaneous administration of insulin is the preferred method for achieving and maintaining glucose control in non-ICU patients with diabetes or stress hyperglycemia. (Level B)
- Sliding scale insulin (SSI) should not be used for management of hyperglycemia in hospitalized patients. (Level A)
- Pre-meal blood glucose target of <140 mg/dL and random blood glucose <180 mg/dL is recommended for majority of the patients. (Level C)
- The target can be lower than this threshold in the following conditions: (Level C)
  (1) Stable patients with optimal glycemic control prior to admission.
  (2) Postoperative ward patients in a background of adequately trained staff for monitoring and treating hypoglycemia.[33,34]
- Sometimes, higher glucose ranges may be acceptable in elderly, terminally ill patients, patients with severe co-morbidities, those in patient-care settings where frequent glucose monitoring or close nursing supervision is not feasible.[4](Level B)
- Blood glucose level should be tested before meals and at bedtime in patients who are eating, or at every 4–6 h in patients who are *nil per oral* or receiving continuous enteral feeding. (Level C)
- To avoid hypoglycemia, reassess and modify diabetes therapy when blood glucose values are d”100 mg/dL. Modification of glucose-lowering treatment is necessary when blood glucose values are <70 mg/dL. (Level C)

Consensus Recommendations

- Oral hypoglycemic agents may be continued in stable hospitalized patients who are not likely to miss their meals. It should ideally be discontinued prior to initiation of insulin therapy. However, metformin can be continued if the patient has no contraindication to the drug. (Level D)

Specific Recommendations for Surgical Patients

- It is prudent to maintain glucose levels <180 mg/dL in the perioperative period. (Level B)
- All patients with type 1 diabetes who undergo minor or major surgical procedures should receive either CII or subcutaneous basal insulin with bolus insulin as required to prevent hyperglycemia during the perioperative period. (Level B)
- When instituting SC insulin therapy in the postsurgical setting, basal (for patients who are nil orally) or basal bolus (for patients who are eating) insulin therapy is the preferred approach. (Level B)

Consensus Recommendations

- Oral hypoglycemic agents can be continued in stable patients going for elective surgery i.e. non critical procedure. (Level D)

- Insulin could be added as a basal component for better fasting control. (Level D)
- Metformin can be continued in such patients. (level D)
- In minor surgical procedures like intraocular lens (IOL) implant, oral hypoglycemic agents may be continued on the day of the procedure. (Level D)
- Target blood glucose should be 110-140 mg/dL. (Level D)

Subcutaneous Insulin Therapy

Scheduled subcutaneous administration of insulin is the preferred method for achieving and maintaining glucose control in non-ICU patients with diabetes or stress hyperglycemia. A basal bolus regimen is indicated in such cases. Basal insulin to cover the basal need and prandial rapid-acting insulin to cover the nutritional need are preferred choice. Supplemental insulin may also be required.[3,4] **(Table- 9)**

- Starting insulin dose is usually 0.5 x body weight.
- Basal dose is 40%–50% of starting dose at bedtime.
- If the patient is able to eat, total bolus dose is 50%–60% of starting dose evenly distributed at each meal.

Correction (supplemental) insulin refers to the use of additional short or rapid acting insulin in conjunction with scheduled insulin doses to treat blood glucose levels above desired targets, is preferred. Correction insulin is required for all patients with blood glucose > 140 mg/dL. Correction bolus = (Blood glucose –100)/Correction Factor (CF). CF = 1500/Daily insulin requirement. **(Table-10)**

If a patient is able to eat, give supplemental insulin (regular or rapid-acting insulin) before each meal and at bedtime. Give half of supplemental insulin dose at bedtime. If a patient is not able to eat, give regular insulin every 6 h or rapid-acting insulin every 4 to 6 h.

Table-9 | Scheduled insulin requirement in non critically ill patients [33,3]

Insulin requirement (U/Kg)		Indication
1.	0.2-0.3	• ≥ 70 years age • Significant renal impairment
2.	0.4	• Blood glucose between 140–200 mg/dL
3.	0.5	• Blood glucose > 200 - 400 mg/dL
4.	1.0	• Obesity and other insulin resistance state • Glucocorticoid treatment • Severe infections • Coronary artery bypass graft (CABG) • Total parenteral nutrition (TPN)

Management of Hyperglycemia in Special Conditions

Cardiac Patients

Evidence for intensive management of hyperglycemia

Studies have reported that nearly 41% of critically ill patients with acute coronary syndromes, 44% of patients with heart failure and 80% of patients after cardiac surgery have hyperglycemia.[8,35,36] In these studies, approximately one third of non-intensive care unit (ICU) patients and approximately 80% of I CU patients had no history of diabetes before admission. Elevated plasma glucose is commonly observed during the early hours of acute myocardial infarction (AMI), not only in patients with diabetes, but also in non-diabetic patients. A prevalence of 49% has been reported in patients without previous unrecognized diabetes that may be a result of stress-hormone response.[37] A meta-analysis of 15 studies demonstrated that nondiabetic AMI patients who had elevated blood glucose levels on admission were at 3.9 times greater risk for mortality than nondiabetics who had lower glucose levels.[38] Recently Zaheer et al carried out

Table-10 | Supplemental insulin (U/dose) [33]

Blood glucose (mg/dL)	Patient unable to eat	Usual patient	Patient insulin resistant
> 141–180	2	4	6
181–220	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
> 400	14	16	18

a prospective, cohort, hospital-based study in 200 Indian patients admitted for acute coronary syndrome (ACS) and in-hospital glycemia and assessed their impacts on outcomes. They reported that in hospital, persistent hyperglycemia is a better discriminator of prognosis than admission glucose alone in patients of ACS.[37] Stress hyperglycemia and established diabetes in AMI patients have nearly the same rates of increased mortality. However, there is still controversy over whether hyperglycemia is a cause or effect of AMI. Nevertheless, optimal glycemic control can reduce post–MI complications such as heart failure and re-infarction. The DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) study was the first clinical trial of tight glucose control in the hospital. This randomized study compared intravenous insulin followed by multiple dose insulin therapy versus standard care for patients with diabetes and acute myocardial infarction. Attentive control of blood glucose from the time of admission to post-discharge period reduced mortality in 1 year by 26%.

Unfortunately, these remarkable results were not confirmed in the DIGAMI 2 study that was designed to investigate whether the decrease in mortality was due to the IV insulin system or to the better metabolic control after discharge (25). The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiologicos Latin America (CREATE-ECLA), also found no decrease in mortality among patients treated with glucose insulin-potassium infusion (GIK).[17] The Portland Diabetes Project was a prospective, nonrandomized interventional study of over 4800 patients with diabetes undergoing cardiac surgery. The introduction of a continuous IV insulin infusion targeting blood glucose levels of <150 mg/dl on the operative day through the first 2 postoperative days resulted in significant reductions in deep sternal wound infections and cardiacrelated mortality.[15]

Guidelines Perspectives

- The AACE and ADA Consensus statement 2009 on inpatient glycemic control recommends that optimal glycemic control is preferable with insulin during and after the episode, to reduce the risk of complications associated with AMI. Rapid control of hyperglycemia in the first few hours is critical[4]. No specific consensus guideline is available in India.

Recommendations

- The role of glucose, insulin and potassium (GIK) in cardiac patients is still inconclusive hence use of GIK is not currently recommended. (Level A)
- In patients undergoing cardiac surgery, hyperglycemia can be managed with an intravenous infusion of short acting insulin titrated to target blood glucose of 110-140 mg/dL. Due to use of inotropes in cardiac surgery the insulin requirement may be high and vary from patient to patient. (Level B)

Peripartum Control of Hyperglycemia

Evidence supporting management of Hyperglycemia

Placental hormones, growth factors and cytokines increases insulin resistance during pregnancy and this significantly enhances insulin requirements. Pregnancies in diabetic patients are associated with an increased risk of congenital malformations, obstetric complications, and perinatal morbidity and mortality.[39] Gestational diabetes mellitus (GDM) complicates approximately 7% of pregnancy, which accounts for more than 2,00,000 cases per year.[40]A recent study from India by Seshiah et al have reported the incidence of GDM as 18.9%.[41]Insulin therapy is the most validated treatment option for treatment of GDM. McCance et al. have demonstrated that there is minimal and no increase in insulin antibodies during pregnancy for either insulin aspart or human long-acting insulin, and that there is no appreciable transplacental transfer of either insulins.[42] Insulin aspart has been studied in large randomised clinical trial in patients with type 1 diabetes. The aim of the study was to compare the outcome in women with type 1 diabetes who were treated with either an insulin analogue aspart and long-acting human insulin combination or an insulin actrapid and long-acting human insulin combination. A total of 322 patients took part in the actual study and 264 completed the whole trial. No significant difference in birth weight or percentage appropriate for gestational age neonates was observed in the two groups. Incidence of major congenital malformation was 4.4% in the aspart group and 6.6% in the actrapid group and difference was non-significant.[43] A large observational study on insulin lispro has shown that there is no indication that the use of insulin lispro is related to a higher incidence of congenital malformations. This was a retrospective multi-national, multi-continental study of 496 women with type 1 or type 2 diabetes mellitus from 1996 to 2001, who had used insulin lispro at least 1 month before conception and throughout the first trimester.[44]

Guidelines Perspectives

- No specific consensus guideline is available in India

Recommendations

- It is recommended that 1 h postprandial blood glucose >140 mg/dL and/or 2 h blood glucose >120 mg/dL is appropriate to initiate insulin therapy to maintain a mean blood glucose level ~105–110 mg/dL for a good fetal outcome. (Level B)
- Short-acting insulin analogues are the drugs of choice in pregnancy. (Level B)
- Patients with diabetes in active labour should be on glucose and IV insulin. However, dose titration is essential on a case to case basis as there is wide variability in insulin resistance after 14 weeks of gestation. (Level B)
- Maternal blood glucose level should be monitored after delivery, 24 hours postpartum and if found to be high, check again on follow-up. During labour, it is essential to maintain good glycemic control, while avoiding hypoglycemia. (Level C)
- After delivery, insulin requirement falls sharply and it is prudent to decrease the insulin dose to 25–40% of the pre-delivery dose to prevent hypoglycemia. In most cases of GDM, there may not be any requirement of insulin in the post-partum period. (Level C)

Patients Receiving Glucocorticoid Therapy

Hyperglycemia is a common complication of glucocorticoid therapy with prevalence ranging from 20 to 50% among patients without a previous history of diabetes.[45] Despite its frequency, the impact of corticosteroid-induced hyperglycemia on clinical outcomes, such as morbidity and mortality is not known due to lack of studies.

Guideline Perspectives

- The AACE and ADA Consensus statement 2009 on inpatient glycemic control and Endocrine Society Clinical Practice guideline 2012 for management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting recommend that blood glucose monitoring should be carried out for at least 48 h in all patients receiving high-dose glucocorticoid therapy, and SC insulin therapy should be started as appropriate. In addition, patients receiving high-dose glucocorticoids and in those with severe hyperglycemia which is difficult to control, the use of CII may also be appropriate.[4,32] No consensus guideline is available in India.

Recommendation

- Patients who are already being treated for hyperglycemia, a 20% increase in total daily insulin doses is recommended. Similarly, during tapering of corticosteroid, insulin dose should be adjusted to avoid hypoglycemia. (Level C)

Patients on Parenteral Nutrition and Enteral Nutrition

Evidence supporting active management of hyperglycemia

The high glucose load in standard parenteral nutrition (PN) frequently results in hyperglycemia, and is associated with a high incidence of complications and mortality in critically ill patients of the ICU. Hyperglycemia in this group of patients is associated with higher risk of cardiac complications, infections, sepsis, acute renal failure, and death.[4]There are several retrospective and prospective studies demonstrating that the use of PN is an independent risk factor for the onset or aggravation of hyperglycemia independent of a prior history of diabetes.[46,47] In a meta-analysis of studies comparing special enteral nutrition formulations with standard formulations, the postprandial rise in blood glucose was reduced by 18–29 mg/dL. It suggests that the majority of hyperglycemic patients will still require insulin therapy for control of hyperglycemia while receiving this type of nutritional support.[48]

Guideline Perspectives

- The AACE and ADA Consensus statement 2009 on inpatient glycemic control and the Endocrine Society Clinical Practice guideline 2012 for management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting recommend use of IV insulin in patients on parenteral nutrition while basal plus multiple SC prandial boluses are preferred for patients on enteral nutrition[4]. No specific consensus guideline is available in India.

Recommendations

- Intravenous insulin is the preferred treatment for control of hyperglycemia in patients receiving parenteral nutrition. (Level B)
- SC insulin should be preferred to control hyperglycemia in indoor patients on enteral nutrition. (Level B)

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"The mind is everything. What you think you become."

— Buddha