Chapter 19- MANAGEMENT OF DIABETES AND HYPERGLYCEMIA IN HOSPITALIZED PATIENTS

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INTRODUCTION

Diabetes is a prevalent metabolic disorder that affects more than 340 million people globally ([1]). In the United States, data from the National Diabetes Statistics recently reported that in 2012, a total of 29.1 million Americans, or 9.3% of the population, had diabetes([2]). The percentage of the population with diagnosed diabetes is expected to rise, with one study projecting that as many as one in three U.S. adults will have diabetes by 2050([3]). Patients with diabetes have a 3-fold greater chance of hospitalization compared to those without diabetes ([4,5]), and it is estimated that more than 20% of all adults discharged have diabetes, with 30% of them requiring 2 or more hospitalizations in any given year ([4-6]). In 2012 in the U.S., there were over 7.7 million hospital stays for patients with diabetes (i.e., diabetes as either a principal diagnosis for hospitalization or as a secondary diagnosis, coexisting condition). Diabetes remains the 7th leading cause of death in the United States in 2010, with 69,071 death certificates listing it as the underlying cause of death, and a total of 234,051 death certificates listing diabetes as an underlying or contributing cause of death ([2]).The care of patients with diabetes imposes a substantial burden on the economy ([7]).The total estimated cost of diagnosed diabetes in the United States in 2012 was $245 billion; including $176 billion in direct medical costs and $69 billion in reduced productivity. The largest components of medical expenditures are hospital inpatient care (43% of the total medical cost) ([7]).

Hyperglycemia and diabetes in the hospital setting affect 38% to 46% of non-critically ill hospitalized patients ([1,2]). Extensive data from observational and randomized controlled trials indicate that inpatient hyperglycemia, in patients with or without a prior diagnosis of diabetes, is associated with an increased risk of complications and mortality, a longer hospital stay, a higher admission rate to the intensive care unit (ICU), and a higher need for transitional or nursing home care after hospital discharge([1,3,4]). It is also well established that improvement in glucose control with goal-directed insulin regimens reduces hospital complications and mortality in critically ill, as well as in general medicine and surgery patients ([6-11]).

Recent studies and meta-analyses have shown that intensive insulin therapy is associated with increased risk of hypoglycemia([12-15]), which has been independently associated with increased morbidity and mortality in hospitalized patients([15]). Thus, while insulin therapy is recommended for the management of hyperglycemia in hospitalized patients([11,16]), the concern about hypoglycemia has led to revised glucose target recommendations from professional organizations ([8,9]), and search of alternative treatment options([17,18]).

This chapter reviews the pathophysiology of hyperglycemia during illness, the mechanisms for increased complications and mortality due to hyperglycemia and hypoglycemia, and reviews the evidence on the different therapies available for the management of inpatient diabetes and hyperglycemia in the critical care and in the general medicine and surgical settings.

PREVALENCE OF DIABETES AND HYPERGLYCEMIA IN THE HOSPITALIZED PATIENT.
Observational studies have reported a prevalence of hyperglycemia and diabetes ranging from 32% to 38% in community hospitals ([6,10]) and in 70-80% of diabetic patients with critical illnesses ([11]) and cardiac surgery ([19,20]). A recent report using point-of-care bedside glucose tests data in 3,484,795 patients (653,359 ICU and 2,831,436 non-ICU) from 575 hospitals in the United States reported a prevalence of hyperglycemia, defined as a glucose level >180 mg/dl, of 32.2% in ICU patients and in 32.0% of non-ICU patients ([21]). These numbers included patients with newly identified or stress hyperglycemia as well as diabetes. The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) consensus on inpatient hyperglycemia defined stress hyperglycemia or hospital-related hyperglycemia as any blood glucose concentration > 7.8 mmol/l (140 mg/dl). Although stress hyperglycemia typically resolves as the acute illness or surgical stress abates, about 60% of such patients had confirmed diabetes at 1 year ([22]). Measurement of an HbA1c is indicated in patients with hyperglycemia without a history of diabetes to differentiate between stress hyperglycemia and previously undiagnosed diabetes ([23,24]).The Endocrine Society recommendations indicate that hospitalized patients with elevated blood glucose an HbA1C of 6.5% (48 mmol/mol) or higher can be identified as having diabetes ([12]).

PATHOPHYSIOLOGY OF HYPERGLYCEMIA DURING ILLNESS
In normal subjects during fasting state, plasma glucose is maintained between 3.9 – 5.6 mmol/l (70-100 mg/dl) by a finely regulated balance between hepatic glucose production and glucose utilization in peripheral tissues. Maintenance of normal glucose level is essential for central nervous system function as the brain can neither synthesize nor store glucose ([13]).Systemic glucose balance is maintained by dynamic, minute-to-minute regulation of endogenous glucose production and of glucose utilization by peripheral tissues ([14-16]). Glucose production is accomplished by gluconeogenesis or glycogenolysis primarily in the liver and in a lesser degree by the kidneys ([16]). Gluconeogenesis results from conversion of non-carbohydrate precursors such as lactate, alanine, and glycerol to glucose in the liver. Excess glucose is polymerized to glycogen, which is mainly stored in the liver and muscle. Hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues (Figure 1) ([17]).

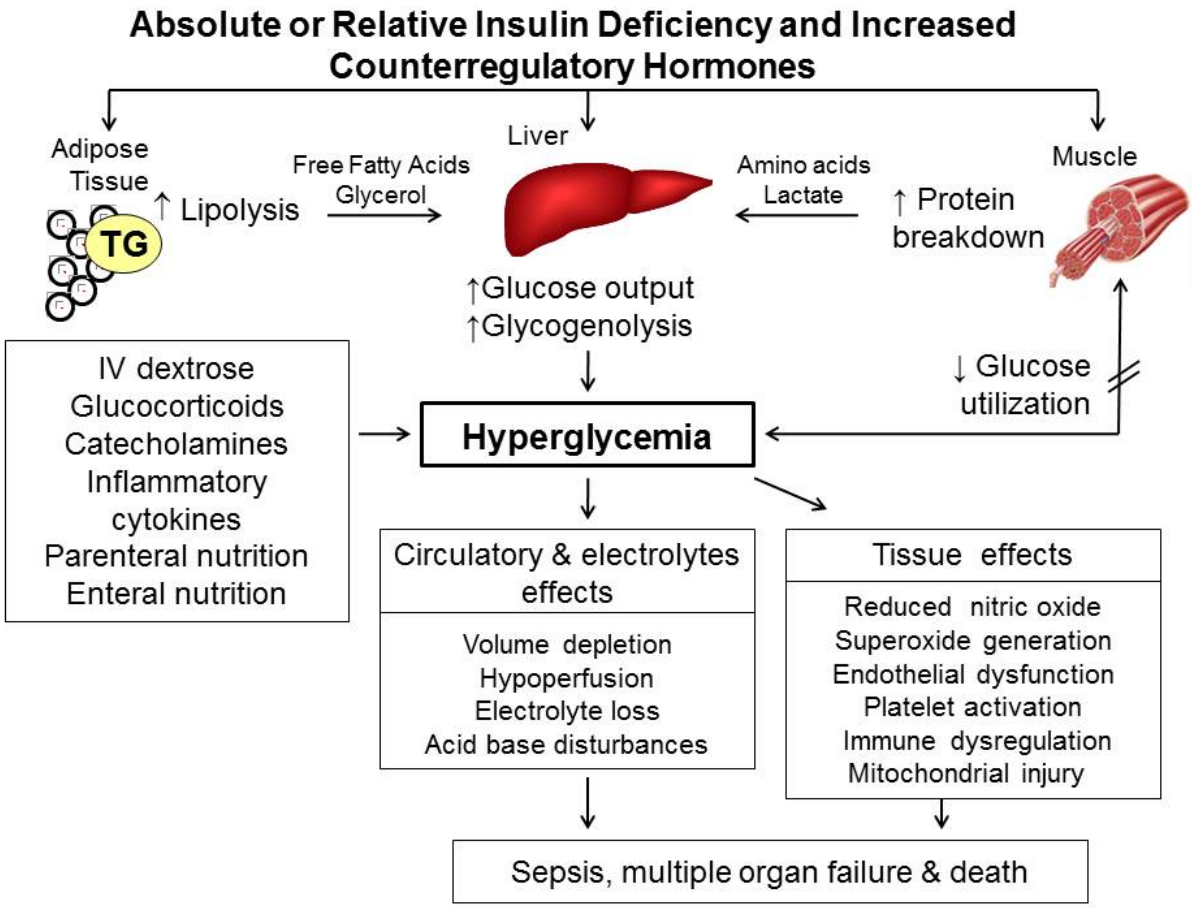

Figure 1. Pathogenesis of hyperglycemia.
Hyperglycemia results from increased hepatic glucose production and impaired glucose utilization in peripheral tissues. Reduced insulin and excess counterregulatory hormones (glucagon, cortisol, catecholamines and growth hormone) increase lipolysis and protein breakdown (proteolysis), and impair glucose utilization by peripheral tissues. Hyperglycemia causes osmotic diuresis that leads to hypovolemia, decreased glomerular filtration rate, and worsening hyperglycemia. At the cellular level, increased blood glucose levels result in mitochondrial injury by generating reactive oxygen species, and endothelial dysfunction by inhibiting nitric oxide production. Hyperglycemia increases levels of pro-inflammatory cytokines such as TNF-α and IL-6 leading to immune system dysfunction. These changes can eventually lead to increased risk of infection, impaired wound healing, multiple organ failure, prolonged hospital stay and death. Adapted from ref ([16]).

From the quantitative standpoint, increased hepatic glucose production represents the major pathogenic disturbance. Increased hepatic glucose production results from the high availability of gluconeogenic precursors including the amino acids alanine and glutamine, as a result of accelerated proteolysis and decreased protein synthesis; lactate as a result of increased muscle glycogenolysis; and glycerol as a result of increased lipolysis; and from the increased activity of gluconeogenic enzymes (phosphoenol pyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase) ([16,18,25]).

Glucose metabolism is maintained by an interaction of glucoregulatory hormones - insulin and counterregulatory hormones (glucagon, cortisol, growth hormone and catecholamines). Insulin controls hepatic glucose production by suppressing hepatic gluconeogenesis and glycogenolysis. In insulin-sensitive tissues such as muscle, insulin promotes protein anabolism, glucose uptake and glycogen synthesis, and inhibits glycogenolysis and protein breakdown ([13,26]). In addition, insulin is a powerful inhibitor of lipolysis, free fatty acid oxidation, and ketogenesis ([13,26]) Counterregulatory hormones (glucagon, cortisol, growth hormone and catecholamines) also play an important role in the regulation of glucose production and utilization. Glucagon is the most important glycogenolytic hormone, and therefore regulates hepatic glucose production during the normal state and in every state of hyperglycemia ([16]) During stress, excess concentration of counterregulatory hormones result in altered carbohydrate metabolism by inducing insulin resistance, increasing hepatic glucose production, and reducing peripheral glucose utilization. In addition, high epinephrine levels stimulate glucagon secretion and inhibit insulin release by pancreatic β-cells ([27]).
The development of hyperglycemia results in an inflammatory state characterized by an elevation of pro-inflammatory cytokines and increased oxidative stress markers ([28,29]). Circulating levels of tumor necrosis factor-α, interleukin [IL]-6, IL1-ß, and IL-8, C-reactive protein are significantly increased two- to fourfold on admission in patients with severe hyperglycemia compared with control subjects, and levels returned to normal levels after insulin treatment and resolution of hyperglycemic crises ([28]). TNF-α leads to insulin resistance by interaction at the level of the insulin receptor and through altered regulation of the insulin-signaling pathway. Increasing evidence indicates that during acute stressful states, increased circulating inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1 can increase insulin resistance by interfering with insulin signaling ([28,30-32]). In addition, TNF-α, by preventing insulin-mediated activation of phosphatidylinositol 3-kinase, reduces insulin-stimulated glucose uptake in peripheral tissues ([33,34]).

CONSEQUENCES OF HYPERGLYCEMIA IN THE HOSPITALIZED PATIENTS

A large body of literature including observational and prospective randomized clinical trials, in patients with and without diabetes, as well as in critically ill and non-critically ill patients has shown a strong association between hyperglycemia and poor clinical outcomes, such as mortality, infections and hospital complications ([6,35-37]). This association correlates with severity of hyperglycemia on admission as well as during the hospital stay ([35,38,39]). Of interest, increasing evidence indicates an increased risk of complications and mortality in patients without a history of diabetes (stress induced) compared to patients with known diagnosis of diabetes ([6,35,40]). It is not clear if stress hyperglycemia is the direct caused of poor outcomes or it is a general marker of severity of illness.
The mechanisms implicated on the detrimental effects of hyperglycemia during acute illnesses are not completely understood. Current evidence indicates that severe hyperglycemia results in impaired neutrophil granulocyte function, high circulating free fatty acids, and overproduction of

pro-inflammatory cytokines and reactive oxygen species (ROS) that can result in direct cellular damage, and vascular and immune dysfunction ([41]).

The majority of evidence linking hyperglycemia and poor outcomes comes from studies in the ICU. Falciglia et al in a retrospective study of over 250,000 veterans admitted to various ICUs reported that hyperglycemia is an independent risk factor for mortality and complications ([35]). In a nonrandomized, prospective study, Furnary followed 3,554 patients with diabetes that underwent coronary artery bypass graft. Patients treated with subcutaneous insulin (SCI) who had an average blood glucose of 11.9 mmol/l (214 mg/dl) and patients treated with continuous insulin infusion (CII) with an average blood glucose of 9.8 mmol/l (177 mg/dl) had significantly more deep sternal wound infections ([39]) and a 50% higher risk-adjusted mortality ([36]). In a different ICU study, patients with blood glucose levels >11.1 mmol/l (>200 mg/dl) were shown to have higher mortality compared to those with blood glucose levels <11.1 mmol/l (<200 mg/dl) (5.0% vs. 1.8%, $p < 0.001$) ([39]).

The association of hyperglycemia and poor outcomes also applies to non-ICU patients admitted to general medicine and surgery services. In such patients, hyperglycemia is associated with poor hospital outcomes including prolonged hospital stay, infections, disability after hospital discharge and death ([6,42]). In a retrospective study of 1,886 patients admitted to a community hospital, mortality in the general floors was significantly higher in patients with newly (stress) diagnosed hyperglycemia and with known diabetes compared to subjects with normal glucose values (10% vs. 1.7% vs. 0.8%, respectively; $p < 0.01$) ([6]). In a prospective cohort multicenter study of 2,471 patients with community-acquired pneumonia, those with admission glucose levels of > 11 mmol/l (198 mg/dl) had a greater risk of mortality and complications than those with glucose < 11 mmol/l (198 mg/dl). The risk of complications increased 3% for each 1 mmol/l (18 mg/dl) increase in admission glucose([43]). In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.1 in those with a blood glucose of 7-8.9 mmol/l (126-160 mg/dl), and 3.4 for those with a blood glucose of >9.0 mmol/l (>162 mg/dl) compared to patients with a blood glucose of 6.0 mmol/l (108 mg/dl) ([44]).

General surgery patients with hyperglycemia during the perioperative period are also at increased risk for adverse outcomes. In a case-control study, elevated preoperative glucose levels increased the risk of postoperative mortality in patients undergoing elective non-cardiac non-vascular surgery ([45]). Patients with glucose levels of 5.6-11.1 mmol/l (110-200 mg/dl) and those with glucose levels of >11.1 mmol/l (>200 mg/dl) had, respectively, 1.7-fold and 2.1-fold increased mortality compared to those with glucose levels < 5.6 mmol/l (<110 mg/dl)([46]). In another study, patients with glucose levels >12.2 mmol/l (> 220 mg/dl) on the first postoperative day had a rate of infection 2.7 times higher than those who had serum glucose levels <12.2 mmol/l ([45]). A more recent study ([47]) showed an increase of postoperative infection rate by 30% for every 2.2 mmol/l (40 mg/dl) rise in postoperative glucose level above 50 mmol/l (110 mg/dl).

GLYCEMIC TARGETS IN ICU AND NON-ICU SETTINGS

The American Diabetes Association (ADA) and American Association of Clinical Endocrinologist (AACE) task force on inpatient glycemic control recommended a change in glycemic targets in the ICU setting([9]) Table 1. These guidelines suggest targeting a blood glucose (BG) level between 7.8 and 10.0 mmol/l (140 and 180 mg/dl) for the majority of ICU patients and a lower glucose targets between 6.1 and 7.8 mmol/l (110 and 140 mg/dl) in selected ICU patients (i.e. centers with extensive experience and appropriate nursing support, cardiac surgical patients, patients with stable glycemic control without hypoglycemia). Glucose targets >10 mmol/l (>180 mg/dl) or <6.1 mmol/l (< 110 mg/dl) are not recommended in ICU patients.

Recent guidelines from the Society of Critical Care Medicine (SCCM) for the management of hyperglycemia in critically ill (ICU) patients ([48]) recommended that a blood glucose ≥ 150 mg/dl (8.3 mmol/l) should trigger interventions to maintain blood glucose below that level and absolutely <180 mg/dl (10 mmol/l). They suggest that the insulin regimen and monitoring system be designed to avoid and detect hypoglycemia (blood glucose < 3.9 mmol/l [70 mg/dl]) and to minimize glycemic variability. The technology to allow this to occur is in development and may be ready for routine clinical use relatively soon([49,50]). In the non-ICU setting, the Endocrine Society and the ADA/AACE Practice Guidelines ([9,12,51]) recommended a pre-meal glucose of <140 mg/dl (7.8 mmol/l) and a random BG of <10.0 mmol/l (180 mg/dl) for the majority of non-critically ill patients treated with insulin. To avoid hypoglycemia <3.9 mmol/l (70 mg/dl), the total basal and prandial insulin dose should be reduced if glucose levels fall between 3.9 mmol/L and 5.6 mmol/l (70-100 mg/dl). In contrast, higher glucose ranges (11.1 mmol/l or 200 mg/dl) may be acceptable in terminally ill patients or in patients with severe comorbidities as a way of avoiding symptomatic hyperglycemia ([12]).

Table 1. Major Guidelines for Treatment of hyperglycemia in a hospital setting.

	ICU	**Non-ICU**
ADA/AACE [9,51]	Initiate insulin therapy for persistent hyperglycemia (glucose >180 mg/dl [10 mmol/l]) Treatment goal: 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	No specific guidelines If treated with insulin, pre-meal glucose targets should generally be <140 mg/dL, with random glucose levels <180 mg/dL More stringent targets may be appropriate for patients with previously tight glycemic control Less stringent targets may be appropriate in patients with severe comorbidities
ACP[8]	Recommends against intensive insulin therapy in patients with or without diabetes in surgical/medical ICUs Treatment goal: target glucose between 140-200 mg/dl, in patients with or without diabetes, in surgical/medical ICUs	
Critical Care Society[48]	BG >150 mg/dl should trigger insulin therapy Treatment goal: maintain glucose <150 mg/dl for most adult patients in ICU Maintain glucose levels <180 mg/dl while avoiding hypoglycemia	—
Endocrine Society[12]	—	Pre-meal glucose target <140 mg/dl and random blood glucose <180 mg/dl A lower target range may be

		appropriate in patients able to achieve and maintain glycemic control without hypoglycemia Glucose <180-200 mg/dl is appropriate in patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia Adjust antidiabetic therapy when glucose falls <100 mg/dl to avoid hypoglycemia
Society of Thoracic Surgeons[117] (Guidelines specific to adult cardiac surgery)	Continuous insulin infusion preferred over SC or intermittent intravenous boluses Treatment goal: Recommend glucose <180 mg/dL during surgery (≤110 mg/dL in fasting and pre-meal states)	
Joint British Diabetes Society[52]		Target blood glucose levels in most people of between 6 and 10 mmol/L (108-180 mg/dl) with an acceptable range of between 4 and 12mmol/L (72 – 216mg/dl)

AACE/ADA, American Association of Endocrinologists and American Diabetes Association joint guidelines; ACP, American College of Physicians; ADA, American Diabetes Association; ICU, intensive care unit; IV

Guidelines from the Joint British Diabetes Society's Inpatient Care Group in the UK ([52]) published over the last few years, aim for target blood glucose levels in most people between 6 and 10 mmol/l (108-180 mg/dl) with an acceptable range between 4 and 12mmol/L (72 – 216mg/dl). Table 1 summarize the currently available guidelines for the management of hyperglycemia in the hospital setting.

EVIDENCE FOR CONTROLLING HYPERGLYCEMIA IN ICU AND NON-ICU SETTINGS

The Leuven SICU study set the stage for intensive glycemic control in the critical care setting a decade ago. This study randomized 1,548 patients admitted to the surgical ICU (63% cardiac cases, 13% with diabetes, most patients received early parenteral nutrition). Patients were randomized to either conventional therapy with a target glucose between 10 and 11.1 mmol/l (180-200 mg/dl) or intensive therapy to a target glucose between 4.4 and 6.1 mmol/l (80-110 mg/dl). Patients in the conventional arm had a mean daily glucose average of 8.5 mmol/l (153 mg/dl) and patients in the intensive arm had an average glucose of 5.7 mmol/l (103 mg/dl). Those in the intensive group had significantly less bacteremia, less antibiotic requirements, lower length of ventilator dependency, lower number of ICU days and an overall 34% reduction in mortality ([20]). Following a similar study design, the same group of investigators randomized medical ICU patients (18% with diabetes) and reported that intensive insulin therapy (mean daily glucose of 6.2 mmol/l (111 mg/dl)) resulted in less ICU and total hospital complications in patients with 3 days of insulin treatment ([53]). These two studies together, based on the positive outcomes on morbidity and mortality, suggested a glycemic target in the ICU of 4.4-6.1 mmol/l (80-110mg/dl) ([9,51]).

A large number of well-designed randomized controlled trials and meta-analyses have, however, shown that such a low glucose target has been difficult to achieve without increasing the risk for severe hypoglycemia ([54-57]). In addition, these studies failed to show improvement in clinical outcomes and have even shown increased mortality risk with intensive glycemic control Table 2 ([54-58]). The Glucontrol trial, a seven-country multicenter trial, randomized patients in medical and surgical ICUs to tight glycemic control (4.4-6.1 mmol/l; 80-110 mg/dl) versus conventional glycemic control (7.8-10 mmol/l; 140-180 mg/dl). The study did not find a difference in mortality between the two groups ([59]). The Efficacy of Volume Substitution and Insulin Therapy in Sepsis (VISEP) study was another trial that attempted to reproduce the data from the Leuven trial. The study was a multicenter study in Germany that randomized patients with sepsis to receive intensive insulin therapy to maintain glucose levels 10-11.1 mmol/l (180-200 mg/dl) versus the intensive arm of 4.4-6.1 mmol/l (80 -110 mg/dl) ([54]). The investigators evaluated differences between the groups in 28- and 90-day mortality, sepsis-related organ failure, ICU stay and frequency of hypoglycemia (BG < 2.2 mmol/l; < 40mg/dl). The trial was stopped prematurely after reaching only ~2/3 of the projected enrollment due to an interim analysis that showed no difference in 28- or 90-day mortality between patients treated in the conventional arm versus those in the intensive arm (21.6% vs. 21.9%; 29.5 vs. 32.8%, respectively), but those in the intensive arm experienced a significantly greater amount of severe hypoglycemia (12.1 vs. 2.1%).

Table 2: Clinical Trials of Intensive Glycemic Control in ICU Populations

Study	Setting	Population	Clinical Outcome
Malmberg[88], 1994	CCU	Mixed	28% decrease mortality After 1 year[88]

Furnary[39], 1999	CCU	DM undergoing CABG	65% decrease in deep sterna wound infection rate[39]
Van den Berghe[20], 2001	Surgical ICU	Mixed, with CABG	34% decrease mortality[20]*
Furnary[36], 2003	CCU	DM undergoing CABG	50% decrease in adjusted mortality rate[36]
Krinsley[38], 2003	Med-surgical ICU	Mixed	27% decrease in mortality[38]
Lazar[118], 2004	OR and ICU	DM with CABG	60% decrease of post-operative atrial fibrillation[118]
Van den Berghe[53], 2006	Medical ICU	Mixed	18% decrease mortality[53]*
Gandhi[119], 2007	Operating Room	Mixed, cardiac surgery	No difference in mortality; increase in stroke rate in IT arm[119]
VISEP[54], 2008	Medical ICU	Mixed w/ sepsis	No difference in 28-day or 90-day mortality, end-organ failure, LOS[54]*
De La Rosa[55], 2008	Med-surgical ICU	Mixed	No difference in 28-day mortality or infection rate[55]
Glucontrol[59], 2009	Med-surgical ICU	Mixed	No difference in 28-day mortality[59]*
NICE-SUGAR[58,120], 2009/2012	Med-surgical ICU	Mixed	No difference in 90-day mortality[58,120]
Boston Children's (SPECS)[121], 2012	Cardiac ICU	Cardiac surgery, non diabetics	No difference in 30-day mortality, length of stay in the cardiac ICU, length of hospital, duration of mechanical ventilation and vasoactive support, or measures of organ failure[121].
ChiP[122], 2014	Pediatric-ICU	Critical illness/injury/major surgery, non diabetics.	No difference in 30-day mortality, increase hypoglycemia in the intensive treated group[122].
CGAO–REA[97,123], 2014	Medical ICU	Mixed	No difference in 90-day mortality, increase hypoglycemia in the intensive treated group[97,123].
Okabayashi[124], 2014	Surgical ICU	Mixed	Decrease surgical site

			infection in the intensive treated group[124].

IT=intensive therapy; CT=conventional therapy
*Study underpowered due to premature discontinuation
Mixed=non diabetics and diabetics

The NICE-SUGAR trial ([56]) randomized over 6000 subjects to receive either conventional glycemic control (<10 mmol/l; <180 mg/dl) or intensive glycemic control (4.5-6 mmol/l; 81-108 mg/dl) and also reported no difference in-hospital mortality, but found increased mortality at 90 days of follow-up (24.9% vs. 27.5%, p=0.02). In a subsequent analysis of the trial, the NICE SUGAR investigators reported a higher frequency of hypoglycemia in the intensive arm (6.8% vs. 0.5%) and those with hypoglycemia had ~2-fold increase in mortality compared to patients without hypoglycemia ([60]).

Today no large studies have been conducted to determine if improved control in non-ICU patients may result in reduced morbidity and mortality in general medicine and surgery patients. A recent randomized controlled trial and a meta-analysis have shown that improved glucose control may reduce hospital complications in general surgery patients ([37]). Improving glucose control with a basal bolus regimen resulted in significantly reduction in the frequency of composite complications including postoperative wound infection, pneumonia, bacteremia, and acute renal and respiratory failure ([61]).

HYPOGLYCEMIA

Hypoglycemia is the commonest side effect of treatment of all types of diabetes in the hospital setting. It presents a major barrier to satisfactory long-term glycemic control. Hypoglycemia results from an imbalance between glucose supply, glucose utilization and current insulin levels. Hypoglycemia is defined as a lower than normal level of blood glucose. For the purposes of hospital inpatients, hypoglycemia is defined as any glucose level <3.9 mmol/l (70 mg/dl). ([62,63]) Severe hypoglycemia has been defined by many as <2.2 mmol/l (40 mg/dl) ([63]). The incidence of severe hypoglycemia among the different trials ranged between 5% and 28% depending on the intensity of glycemic control in the ICU ([64]) while rates from trials using subcutaneous insulin in non-critically ill patients range from less than 1% to 33% ([65,66]). In 2012, the UK National Diabetes Inpatient Audit (NaDIA) data showed 22.4 % of patients with diabetes experienced one or more hypoglycemic episodes with a blood glucose less than 4.0 mmol/l (72mg/dl), with 10.5% experiencing one or more hypoglycemic episodes less than 3.0mmol/L (54mg/dl)(13). The NaDIA data from 2012 showed that patients with type 1 diabetes had the highest prevalence with 40.4% experiencing a hypoglycemic episode between 3-4 mmol/l and 28.8% experiencing a hypoglycemic episode <3mmol/L. The same data showed that the highest proportion of episodes took place overnight (34.3%) between 9pm and 9am when snack availability was likely to have been lowest([67]).

Further, recent data published from NaDia using data from 41 Trusts showed 12 serious adverse events including three deaths; two cases of permanent cerebral damage; two successfully resuscitated cardiac arrests; three seizures; and two undefined events. Insulin therapy was implicated in 10 events([68]). The key predictors of hypoglycemic events in hospitalized patients include older age, greater illness severity, diabetes, and the use of oral glucose lowering medications and insulin ([69,70]). In-hospital processes of care that contribute to risk for hypoglycemia include unexpected changes in nutritional intake that are not accompanied by associated changes in the glycemic management regimen (e.g., cessation of nutrition for procedures, adjustment in the amount of nutritional support), interruption of the established routine for glucose monitoring, deviations from the established glucose control protocols, and failure to adjust therapy when glucose is trending down or steroid therapy is being tapered ([71,72]). A common cause of inpatient hypoglycemia is insulin prescription errors including

misreading poorly written prescriptions – when 'U' is used for units (i.e. 4U becoming 40 units) or confusing the insulin name with the dose (e.g. Humalog Mix25 becoming Humalog 25 units). Table 3 describes the most common risk factors for developing hypoglycemia in hospital[73]. However, other factors may also be involved, such as concurrent use of drugs with hypoglycemic agents e.g. warfarin, quinine, salicylates, fibrates, sulphonamides (including cotrimoxazole), monoamine oxidase inhibitors, NSAIDs, probenecid, somatostatin analogues, SSRIs. Secondary causes of inpatient hypoglycemia include loss of counter-regulatory hormone function, e.g. Addison's disease, growth hormone deficiency, hypothyroidism, hypopituitarism.

Table 3. Common risk factors for developing hypoglycemia in the hospital.

Prior episode of hypoglycemia
Older age
Chronic kidney disease
Congestive heart failure
Malnutrition
Erratic eating patterns/Nutritional interruptions
Malignancies
Insulin regimen
Type 1 diabetes
Mental status changes
Certain concomitants use of medications
Duration of diabetes

The development of hypoglycemia is associated with poor hospital outcome ([53,58,74-80]). Turchin et al examined data from 4368 admission episodes for people with diabetes of which one third were on regular insulin therapy ([81]). Patients experiencing inpatient hypoglycemia experienced a 66% increased risk of death within one year and spent 2.8 days longer in hospital compared to those not experiencing hypoglycemia. The odds ratio (95% confidence interval) for mortality associated with one or more episodes was 2.28 (1.41-3.70, p=0.0008) among a cohort of 5,365 patients admitted to a mixed medical-surgical ICU ([69]). In a larger cohort of over 60,000 patients, hypoglycemia was associated with longer ICU stay and greater hospital mortality especially for patients with more than one episode of hypoglycemia.

Hypoglycemia has been associated with adverse cardiovascular outcomes, such as prolonged QT interval, ischemic electrocardiogram changes, angina, arrhythmias, sudden death, and increased inflammation ([82,83]). The mechanisms for the poor outcome are not completely understood, but hypoglycemia has been associated with increases in proinflammatory cytokines (TNFα, IL-1β, IL-6, and IL-8), markers of lipid peroxidation, and oxidative stress ([84,85]). In addition, acute hypoglycemia creates a prothrombotic environment, with increased levels of vasoconstrictors, endothelial dysfunction and vasoconstriction ([84,86]).

Despite these observations, the direct causal effect of iatrogenic hypoglycemia on outcomes is still debatable. Kosiborod et al ([77]) reported that spontaneous hypoglycemia, but not insulin-induced hypoglycemia was associated with higher in hospital mortality. Similarly, a recent study among 31,970 patients also reported that hypoglycemia is associated with increased in-hospital mortality, but the risk was limited to patients with spontaneous hypoglycemia and not to patients with drug-associated hypoglycemia([87]). These studies raised the possibility that hypoglycemia, similar to hyperglycemia, is a marker of disease burden rather than a direct cause of death.

RECOMMENDATIONS FOR MANAGING HYPERGLYCEMIA IN THE HOSPITAL ENVIRONMENT

Management of inpatient hyperglycemia in the ICU

Insulin is the best way to control hyperglycemia in the inpatient setting specially in the critically ill patient. Intravenously administered insulin is the preferred method to achieve the recommended glycemic target. The short half-life of intravenous insulin makes it ideal in this setting because of flexibility in the event of unpredicted changes in patient's health, medications and nutrition. When a patient is identified as having hyperglycemia (blood glucose equal or more than 10 mmol/l (180 mg/dl) intravenous insulin infusion should be started to maintain blood glucose levels below 10 mmol/l (180 mg/dl). A variety of intravenous infusion protocols have been shown to be effective in achieving glycemic control with a low rate of hypoglycemic events, and in improving hospital outcomes ([20,36,39,88-91]). A proper protocol should allow flexible blood glucose targets, modified based on the patient's clinical situation. Further, it should have clear instructions about the blood glucose threshold for initiating insulin infusion and the initial rate. It should be validated in order to avoid hyperglycemia if adjusted too slowly and hypoglycemia if adjusted too fast. Accurate insulin administration requires a reliable infusion pump that can deliver the insulin dose in increments of 0.1 unit per hr ([92]).

There is no ideal protocol for the management of hyperglycemia in the critical patient. In addition, there is no clear evidence demonstrating the benefit of one protocol/algorithm versus the other. The protocol should be based on the institution- ICU resources such as trained nursing personnel. The implementation of any of these algorithms requires close follow up by the nursing staff and is prone to human errors. Some institutions have developed computerized

protocols that can be implemented in order to avoid errors in dosing. Essential elements that increase protocol success in continuous insulin infusion are: 1) rate adjustment considers the current and previous glucose value and the current rate of insulin infusion, 2) rate adjustment considers the rate of change (or lack of change) from the previous reading, and 3) frequent glucose monitoring (hourly until stable glycemia is established, and then every 2-3 hours) ([64,91,93]).

Several computer-based algorithms aiming to direct the nursing staff adjusting the insulin infusion rate have become commercially available ([94,95]). Controlled trials have reported more rapid and tighter glycemic control with computer-guided algorithms than standard paper form protocols in ICU patients ([96]),as well as lower glycemic variability than patients treated with the standard insulin infusion regimens. Despite differences in glycemic control between insulin algorithms, a recent study showed no difference between computerized protocols versus conventional glucose control[97]. Thus, most insulin algorithms appear to be appropriate alternatives for the management of hyperglycemia in critically ill patients, and the choice depends upon physician's preferences and cost considerations ([91,98,99]).

Managing Hyperglycemia in the non- ICU setting

Subcutaneous insulin is the preferred therapeutic agent for glucose control in general medicine and surgery patients admitted to non-ICU areas. Several studies have shown that the commonly used subcutaneous sliding scale insulin (SSI) is not acceptable as the single regimen in patients with diabetes, as it results in undesirable levels of hypoglycemia and hyperglycemia ([100,101]). It has become evident in recent years that the use of scheduled subcutaneous insulin therapy with basal (glargine or determir) once daily or with intermediate acting insulin (NPH) given twice daily alone or in combination with short (regular) or rapid acting insulin (lispro, aspart, glulisine) prior to meals is effective and safe for the management of most patients with hyperglycemia and diabetes ([102,103]).

The basal bolus (prandial) insulin regimen is considered the physiologic approach as it addresses the three components of insulin requirement: basal (what is required in the fasting state), nutritional (what is required for peripheral glucose disposal following a meal), and supplemental (what is required for unexpected glucose elevations, or to dispose of glucose in hyperglycemia)([103]).

A prospective, randomized multi-center trial compared the efficacy and safety of a basal/bolus insulin regimen with basal bolus regimen and SSI in patients with type 2 diabetes admitted to a general medicine service ([65]). The use of basal-bolus insulin had greater improvement in blood glucose control than sliding scale alone. A blood glucose target 7.8 mmol/l (< 140 mg/dl) was achieved in 66% of patients in the glargine plus glulisine group and 38% in the sliding scale group. The incidence of hypoglycemia, defined as a BG <3.3 mmol/l (<60 mg/dl), was less than 5% in patients treated with basal bolus or SSI. A different study in general surgery patients also compared efficacy and safety of a basal bolus regimen to SSI in patients with type 2 diabetes ([66]). The basal bolus regimen resulted in significant improvement in glucose control and in a reduction in the frequency of the composite of postoperative complications including wound infection, pneumonia, respiratory failure, acute renal failure and bacteremia.

The use of multi-dose human NPH and regular insulin has been compared to basal bolus treatment with insulin analogs in an open-label, controlled, multicenter trial in 130 medical patients with type 2 diabetes ([104]). This study found that both treatment regimens resulted in significant improvements in inpatient glycemic control with a glucose target of less than 140 mg/dl before meals, as well as no difference in the rate of hypoglycemic events. Thus, it appears that similar improvement in glycemic control can be achieved with either basal bolus therapy with insulin analogs or with NPH/regular human insulin in patients with type 2 diabetes.

Most patients in the hospital have reduced caloric intake due to lack of appetite, medical procedures or surgical intervention. In such patients, the recent Basal Plus trial ([105]) randomized patients with type 2 diabetes who were treated with diet, oral antidiabetic agents, or low-dose insulin (≤ 0.4 unit/kg/day) prior to admission to receive a standard basal bolus regimen with glargine once daily and glulisine before meals and a single daily dose of glargine and supplemental doses of glulisine for correction of hyperglycemia (>140 mg/dl) per sliding scale (Basal Plus trial). This study reported that the basal approach resulted in similar improvement in glycemic control and in the frequency of hypoglycemia compared to a standard basal bolus regimen. Thus, in insulin naive patients or in those receiving low-dose insulin on admission (less than 0.4 units/kg/day), as well as patients with reduced oral intake, the use of a basal plus regimen is an effective alternative to basal bolus.
The recommended total daily insulin dose for most patients should start between 0.3 to 0.5 units per Kg ([65,72,106,107]). Starting doses greater than 0.6-0.8 unit/kg/day have been associated with a 3-fold higher odds of hypoglycemia than doses lower than 0.2 U/kg/day. In elderly patients in subjects with impaired renal function, lower initial daily doses (≤ 0.3 units/kg) may lower the risk of hypoglycemia ([24,108]).

GLUCOSE MONITORING IN HOSPITAL

All patients admitted to the hospital with a diagnosis of diabetes and those with newly discovered hyperglycemia should be monitored closely. The frequency of monitoring and the schedule of the blood glucose checks will be dependent on the nutritional intake, patient treatment and schedule of insulin. There is some controversy regarding the best method to monitor blood glucose. However, considering the convenience and wide availability of the capillary point of care (POC) testing we suggest this as the best approach as long as it is done with a monitoring device that has demonstrated accuracy. When using POC blood glucose levels keep in mind clinical conditions that might affect the POC value such as hemoglobin level, perfusion, and medications. Below, we present Table 4 summarizing potential schedules for blood glucose monitoring based on patient nutritional intake and medical regimen.

Table 4. Glucose monitoring schedule based on nutritional intake, insulin regimen and special patient situation.

Diet	**Regimen**	**Glucose monitoring schedule**	**Special caveats.**
NPO	Intravenous insulin infusion	Every 1-2 Hrs.	
NPO	SC regular insulin every 6 hrs (6 am, noon, 6pm, midnight)	Every 6 hrs (6 am, noon, 6pm, midnight) prior to SC insulin dose	
NPO	Basal insulin alone (Glargine or Levemir)	Every 6 hr (6 am, noon, 6pm, midnight)	
Eating 3 meals per day	Basal/bolus regimen with long acting (Glargine, Levemir) and rapid-acting insulin with meals (aspart, lispro, glulisine)	4 times per day: before breakfast, before lunch, before dinner, and bedtime.	Consider a 3 am blood glucose check in patients at risk for hypoglycemia
Nocturnal tube feeds and daytime oral intake	Regimen varies depending on clinical status. Basal insulin plus corrections or basal	5 times per day: before breakfast, before lunch, before dinner, bedtime and 3 am.	

	bolus with long and rapid-acting insulin. Basal in AM and low-dose NPH insulin at the start of the nocturnal tube feeds.		
Continued tube feeds	Basal insulin plus correction with regular insulin every 4-6 hours. NPH 2 or 3 times daily or regular insulin every 6 hrs.	Every 6 hrs (6 am, noon, 6pm, midnight)	
Patients eating small multiple meals per day. (e.g. cystic fibrosis)	Basal/bolus with long acting insulin and rapid-acting insulin with meals. (carbohydrate counting)	At least 4 times per day: before breakfast, before lunch, before dinner, and bedtime	More frequent checks might be warranted in order to include post-prandial blood glucose.
Patient on high-dose corticosteroids	Basal/bolus with long acting insulin and rapid-acting insulin with meals. May add small dose of NPH to basal bolus regimen in patients on morning dose of steroids.	4 times per day: before breakfast, before lunch, before dinner, and bedtime	
NPO or eating 3 meals per day	Patients on insulin pumps	4 -8 times per day: before breakfast, lunch, dinner, and bedtime. Consider postprandial checks.	

MEDICAL NUTRITION THERAPY (MNT) IN HOSPITALIZED PATIENTS WITH DIABETES.
Medical nutrition therapy is a key component of the comprehensive management of diabetes and hyperglycemia in the inpatient setting. Maintaining adequate nutrition is important for glycemic control and to meet adequate caloric demands. Caloric demand in acute illness will differ from that in the outpatient setting. Achieving the proper nutritional balance in the inpatient setting is challenging. All patients admitted to the hospital with diabetes or hyperglycemia should be assessed to determine the need for a modified diet in order to achieve caloric demands.

The general approach to address MNT in the inpatient setting is usually based on expert opinions and patient need. There is limited data regarding what is the best approach or method to achieve the ideal caloric supply. To determine the best approach, method, and caloric need of their patients, providers should work closely with the nutrition professional.
All patients with diabetes or hyperglycemia should receive an individualized assessment. In general, most patient will receive adequate caloric needs with 3 discrete meals per day. Further, the metabolic need for patients with diabetes is usually provided by 25 to 35 calories/kg where some critically ill patients might require less 15 to 25 calories/kg per day([109]). A consistent carbohydrate meal-planning system might help to facilitate glycemic control and insulin dosing in the inpatient setting. Most patients will require at 1,500-2000 calories per day with 12-15 grams of carbohydrates per meal([12]). Ideally, the carbohydrates should come from low glycemic index foods such as whole grains and vegetables.
Patients not able to achieve these goals should be evaluated in order to determine the need for enteral or parenteral nutrition. Enteral nutrition is the second best option after oral nutrition and should be preferred over parenteral nutrition in hospitalized patients ([110,111]). There are several advantages of enteral feeding versus parenteral feeding including: low cost, low risk of complications, physiologic route and less risk for gastric mucosa atrophy and lower risk of infectious and thrombotic complications compared with the latter form of therapy ([112,113]). The benefit of parental nutrition has been documented in the critically ill patient. However, some research has shown a detrimental effect on patients with diabetes and hyperglycemia. Parental nutrition should be considered only in patients that are not able to receive enteral nutrition and should be coordinated with the institution parenteral nutrition team.

Enteral and parenteral nutrition can prevent the effects of starvation and malnutrition ([110,111]). The preference for use of enteral over parenteral nutrition whenever possible is due to a lower risk of infectious and thrombotic complications ([112,113]). Standard enteral formulas reflect the reference values for macro- and micronutrients for a healthy population and contain 1-2 cal/ml. Most standard formulas contain whole protein, lipid in the form of long-chain triglycerides, and carbohydrates. Standard diabetes-specific formulas provide low amounts of lipids (30% of total calories) combined with a high carbohydrates (HCH) content (55–60% of total calories); however, newer diabetic formulas have replaced part of carbohydrates with monounsaturated fatty acids (up to 35% of total calories) and also include 10-15 g/l dietary fiber and up to 30% fructose ([114,115]).
Diabetic enteral formulas containing low-carbohydrate high–monounsaturated fatty acid (LCHM) are preferable to standard high-carbohydrate formulas in hospitalized patients with type 1 and type 2 diabetes.([114,116]) In a meta-analysis of studies comparing newer enteral LCHM formulas with standard formulations, the postprandial rise in blood glucose was reduced by 18-29 mg/dl with the newer formulations([116]). Table 5 depicts the composition of standard and diabetic specific enteral formulas commonly used in hospitalized patients.

Table 5. Composition of standard and diabetic specific enteral formulas commonly used in hospitalized patients.

	Calories (kcal/mL)	Carbohydrate (g/L)	Fat (g/L)	Protein (g/L)	Manufacture
Standard formula					
Jevity® 1.0 Cal	1.0	155	35	44	Abbott Nutrition
Nutren® 1.0	1.0	127	38	40	Nestle Nutrition
Osmolite® 1.2 Cal	1.2	158	39	55	Abbott Nutrition
Jevity® 1.2	1.2	169	39	56	Nestle Nutrition
Fibersource® HN	1.2	160	39	53	Nestle Nutrition
Isosource® 1.5 Cal	1.5	170	65	68	Nestle Nutrition
Jevity® 1.5	1.5	216	50	64	Nestle Nutrition
Diabetes specific formula					
Glucerna ® 1.0 Cal	1.0	96	54	42	Abbott Nutrition
Nutren® Glytrol®	1.0	100	48	45	Nestle Nutrition
Glucerna ® 1.2 Cal	1.2	115	60	60	Abbott Nutrition
Diabetisource® AC	1.2	100	59	60	Nestle Nutrition
Glucerna ® 1.5 Cal	1.5	133	75	82	Abbott Nutrition

CORTICOSTEROID THERAPY – IMPACT ON BLOOD GLUCOSE

Steroids may be administered by various regimes and at variable doses. A single daily dose of steroid (e.g. prednisolone/prednisone) in the morning may be the commonest mode of administration. In susceptible patients, this will often result in a rise in blood glucose by late morning that continues through to the evening. Overnight the blood glucose generally often falls back to baseline levels by the next morning. Thus treatment should be tailored to treating the hyperglycemia, whilst avoiding nocturnal and early morning hypoglycemia. Multiple daily doses of steroid, be it intravenous hydrocortisone or oral dexamethasone, can cause a hyperglycemic effect throughout the 24-hour period. It may be, however, that a twice daily premixed or basal bolus regimen may need to be started if oral medication, or once daily insulin proves insufficient to control hyperglycemia. Close attention will therefore need to be paid to blood glucose monitoring and early intervention may be necessary.

levels in most individuals can be predicted to rise approximately 4 to 8 hours following the administration of oral steroids, and sooner following the administration of intravenous steroids. Again, capillary blood glucose monitoring is paramount to guide appropriate therapeutic interventions. Conversely, glucose levels may improve to pre-steroid levels 24 hours after intravenous steroids are discontinued. If oral steroids are weaned down over several weeks, the glucose levels may decline in a dose dependent fashion, but this may not occur, particularly in those with pre-existing undiagnosed diabetes.

At the commencement of steroid therapy, or for those already on a supraphysiological dose of corticosteroid, capillary blood glucose testing should occur before meals and at bedtime, in particular before lunch or evening meal, when the hyperglycemic effects of a morning dose of steroid is likely to be greatest.

t is likely that subcutaneous insulin using a basal, or multiple daily injection regimen will be the most appropriate choice to achieve glycemic control in the event of hyperglycemia for the majority of patients. Morning administration of basal human insulin may closely fit the glucose excursion induced by a single morning dose of oral steroid. Basal analogue insulin may be appropriate if hyperglycemia is present for more prolonged periods. However, care should be taken to identify and protect against hypoglycemia overnight and in the early morning if long acting insulin analogues are used in this context. Subsequent titration of the insulin dose may be required to allow maintenance of glucose control in the face of increasing or decreasing steroid dose.

When a patient is discharged from the hospital on steroid therapy, a clear strategy for the management of hyperglycemia or potential hyperglycemia, and the titration of therapy to address the hyperglycemia, should be communicated to the community diabetes team and primary care team. Patients commenced on steroids as an inpatient and discharged after a short stay with the intention of continuing high dose steroids, should receive standard education in regard to diabetes, encompassing the risks associated with hyperglycemia and hypoglycemia.

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