CHAPTER

46

In Hospital Management of Diabetes Mellitus

Jothydev Kesavadev

INTRODUCTION

Diabetes and its complications are a major cause of hospitalizations. Number of diabetes related deaths in India was estimated to be 1.02 million.[1] Various co-morbidities associated with diabetes such as dyslipidemia, hypertension, chronic kidney disease, cardiovascular disease, chronic obstructive pulmonary disease (COPD), nonalcoholic fatty liver disease, lower extremity amputations, obesity, infections, depression, etc. make patients susceptible to frequent hospitalizations. The presence of comorbidities can further complicate the diabetes treatment. For instance, patients who need to be treated with steroids for pneumonia or COPD have to be shifted to insulin regimen from oral agents. The occurrence of hyperglycemic and hypoglycemic episodes might also lead to serious events including death[2,3] and hence the major hospital goals for an individual with diabetes should definitely consist of reducing or preventing these fluctuations aiding in an effective disease management. Individuals of high risk groups should be identified soon after hospitalization and properly monitored to ensure adequate treatment as well as to avoid complications.[4] Special attention must be taken to minimize the disruption of the metabolic state, prevent an untoward result, and return the patient to a stable glycemic balance as quickly as possible. The stress from acute illness raises the chances for hyperglycaemia whereas; illness related anorexia or need of fasting for certain procedures often culminates in hypoglycemia. This makes the glycemic status of the patient highly unpredictable and thus the glycemic targets must be carefully set and reviewed frequently so as facilitate timely therapeutic decisons.

HYPERGLYCEMIA

Umpierrez et al reported that hyperglycaemia was present in 38% of patients at the time of hospitalisation and that one-third of these patients had no known history of diabetes before the admission.[5] In patients with diabetes, missing an insulin injection or oral hypoglycaemic agent; or ingesting large quantities of carbohydrates, low physical activities etc. can all trigger hyperglycaemic events. Acute illness leads to various physiological changes (e.g. increases in circulating concentrations of stress hormones) or therapeutic choices (e.g. glucocorticoid use) that can exacerbate hyperglycaemia. This, in turn, causes physiological changes that can exacerbate acute illness, such as decreased immune function and increased oxidative stress. This leads to a vicious cycle of worsening illness and poor glucose control.[6] Infections and fever are known to activate medulla and cortex to produce epinephrine and cortisol subsequently resulting in severe hyperglycaemia. Moreover, elevations in blood glucose (BG) support infectious process and thereby slow down the healing process. To control such exacerbations, anti-diabetic medications should be appropriately modified in subjects with diabetes in case of infections.[7]

Hyperglycaemia goals in hospitalised patients

The studies on tight glycemic control (TGC) by intensive insulin therapy brought out special interests in hyperglycemia management in hospitalised patients. In the Leuven proof-of-concept studies, the BG levels were kept tightly between 80 and 110 mg/dl. This approach, decreased mortality and morbidity in surgical critically ill patients and morbidity in medical critically ill patients.[8,9] Several International guidelines incorporated these results, and intensive care units (ICU) started implementing TGC. However, data from the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study,[10] contradicted and overrode the Leuven Trials and demonstrated increased mortality among medical and surgical ICU patients who received TGC. As a result, TGC in the ICU to a goal <110 mg/dL is no longer recommended.

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) consensus statement, recommend that insulin therapy should be initiated for treatment of persistent hyperglycemia, starting at a threshold of no greater than 180 mg/dL. Once insulin therapy is started, a target glucose range of 140–180 mg/dL should be set for the majority of critically ill patients and non-critically ill patients. More stringent goals, such as 110–140 mg/dL should be considered for selected critically ill patients, as long as this can be achieved without significant hypoglycaemia. (2). ADA recommended glycemic goals for hyperglycemia treatment is given in Table 1.

Managing hyperglycaemia in hospitalised patients

In most instances in the hospital setting, insulin is the preferred treatment for glycemic control.[2] Oral anti-hyperglycemic agents are not suitable due to difficulty in titrating their dose to meet fluctuating blood glucose levels, associated co-morbid conditions like hepatic and renal impairment, and most importantly the need for quick achievement of target blood sugar levels.[12] However, in certain circumstances, it may be appropriate to continue well-controlled patients (who are eating, and in whom no change in their medical condition or nutritional intake is anticipated) on their prior out-patient oral regimen. It

Tabel 1: ADA recommended glycemic targets for hyperglycemia treatment in a hospital setting[11]

ICU	Non-ICU
Initiate insulin therapy for persistent hyperglycemia (glucose >180 mg/dl [10 mmol/l]) For most patients, target a glucose level between 140-180 mg/dl. More stringent goals (110-140 mg/dl) may be appropriate for selected patients, if achievable without significant risk for hypoglycemia	A glucose target between 140-180 mg/dL, (between 7.8 and 10.0 mmol/L) is recommended. Hospitalised patients who are clinically stable and has a prior history of successful tight glycemic control target for BG <140 mg/dL (7.8 mmol/L) Less stringent targets may be appropriate in patients with severe comorbidities

is often also reasonable to resume oral agents in some patients when preparing for hospital discharge.[13]

If a patient was previously eating but is unable to eat after the evening meal in order to prepare for a procedure the next morning, oral hypoglycaemic drugs should be omitted on the day of procedure (surgical or diagnostic). If procedures are arranged as early in the day as possible, anti-hyperglycemic therapy and food intake can then be shifted to later in the day.

Insulin therapy

The common themes in the insulin infusion protocols are the use of regular insulin for continuous insulin infusion and a basal/bolus subcutaneous insulin regimen including a long-acting insulin analog (insulin degludec, glargine or detemir) and prandial and correctional doses of a rapid-acting insulin (insulin aspart, glulisine, or lispro).

Sliding scale insulin therapy

The widespread use of the Sliding Scale Insulin (SSI) administration began during the era of urine glucose testing and it increased after the introduction of rapid capillary blood glucose testing in the last two to three decades. At the present, the sole use of SSI in the inpatient hospital setting is strongly discouraged.[2] In most SSI therapy regimens, BG is measured about four times a day (every 5 to 6 hours, or before meals and at bedtime) and accordingly insulin (mostly rapid acting) is administered. However, there are few data to support its benefit and some evidence of potential harm when the "sliding scale" is applied in a rote fashion, that is, when all patients receive the same orders. In fact, when the sole form of insulin administered is rapid acting insulin every four to six hours without underlying provision of basal insulin, they are associated with an increased rate of hyperglycemic episodes.[14]

Continuous intravenous insulin infusions (CIVII) for critical care setting

CIVII is the best method for achieving glycemic targets in a critical care setting and should be done with validated protocols so as to allow for predefined adjustments in the infusion rate, accounting for glycaemic fluctuations and insulin dose.[2,15] With CIVII, frequent BG monitoring should be done to minimize the occurrence of hypoglycemia and to achieve optimal glucose control. Regular human insulin is commonly used for IV infusion and a recent study has shown that rapid acting insulin analog can also be effective, well tolerated option for managing inpatient hyperglycemia.[16]

Basal plus correction insulin regimen/ Basal–bolus subcutaneous insulin injections for noncritical care setting

Administration of subcutaneous insulin injections should align with meals and bedtime or every 4–6 h if no meals or if continuous enteral/ parenteral therapy is used.[2] For patients with poor oral intake or those who are taking nothing by mouth (NPO), a basal plus correction insulin regimen is the preferred treatment.[17] An insulin regimen with basal, nutritional, and correction components (basal–bolus) can be chosen for patients with good nutritional intake.[13] BG should be monitored immediately before meals and if oral intake is poor, it is safer to administer the short-acting insulin after meals or to count the carbohydrates and cover the amount ingested. Basal–bolus treatment has been found to improve glycaemic control as well as reduce hospital complications than SSI in general surgery patients with T2DM.[18]

Insulin therapy in Type 1 Diabetes- Patients who have a known history of T1DM are insulin deficient and hence, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or calorie intake, increasing both hypoglycemia and hyperglycemia risks and potentially leading to diabetic ketoacidosis (DKA). Typically basal insulin dosing schemes are based on body weight, with some evidence that patients with renal insufficiency should be treated with lower doses.[19]

Insulin therapy in patients using insulin pumps

Continuous Subcutaneous Insulin Infusion (CSII) or Insulin Pump Therapy (IPT) when compared to other conventional insulin delivery methods provides the advantage of achieving better glycaemic control, minimising glucose variability and thereby, preventing or reducing the risk of microvascular and macrovascular complications in patients with diabetes. A cross-sectional survey conducted among T2DM patients demonstrated that IPT brought out significant improvement in their quality of life. The attitude and behaviour of these individuals were also found to be very positive and promising.[20] Patients on IPT do not necessarily discontinue this form of therapy during hospitalization. However, to ensure a collaborative relationship between the hospital staff and the patient and to ensure patient safety, hospitals should have clear policies and procedures in place to guide the continued use of IPT in the inpatient setting.[21] During admission, patients must be assessed for their physical and mental competency to continue the use of their insulin pumps. The patient should also have adequate insulin pump supplies. If the patient cannot

competently demonstrate and/or describe the above-mentioned actions, insulin pump therapy should be discontinued and the patient placed on a subcutaneous insulin regimen or CIVII.[22]

Transition from intravenous to subcutaneous insulin therapy

A transition protocol is recommended for discontinuing intravenous insulin in order to reduce morbidity and costs of care.[23] To maintain adequate levels of insulin, it is necessary to administer subcutaneously short/ rapid-acting insulin 1–2 h before or intermediate or long-acting insulin 2–3 h before discontinuation of the CIVII. For the transitional process, subcutaneous insulin with appropriate duration of action may be administered as a single dose or repeatedly to maintain basal effect until the time of day when the choice of insulin or analog preferred for basal effect normally would be provided.[3] Converting to basal insulin at 60–80% of the daily infusion dose has been shown to be effective.[11]

PREVENTING HYPOGLYCEMIA

Hypoglycemia, especially in insulin-treated patients, is the leading limiting factor in the glycemic management of patients with diabetes.[3] In a retrospective cohort study done by Jothydev et al, a telemedicine (DTMS®) based follow-up and multidisciplinary care accompanied by self-monitoring of blood glucose was proven beneficial in the intensive treatment of T2DM. Compared to the traditional healthcare approach, DTMS® aided patients in achieving glycaemic targets without any serious symptomatic hypoglycaemia or other co-morbidities and also reduced the frequency of their hospital visits.[24] Hypoglycemia in hospitalized patients has been defined as blood glucose, 70 mg/dL and in cases of severe hypoglycemia as, 40 mg/dL.[25] In the hospital, multiple additional risk factors for hypoglycemia are present, even among patients who are neither "brittle" nor tightly controlled. Patients with or without diabetes may experience hypoglycemia in the hospital, in association with factors such as altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis.[26,27] Iatrogenic hypoglycemia can also be triggered by sudden reduction of corticosteroid dose, altered ability of the patient to report symptoms, and reduced oral intake, emesis, new NPO status, inappropriate timing of short-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, and unexpected interruption of oral, enteral, or parenteral feedings. Under-prescribing anti-hyperglycemic therapy than the advisable range is not always fully protective against such causes of hypoglycemia. Standardized treatment protocols to address mild, moderate and severe hypoglycaemia should be implemented in hospitals and healthcare team should be educated about factors that increase the risk of hypoglycaemia.[22] Common preventable sources of iatrogenic hypoglycemia are improper prescribing of hypoglycemic medications, inappropriate management of the first episode of hypoglycemia, and nutrition–insulin mismatch, often related to an unexpected interruption of nutrition. A study of "bundled" preventative therapies including proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management showed that hypoglycemic episodes in the hospital could be prevented.[28]

MANAGEMENT OF DIABETIC EMERGENCIES

Diabetic ketoacidosis (DKA) and Hyperglycemic Hyperosmolar Nonketotic syndrome (HHNS, otherwise called Hyperosmolar hyperglycemic state (HHS) or Hyperosmolar Hyperglycemic Nonketotic Coma (HHNC)) are diabetic emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and absolute insulin deficiency (in the case of T1DM) or high catecholamine levels suppressing insulin release (in the case of T2DM). In DKA, ketoacidosis is prominent, while in HHNS, the main features are ECFV depletion and hyperosmolarity.[29]

DKA is a commonly confronted by T1DM patients and also occasionally occurs in T2DM patients who are completely or almost insulin deficient. DKA can occur with infection, steroid treatment, stress etc. but recurrent DKA is often due to omitted insulin doses. Classic symptoms include polyuria, polydipsia and polyphagia with weight loss. Classic signs are Kussmaul's respiration (labored breathing) and dehydration. Diagnosis is confirmed with an elevated BG level and initial screens should include electrolytes (basic/ comprehensive metabolic panel) and perhaps arterial blood gas. BG levels can vary from >126 mg dl to more than 3000 mg/dl. Sodium potassium levels, pH, bicarbonate levels and anion gap and serum creatinine levels are of significance for understanding the state of acidosis and hydration.[7]

HHNS is most often seen in individuals (mostly older than 60 yrs and rarely in children) with T2DM or in those who have no previous diagnosis of diabetes. The cause of this condition is relative insulin deficiency sufficient to produce hyperglycemia but not severe to allow ketonemia. The person may have classic signs of diabetes (polyuria, polydipsia and weight loss) but no or little ketonemia or ketonuria. Distinguishing features of this condition are marked serum hyperosmolarity, very high BG (900-3000 mg/dL), frequent hypernatremia, severe dehydration and hypokalemia, coma not associated with ketosis or acidosis.[7]

The therapeutic goals of DKA and HHNS management include restoration of volume status, correction of hyperglycemia and ketoacidosis (in DKA), correction of electrolyte abnormalities, treatment of precipitating factors, and prevention of the complications of DKA and HHNS.[30] Lesser insulin is required for HHNS than DKA since the patient is not ketotic, but fluid requirements are higher due to extreme hyperosmolarity. Patients are usually older, and may have renal insufficiency and/ or congestive heart failure. Fluid administration must be done carefully to prevent fluid overload and nephrology

and cardiology service might be required.[7] A suggested protocol for the management of DKA and HHNS.[31]

CONCLUSION

Patients with diabetes meet with frequent hospitalizations for diabetes related or unrelated complications. Owing to highly unstable glycemic control seen in these individuals (because of stress of the illness or procedure, changes in diet and physical activities etc.), they deserve best possible hospital care. Sliding scale insulin protocols should be totally discouraged and doctors and supporting staff irrespective of the speciality of care should have the basic understanding of the duration of action and frequency of commonly used insulin preparations. The glycemic targets should be individualised considering the severity of illness and risk benefit ratio. Though tight metabolic control may be beneficial in a subgroup, the occurrence of hypoglycemia could be fatal in the critically ill.

REFERENCES

1. IDF Diabetes Atlas. Brussels, Belgium: International Diabetes Federation, 2015.
2. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; 32:1119-31.
3. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004; 27:553-91.
4. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism* 2012; 97:16-38.
5. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *The Journal of Clinical Endocrinology & Metabolism* 2002; 87:978-82.
6. Inzucchi SE. Management of hyperglycemia in the hospital setting. *N Engl J Med* 2006; 355:1903-11.
7. Dr. Diana W. Guthrie PDBCADMCDEF, Dr. Richard A. Guthrie MDF. Management of Diabetes Mellitus: A Guide to the Pattern Approach, Sixth Edition: Springer Publishing Company; 2008.
8. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359-67.
9. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449-61.
10. Investigators N-SS. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 2009:1283-97.
11. Diabetes Care in the Hospital. Diabetes Care. 2016; 39(Supplement 1):S99-S104.
12. Bhoraskar A. Inpatient management of diabetes mellitus. *J Assoc Physicians India* 2011; 59:29-31.
13. Maynard G, Wesorick DH, O'Malley C, Inzucchi SE, Force SoHMGCT. Subcutaneous insulin order sets and protocols: effective design and implementation strategies. *J Hosp Med* 2008; 3(5 Suppl):29-41.
14. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Arch Intern Med* 1997; 157:545-52.
15. Umpierrez G, Cardona S, Pasquel F, Jacobs S, Peng L, Unigwe M, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. *Diabetes Care* 2015; 38:1665-72.
16. Udwadia F, Bhattacharyya A, Seshiah V, Kumar Sethi B, Kumar S, Kumar Subbanna P, et al. Intravenous insulin aspart in a hospital setting: results from an observational study examining patient outcomes and physician preferences. *Diabetes Management* 2012; 2:103-10.
17. Umpierrez GE, Smiley D, Hermayer K, Khan A, Olson DE, Newton C, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes. *Diabetes Care* 2013; 36:2169-74.
18. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; 34:256-61.
19. Baldwin D, Zander J, Munoz C, Raghu P, DeLange-Hudec S, Lee H, et al. A randomized trial of two weight-based doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency. *Diabetes Care* 2012; 35:1970-4.
20. Kesavadev J, Shankar A, Pillai P, Saboo B, Joshi S, Krishnan G, et al. CSII as an Alternative Therapeutic Strategy for Managing Type 2 diabetes: Adding the Indian Experience to a Global Perspective. Current diabetes reviews. 2015.
21. Bailon R, Partlow B, Miller-Cage V, Boyle M, Castro J, Bourgeois P, et al. Continuous subcutaneous insulin infusion (insulin pump) therapy can be safely used in the hospital in select patients. *Endocrine Practice* 2009; 15:24-9.
22. Houlden R, Capes S, Clement M, Miller D. In-hospital Management of Diabetes. *Canadian Journal of Diabetes* 37:S77-S81.
23. Schmeltz LR, DeSantis AJ, Thiyagarajan V, Schmidt K, O'Shea-Mahler E, Johnson D, et al. Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. *Diabetes Care* 2007; 30:823-8.
24. Kesavadev J, Shankar A, Pillai PBS, Krishnan G, Jothydev S. Cost-effective use of telemedicine and self-monitoring of blood glucose via Diabetes Tele Management System (DTMS) to achieve target glycosylated hemoglobin values without serious symptomatic hypoglycemia in 1,000 subjects with type 2 diabetes mellitus—A retrospective study. *Diabetes Technology & Therapeutics* 2012; 14:772-6.
25. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; 36:1384-95.
26. Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M. Hypoglycemia in hospitalized nondiabetic older patients. *J Am Geriatr Soc* 1998; 46:978-82.

27. Fischer KF, Lees JA, Newman JH. Hypoglycemia in hospitalized patients. *N Engl J Med* 1986; 315:1245-50.

28. Maynard G, Kulasa K, Ramos P, Childers D, Clay B, Sebasky M, et al. Impact of a hypoglycemia reduction bundle and a systems approach to inpatient glycemic management. *Endocrine Practice* 2014; 21:355-67.

29. Goguen J, Gilbert J. Hyperglycemic emergencies in adults. *Canadian Journal of Diabetes* 2013; 37 (suppl 1):S1-S212.

30. Lupsa BC, Inzucchi SE. Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome. Endocrine Emergencies: Springer; 2014. p. 15-31.

31. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic Crises in Adult Patients With Diabetes. A consensus statement from the American Diabetes Association. 2006; 29:2739-48.