Management of Diabetes in hospital setting
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Introduction
The epidemic of Diabetes continues to flourish throughout the world. Nowhere is the Diabetes epidemic as apparent as in the inpatient hospital setting. Diabetes mellitus increases the risk of disorders such as coronary artery disease, cerebrovascular occlusion, peripheral artery disease, renal insufficiency, peripheral neuropathy, lower-extremity infection, ulceration, amputation and other disorders. Such complications frequently require admission into the hospital for evaluation and treatment. It is not surprising, therefore, that patients with Diabetes compose a disproportionately high number of hospital inpatients. People with Diabetes are more likely to be hospitalized and to have longer durations of hospital stay than those without diabetes. A recent survey estimated that 22% of all hospital inpatient days were incurred by people with Diabetes.1 Although hyperglycemia is associated with adverse patient outcomes, intervention to normalize glycaemia has yielded inconsistent results. Indeed, recent trials in critically ill patients have failed to show a significant improvement in mortality with intensive glycaemic control2,3 or have even shown increased mortality risk.4 Moreover, these recent RCTs have highlighted the risk of severe hypoglycemia resulting from such efforts.2,7 These outcomes have contributed to confusion regarding specific glycemic targets and the means for achieving them in both critically ill and noncritically ill patients.

Evidence that improving glucose control outcomes
Hyperglycemia in hospitalized patients, irrespective of its cause, is unequivocally associated with adverse outcomes.8-15 Hyperglycemia occurs in patients with known or undiagnosed Diabetes, or it occurs during acute illness in those with previously normal glucose tolerance (termed "stress hyperglycemia").16 Intervention directed at reducing blood glucose (BG) levels has resulted in improved outcomes in some, but not all, studies.8-15 Several recent clinical trials in critically ill patients have reported no reduction in mortality from intensive treatment targeting near-euglycemia versus conventional management targeting BG <10.0 mmol/L. Of considerable concern are reports of harm, with higher rates of severe hypoglycemia and even increased mortality resulting from intensive glycemic control.17,18 This variability in results may be attributable to several factors, including differences in intravenous (IV) Insulin treatment protocols and their implementation, glycemic targets, patient populations, methods for glucose monitoring, and Insulin adjustment.2,19 The following section focuses primarily on results of recent studies with RCT design that investigated patient outcomes with protocols targeting near-normalization of BG levels.

Data derived from surgical and medical intensive care units
Observational studies have documented that hyperglycemia after cardiothoracic surgical procedures is associated with higher rates (approximately 2-fold) of wound infection.10,20 Interventions to reduce hyperglycemia in this setting with IV Insulin therapy decrease www.orion-group.net/journals
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infection rates\textsuperscript{9,11,21} and cardiac-related mortality,\textsuperscript{22} in comparison with historical control subjects. Intensive Insulin therapy targeting arterial glucose levels of 4.4 to 6.1 mmol/L in a primarily surgical ICU patient population resulted in a significant decrease in morbidity and mortality. A 6-fold increase in severe hypoglycemic events (BG 2.2 mmol/L) was observed in the intensively treated group (18.7\% versus 3.1\%), and hypoglycemia was identified as an independent risk factor for mortality.\textsuperscript{6}

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 (17\% versus 4.1\%; \(P<.001\)).\textsuperscript{13} Hypoglycemia BG <2.2 mmol/L was identified as an independent risk factor for mortality (relative risk, 2.2 at 28 days; 95\% confidence interval, 1.6 to 3.0). Similarly, intensive glycemic control in a mixed medical and surgical ICU resulted in no decrease in morbidity or mortality, while increasing the rate of hypoglycemia 5-fold.\textsuperscript{18}

The largest study to date, Normoglycemia in Intensive Care Evaluation- Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a multicenter, multinational RCT, tested the effect of tight glycemic control on outcomes among 6,104 critically ill participants, the majority of whom (>95\%) required mechanical ventilation.\textsuperscript{4} The 90 days mortality was significantly higher in the intensively treated versus the conventionally treated group (78 more deaths; 27.5\% versus 24.9\%; \(P = 0.02\)) in both surgical and medical patients. Mortality from cardiovascular causes was more common in the intensively treated group (76 more deaths; 41.6\% versus 35.8\%; \(P = .02\)). Severe hypoglycemia was also more common in the intensively treated group (6.8\% versus 0.5\%; \(P<.001\)). A recent meta-analysis of RCTs reported comparisons between intensive Insulin therapy with glycemic targets of 4.0 to 7.0 mmol/L and less intensive therapy with targets of <8.3 to 12.2 mmol/L. Among 8,432 critically ill patients, there was no significant difference in mortality between intensive therapy and control groups (21.6\% versus 23.3\%, respectively).\textsuperscript{2} A decrease in septicemia and a 5-fold increase in hypoglycemia (13.7\% versus 2.5\%) were observed. In a second meta-analysis including 13,567 critically ill patients, a favorable effect of intensive therapy on mortality was noted only in surgical ICU patients (relative risk, 0.63; confidence interval, 0.44 to 0.91).\textsuperscript{7} There was a 6-fold increase in the rate of occurrence of hypoglycemia with use of intensive therapy in all ICU patients.\textsuperscript{7} The higher rates of severe hypoglycemia associated with intensive Insulin therapy raise the possibility that serious adverse events in the subgroup of patients experiencing hypoglycemia offset,\textsuperscript{7,8} at least in part, any benefit derived from strict glycemic control in the much larger subgroup of patients without hypoglycemic events.\textsuperscript{3,6} Hypoglycemic events, however, have been infrequently linked to mortality; this finding suggests that severe hypoglycemia may be a marker of more serious underlying disease.\textsuperscript{3,4,6}

Data derived from patients with acute myocardial infarction
Although hyperglycemia is associated with adverse outcomes after acute Myocardial Infarction (AMI), reduction of glyceria per se, and not necessarily the use of Insulin, is associated with improved outcomes.\textsuperscript{23-27} It remains unclear, however, whether hyperglycemia is a marker of underlying health status or is a mediator of complications after AMI. Non-iatrogenic hypoglycemia has also been associated with adverse outcomes and is a predictor of higher mortality.\textsuperscript{28,29} Several studies have attempted to reproduce the favorable outcomes observed with early implementation of Insulin therapy reported in the first Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial.\textsuperscript{30} DIGAMI 2, a multicenter RCT of 1,253 patients with AMI and Diabetes, failed to show
a decrease in mortality with such intervention. The Hyperglycemia Intensive Insulin Infusion in Infarction (HI-5) study randomly assigned patients with AMI to 24-hour infusions of Insulin plus glucose for 24 hours (BG goal <10.0 mmol/L) or usual care. There were no significant differences in mortality, although there was a decreased incidence of Congestive Heart Failure and reinfarction at 3 months in the intensively treated group. The very large 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 in post-AMI patients and found no decrease in mortality. A failure to achieve a prespecified glycemic target with intensive therapy that differed from those in the control group may have contributed to these negative results.

Data derived from other critically ill patients
Several retrospective studies have examined the relationship between glycemia and clinical outcomes in patients with extensive burns, body trauma, or traumatic brain injury or those who have undergone surgical treatment for cerebral aneurysms. In patients with subarachnoid hemorrhage, hyperglycemia was associated with impaired cognition and deficits in gross neurologic function at 3 months. Patients without Diabetes who had severe blunt injury and hyperglycemia BG >11.1 mmol/L were found to have a 2.2 fold higher rate of mortality than those with admission glucose of less than 11.1 mmol/L.

Data derived from studies on intraoperative glycemic management
In a double-blind, placebo-controlled RCT involving 82 adults, intraoperative glucose-Insulin-potassium infusion during a coronary artery bypass grafting procedure did not reduce myocardial damage, mortality, or length of stay. In a study of 399 patients undergoing cardiac surgical procedures, intensive Insulin therapy (target BG, 4.4 to 5.6 mmol/L) intraoperatively resulted in no difference in patient outcomes; postoperatively, however, both groups were treated to similar glycemic targets.

Hyperglycemia in hospitalized medical and surgical patients in non-ICU settings
No RCTs 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.

Factors influencing glucose control in hospitalized patients
Insulin resistance and Insulin secretory capacity in hospitalized patients are affected by numerous factors, including the severity of illness and medications (in particular, glucocorticoids and pressors); in addition, a patient’s diet is often unpredictable in the hospital, and tests and procedures frequently interrupt both meal and medication schedules, further complicating the management of glucose levels. It is important to know whether a patient has a history of Diabetes and, if so, the type (since patients with type 1 Diabetes have an increased risk of ketosis), as well as the regimen used to control glucose levels before hospitalization. Also important is the patient’s nutritional status (which will determine the need for basal or prandial Insulin) and prevailing glucose level (which will guide decisions about the aggressiveness of the initial regimen and the pace at which it is advanced). Determining whether aggressive glucose control is practical will depend in part on the expected course of treatment during hospitalization and in part on the anticipated length of stay. Decisions regarding inpatient glucose control will also be influenced by the quality of the patient’s control before admission. In those with established Diabetes, a glycated hemoglobin test will provide a rapid assessment of control on the outpatient regimen. Such
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information will help guide the need for more intensive efforts.

**Glycemic goal for hospitalized patients**
The management of hyperglycemia in the hospital presents unique challenges that stem from variations in a patient's nutritional status and level of consciousness, the practical limitations of intermittent glycemic monitoring, and the ultimate importance of patient safety. Accordingly, reasonable glucose targets in the hospital setting are modestly higher than may be routinely advised for patients with Diabetes in the outpatient setting.

1. Glycemic goal for critically ill patients: On the basis of the available evidence, Insulin infusion should be used to control hyperglycemia in the majority of critically ill patients in the ICU setting, with a starting threshold of no higher than 10.0 mmol/L. Once IV Insulin therapy has been initiated, the glucose level should be maintained between 7.8 to 10.0 mmol/L, and greater benefit may be realized at the lower end of this range. Although strong evidence is lacking, somewhat lower glucose targets may be appropriate in selected patients. Targets less than 6.1 mmol/L, however, are not recommended. Use of Insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of occurrence of hypoglycemia, is highly recommended.

2. Glycemic goal for non-critically ill patients: With no prospective, RCT data for establishing specific guidelines in noncritically ill patients, based on clinical experience and judgment, for the majority of noncritically ill patients treated with Insulin, premeal glucose targets should generally be <7.8 mmol/L in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved. For avoidance of hypoglycemia, consideration should be given to reassessing the Insulin regimen if BG levels decline below 5.6 mmol/L. Modification of the regimen is necessary when BG values are <3.9 mmol/L, unless the event is easily explained by other factors (such as a missed meal). Occasional clinically stable patients with a prior history of successful tight glycemic control in the outpatient setting may be maintained with a glucose range below the aforementioned cut points. In contrast, higher glucose ranges may be acceptable in terminally ill patients or in patients with severe co-morbidities, as well as in those in patient-care settings where frequent glucose monitoring or close nursing supervision is not feasible.

**Treatment options for achieving optimal glycemic targets**

1. Oral hypoglycemic agent: There are many treatment options to control glucose levels in the outpatient setting. Unfortunately, few of these medications translate well into inpatient or acute illness therapy. Some agents are ineffective in acute illness, require long periods of time to be practical in the hospital environment, or may even be detrimental when patients are seriously ill. Sulfonylureas are very commonly used as an outpatient therapy for type 2 Diabetes, typically as a first or second line oral agent. In the inpatient setting, they pose significant risk of hypoglycemia because they usually stimulate Insulin release from pancreatic ß-cells. Patients using these agents may develop hypoglycemia in the fasting state, which is common in the hospital setting because of illness or diagnostic testing. The long half-life of these agents causes them to be relatively nonamenable to acute titration, initiation of therapy, or stopping therapy while patients are hospitalized. Additionally, there is lack of adequate study of such medications showing efficacy in the hospital setting. Metaglinide medications such as nateglinide or repaglinide, although possessing a shorter half-life, could also predispose to hypoglycemia and also lack safety and efficacy data. When initiated, they may also induce nausea. These Insulin secretagogues, therefore, do not lend themselves well to hospital use.

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sulfonylureas, but they have a very delayed onset and are not particularly potent agents. Their major action is to control postprandial glucose levels, and therefore they are not attractive agents for the inpatient setting, where many patients are fasting or eating unreliable. They also lack clinical trial data in the inpatient setting. Thiazolidinediones do not act acutely and in fact may require several months to exert full effect. Additionally, they increase intravascular volume, which may exacerbate Congestive Heart Failure or other conditions of hemodynamic instability. These agents do not appear useful in the inpatient setting. Metformin, although typically a first-line agent in the treatment of type 2 Diabetes, has several drawbacks in the inpatient setting. It possesses a very slow onset of action, although the risk of hypoglycemia is relatively low. The major risk regarding metformin is that of lactic acidosis, a rare but potentially fatal complication of Metformin therapy. Risk factors for developing lactic acidosis include using Metformin in the setting of Congestive Heart Failure, Hypoxic states, Renal insufficiency, and other causes of hypoperfusion. Because most hospitalized patients are at significant risk to develop such conditions, it is advisable to avoid Metformin use in inpatients.

2. **Insulin**: In the ICU, Insulin is usually administered by continuous intravenous infusion; optimally, a standardized algorithm is followed. Several validated protocols are available. The most effective are those that use dynamic scales, incorporating the rate of change in glucose into dose adjustments. Frequent monitoring of glucose levels (usually hourly) is imperative to minimize the risk of hypoglycemia. As the patient’s clinical status improves, the transition to subcutaneous Insulin can be made, with the use of the most recent infusion rate to approximate the overall daily requirement, dividing this into basal and prandial components. Also, proper overlap between intravenous and subcutaneous Insulin must be ensured. Patients with type 2 Diabetes who require less than 2 U of Insulin per hour may do well with less intensive regimens; oral agents may be sufficient in some patients.

Therapies that involve some basal (i.e., intermediate to long-acting) Insulin, with short- or rapid-acting Insulin provided before meals to blunt postprandial spikes in glucose (mealtime, or prandial, bolus), provide results that most closely resemble physiologic patterns of glucose control. Rapid-acting Insulin analogues (lispro, aspart, and glulisine) should be given immediately before a meal. A prudent approach is to provide the Insulin only when the meal tray is in front of the patient. Regular human Insulin should ideally be given 30 minutes before meals a goal that may be difficult to meet in the busy hospital setting. Also, the rapid-acting analogues provide better postprandial control. In patients whose dietary intake is uncertain, prandial Insulin dosing should be conservative. One alternative is to allow a rapid-acting Insulin analogue to be administered immediately after a meal, on the basis of the amount the patient actually consumed. Adjustable supplementary doses ("correction" Insulin) of identical type may be combined with the prandial Insulin to compensate for premeal hyperglycemia. Insulin-sensitive patients (most patients with type 1 Diabetes, lean persons, those receiving relatively low total daily doses of Insulin [<30 to 40 U per day], or those prone to hypoglycemia) will require only modest doses (e.g., 1 U to correct blood glucose levels of 8.3 mmol per liter, 2 U to correct levels of 11.1 mmol per liter, and so on). Most patients with type 2 Diabetes (those who are overweight or who are receiving moderate doses of Insulin [40 to 100 U per day]) will require moderate correction doses (e.g., 2 U to correct blood glucose levels of 8.3 mmol per liter, 4 U to correct levels of 11.1 mmol per liter, and so on). Some patients with type 2 Diabetes and severe Insulin resistance (those who are very obese, those receiving large amounts of Insulin [>100 U per day], or those taking corticosteroids) may require large corrective doses (e.g., 4 U for blood glucose levels of 8.3
mmol per liter, 8 U for levels of 11.1 mmol per liter, and so on). Insulin sensitivity may change rapidly as the underlying illness improves. The basal Insulin dose is adjusted depending on the overall glucose profile. If glargine or detemir is used, the dose adjustment should be based on the morning fasting blood glucose level. If NPH is used, the dose adjustment should be based on the morning fasting blood glucose level or the blood glucose level measured before the evening meal. Adjustments of prandial Insulin doses are based on the level of postprandial glycemia. The correction Insulin dose may be adjusted after an assessment of the patient’s response to prior doses. To ensure patient safety, Insulin requirements should be reassessed immediately after any change in nutritional status. Some patients with type 2 Diabetes may have a response to less aggressive Insulin strategies, such as basal Insulin alone (e.g., glargine once daily, detemir once or twice daily, or NPH twice daily) or convenient premixed formulations involving intermediate and short- or rapid-acting Insulins (e.g., “70/30”). These strategies may be acceptable for those with hyperglycemia that is not severe, especially if discharge is imminent and there is no time for titration of more complex regimens. In Insulin-treated patients who are not eating, basal Insulin should be provided, with regular Insulin administered every 6-8 hours as necessary. This is mandatory in patients with type 1 Diabetes and advisable in patients with type 2 diabetes. (Insulin infusion can also be used in this setting, or if the adequacy of subcutaneous absorption is in doubt.) In Insulin-treated patients who are eating, the regimen used before hospitalization can be continued if it was successful and if the glucose level is acceptable on admission. As with oral agents, depending on the clinical circumstances, modest dose reductions, particularly for patients with type 2 diabetes, should be considered because of the anticipated reduction in caloric intake. If the glucose level is high on admission (more than levels of 11.1 mmol per liter), the Insulin dose should generally be increased. A change to a basal-prandial correction strategy should be considered. Intravenous infusions of Insulin should be considered if marked hyperglycemia (glucose levels of 16.7 to 22.2 mmol per liter or more) persists for more than 24 hours and is not controlled by increasing the dose of subcutaneous Insulin. Intravenous Insulin works rapidly, and the dose can be titrated more precisely than can the dose of subcutaneous injections. Also, because intravenous Insulin has a very short half life (5 to 9 minutes), hypoglycemia, if it occurs, can be quickly reversed. For safety reasons, a higher glycemic target than is used in ICUs is advisable when Insulin infusions are used on general wards. Adequate nursing resources are needed for safe monitoring and titration. The glucose levels in patients receiving continuous enteral tube feeding are optimally managed mainly with the use of basal Insulin, with correction doses of regular Insulin added as needed every 6 to 8 hours. If feeding is interrupted, an amount of carbohydrate (i.e., dextrose) similar to that being used enteraly should be administered intravenously to prevent hypoglycemia. For patients receiving total parenteral nutrition, regular Insulin can be added to the intravenous bags; the dose is gradually titrated in increments of 5 to 10 U per liter to achieve glycemic control.

Close monitoring of glucose levels is needed, regardless of the Insulin regimen, with frequent adjustments made (as often as every 1 to 2 days) to optimize control. Before doses are increased, however, it is important to consider factors that may contribute to hyperglycemia (e.g., missed doses excess snacking, or new infection) and to address them. The mistiming of glucose measurement (in a finger-stick blood sample), meal ingestion, and prandial Insulin administration is another frequent culprit of glycemic lability in the hospital. Proper coordination between dietary and nursing services is mandatory for quality inpatient glucose management.
Strategies for transition to outpatient care
Preparation for transition to the outpatient setting is an important goal of inpatient Diabetes management and begins with the hospital admission. Before the patient is discharged, the Insulin regimen may need to be simplified, depending on the capacities of the patient. Once-daily, long-acting Insulin alone is practical in some patients with type 2 diabetes. In others, who have required little Insulin in the hospital or whose control has been excellent when receiving less than 25 to 30 U per day, diet therapy or oral agents may eventually be adequate. Follow-up is warranted within 1 to 2 weeks after discharge if treatment with antihyperglycemic medications was initiated or stopped or if the dose was changed during hospitalization. Similar recommendations apply to hospitalized patients with newly diagnosed hyperglycemia, although some patients may no longer require glucose-lowering therapy after they have recovered from acute illness. Fasting glucose levels (and perhaps glycated hemoglobin values) should be reassessed 1 to 2 months after discharge in these patients. It is recommended that the following areas be reviewed and addressed before the patient is discharged from the hospital:

- Level of understanding related to the diagnosis of diabetes.
- Self-monitoring of BG and explanation of home BG goals.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Identification of health care provider who will be responsible for Diabetes care after discharge.
- Information on consistent eating patterns.
- How and when to take BG-lowering medications, including administration of Insulin (if the patient is receiving Insulin for ongoing management at home).
- Sick-day management.
- Proper use and disposal of needles and syringes.

Conclusions
Patients admitted into the hospital with Diabetes should have Diabetes clearly labeled in their medical records. In critically ill patients, Insulin therapy should be initiated for treatment of persistent hyperglycemia, starting at a threshold of no greater than 10.0 mmol/L. Once Insulin therapy has been started, a glucose range of 7.8 to 10.0 mmol/L is recommended for the majority of critically ill patients. Intravenous Insulin infusions are the preferred method for achieving and maintaining glycemic control in critically ill patients. Validated Insulin infusion protocols with demonstrated safety and efficacy, and with low rates of occurrence of hypoglycemia, are recommended. With IV Insulin therapy, frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to achieve optimal glucose control.

In noncritically ill patients, the majority patients treated with Insulin, the premeal blood glucose target should generally be <7.8 mmol/L in conjunction with random blood glucose values <10.0 mmol/L, provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in terminally ill patients or in patients with severe co-morbidities. Scheduled subcutaneous administration of Insulin, with basal, nutritional, and correction components, is the preferred method for achieving and maintaining glucose control. Prolonged therapy with sliding scale Insulin as the sole regimen is discouraged. Oral antihyperglycemic agents are not appropriate in most hospitalized patients who require therapy for hyperglycemia. Clinical judgment and ongoing assessment of clinical status must be incorporated into day-to-day decisions regarding treatment of hyperglycemia. All patients receiving therapy for Diabetes should have a plan for treatment of hypoglycemia.

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Preparation for transition to the outpatient setting should begin at the time of hospital admission. Discharge planning, patient education, and clear communication with outpatient providers are critical for ensuring a safe and successful transition to outpatient glycemic management. Patients with hyperglycemia in the hospital who do not have a previous diagnosis of Diabetes should have follow-up testing performed after discharge.

As Diabetes is increasing throughout the world, more and more patients are placed at risk of developing acute and severe illnesses such as MI, congestive heart failure, stroke, and other diseases. These acute illnesses frequently require acute hospitalization, both during their initial onset and also as a result of exacerbations or their sequelae. It is very important, therefore, for physicians working in the world of inpatient medicine to be very adept at treating diabetes. Familiarity with such treatment will likely help improve patient outcomes and minimize complications.

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