Updates on the Management of Hyperglycemia in Hospitalized Adult Patients

Laleh Razavi Nematollahi * and Caitlin Omoregie

Abstract: The prevalence of diabetes is rising globally; currently, 537 million people worldwide and 37.3 million people in the US are affected. Patients with diabetes have a four-times-greater risk of hospitalization with longer hospital stays and a greater chance of readmission compared to patients without diabetes. Spending on diabetes care as a proportion of global GDP is also projected to increase from 1.8% in 2015 to 2.2% in 2030. The largest component of this medical expenditure is inpatient care in hospitalized patients, accounting for USD 69.7 billion of the total medical cost. Hospitalized patients can develop hyperglycemia without a history of pre-existing diabetes. It has been shown that hyperglycemia in patients without a history of diabetes is also associated with poor hospital outcome. In this review, we discuss the adverse effects of hyperglycemia and hypoglycemia on hospital outcomes; we review recent glycemic targets, recent guidelines’ recommendations, and landmark trials with a brief review on discharge planning, updates on hyperglycemic emergencies, and the use of newer technologies in hospitalized patients such as continuous glucose monitoring devices.

Keywords: inpatient hyperglycemia; stress hyperglycemia; inpatient glycemic targets

1. Introduction

The prevalence of diabetes is rising globally, currently affecting 537 million people worldwide and 37.3 million people in the US [1,2]. Patients with diabetes have a four-times-greater risk of hospitalization with longer hospital stays and a greater chance of readmission compared to patients without diabetes [3]. People with diabetes have a 35% greater chance for elective surgeries [4]. Spending on diabetes care as a proportion of global GDP is also projected to increase from 1.8% in 2015 to 2.2% in 2030 [5]. The total estimated cost of treating people with diabetes and hyperglycemia in the United States in 2017 was USD 414 billion or 24% of all health care spending. The largest component of this medical expenditure was hospital inpatient care, accounting for USD 69.7 billion of the total medical cost [6].

In the fasting state, blood glucose is maintained at 70–100 mg/dL (3.9–5.5 mmol/L) and finely regulated by hepatic glucose production and glucose utilization. The stress of acute illness and surgery in hospitalized patients increases the production of counter regulatory hormones (including cortisol, glucagon, and growth hormone) and proinflammatory cytokines (such as TNF-α, IL-6, and IL-1β), which can lead to increased hepatic gluconeogenesis, muscle catabolism, and lipolysis. These changes can induce acute hyperglycemia in hospitalized patients with and without a history of diabetes [7]. Hyperglycemia (blood glucose > 140 mg/dL or 7.8 mmol/L) in hospitalized patients without a history of diabetes is defined as stress hyperglycemia [8], and is reported in 32.2% of critically ill patients in intensive care units (ICUs) and 30% of noncritically ill hospitalized patients [9,10]. It has been frequently reported in up to 60% of hospitalized patients after cardiac surgery [11]. Additionally, 30–60% of hospitalized patients with stress hyperglycemia (without a history of pre-existing diabetes) have been diagnosed with impaired glucose tolerance or prediabetes and up to 60% of these patients will develop diabetes in a year after the hospital...
admission [12,13]. Stress hyperglycemia in patients without diabetes can be seen on the first postoperative day and may persist for 9–21 days following the surgery, and patients may need to be discharged on new hyperglycemic treatments with further adjustments by outpatient healthcare providers [14,15]. To differentiate undiagnosed diabetes vs. stress-induced hyperglycemia in hospitalized patients, the Endocrine Society guidelines recommend a measurement of HbA1c on admission. The presence of fasting blood glucose > 140 mg/dL (7.8 mmol/L) and HbA1c > 6.5% confirms the diagnosis of pre-existing diabetes [8,16]. Several studies have shown that hyperglycemia with or without diabetes has been associated with increased mortality and morbidity in hospitalized patients [8–10,16]. Therefore, insulin therapy is recommended for the management of hyperglycemia in hospitalized patients [8,14,15]. However, further studies revealed that tight glucose control can be associated with an increased risk of insulin-induced hypoglycemia and increased mortality in hospitalized patients [17–19]. Accordingly, glycemic targets have been revised by professional organizations to avoid tight or intensive glycemic control in hospitalized patients [8,19].

In this review, we discuss the adverse outcomes of hyperglycemia and hypoglycemia in hospitalized patients and review the evidence supporting various glycemic targets and hyperglycemic treatments in critically ill patients in ICUs and noncritically ill patients in general medicine and surgical wards.

2. Hyperglycemia and Hospitalization Outcomes

Hyperglycemia alters immune response by inhibiting chemotaxis and phagocytosis. It affects the bactericidal ability of immune cells by decreasing the production of superoxide radicals [17]. Hyperglycemia also induces osmotic diuresis, endothelial injury, and mitochondrial dysfunction, which can lead to shock and multiple organ failure in hospitalized patients [18]. It has been shown that hyperglycemia in hospitalized patients is associated with an increased risk of complications, mortality, a higher rate of admission to ICUs, and a higher need to transition to rehabilitation facilities after discharge [19,20]. It has been reported that the risk of postoperative infections in general surgery patients increases by 30% for every 40 mg/dL (2.2 mmol/L) rise in blood glucose over normoglycemia (blood glucose of 110 mg/dL or 6.1 mmol/L) [21]. In a case–control study of 2236 surgical patients, patients with glucose levels of 110 to 200 mg/dL (6.1–11.1 mmol/L) and glucose levels above 200 mg/dL (>11.1 mmol/L) had a 1.7- and 2.1-fold increase in mortality (respectively) compared to patients with blood glucose less than 110 mg/dL (<6.1 mmol/L) [22]. In a prospective study of 2471 patients with community-acquired pneumonia, patients with admission blood glucose above 198 mg/dL (11 mmol/L) had a greater mortality and complications compared to patients with blood glucose less than 198 mg/dL (<11 mmol/L) (13% vs. 9%, p = 0.03) [23]. In this study, the risk of complications in these patients increased by 3% for each 18 mg/dL (1 mmol/L) rise in admission blood glucose above 110 mg/dL (6.1 mmol/L) [23]. Many other studies have also suggested that the early intervention and treatment of inpatient hyperglycemia can reduce the risks of hospital-acquired infections and decrease the length of hospital stay and mortality [24,25].

A recent meta-analysis on 5053 surgical patients showed tight blood glucose control (<110–120 mg/dL or 6.1–6.7 mmol/L) as compared to conventional blood glucose control (<200 mg/dL or <11.1 mmol/L) was associated with a lower risk of postoperative infections (9.4% vs. 15.8%, p < 0.001), lower wound infection rates (4.6% vs. 7.2%, p = 0.015), and higher post-operation hypoglycemia rates (22.3% vs. 11%, p < 0.001). However, the short-term mortality was not significantly different in both groups. Therefore, it was suggested that the higher risk of hypoglycemic events in tight blood glucose control group had contributed to the mortality rate in this group [26]. In another study in patients in the ICU, patients with blood glucose levels more than 200 mg/dL (>11.1 mmol/L) were found to have higher mortality comparing to patients with blood glucose levels less than 200 mg/dL (<11.1 mmol/L) (5.0% vs. 1.8%, p < 0.001) [27].
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More recent studies during the COVID-19 pandemic also showed that hyperglycemia was commonly seen in hospitalized patients with COVID-19 in ICUs (65.5% of patients), which reflected the severity of the condition and was also related to the treatment with steroids and was associated with poorer outcomes (HR 3.535, 95% confidence interval [CI] 1.338–9.338) \[28,29\].

3. Hypoglycemia and Hospitalization Outcomes

Hypoglycemia in hospitalized patients is categorized in three levels by the American Diabetes Association (ADA) Standards of Care. Level 1 is defined as blood glucose between 54 mg/dL (3 mmol/L) and 70 mg/dL (3.9 mmol/L); level 2 is a blood glucose < 54 mg/dL (<3 mmol/L), which is the threshold for neuroglycopenic symptoms; and level 3 is any blood glucose level with altered mental and/or physical status that requires assistance from others for recovery \[30\].

It has been shown that hypoglycemia is associated with increased levels of proinflammatory cytokines (TNF-\(\alpha\), IL-1\(\beta\), IL-6, and IL-8), markers of lipid peroxidation, and oxidative stress and these changes can contribute to adverse cardiovascular events associated with hypoglycemia \[31\]. It has been reported that hypoglycemia in hospitalized patients is associated with poor cardiovascular outcomes including prolonged QT interval, angina, ischemic changes, arrhythmia, and sudden death \[32,33\].

The incidence of severe hypoglycemia (blood glucose < 40 mg/dL or 2.2 mol/L) in ICU patients has been reported in 28% of patients, and in non-ICU settings, as high as 33% of patients \[34\]. The risk of hypoglycemic events increases in hospitalized patients with older age, the use of oral hypoglycemic medications, the presence of severe illness, and unexpected changes in nutritional intake and steroid tapering \[35\].

In a cohort of 5365 patients in a medical–surgical ICU, the odds ratio for mortality associated with one or more episode of hypoglycemia was 2.28 (1.41–3.7, \(p = 0.0008\) \[36\]. A 2019 systemic review suggested that hospitalized patients on general medical–surgical wards with an episode of blood glucose less than 72 mg/dL (4 mmol/L) had higher in-hospital mortality than patients without hypoglycemia (95% confidence interval [CI]: 1.64–2.67) \[37\].

4. Glycemic Targets and Management of Hyperglycemia in Critically Ill Patients in Intensive Care Units (ICUs)

4.1. Glycemic Targets in ICU Settings

Based on compelling evidence, it has been shown that glycemic excursions including hyperglycemia and severe hypoglycemia are associated with increased adverse outcomes in hospitalized patients. Therefore, many clinical investigators have tried to define optimal glucose targets for glycemic control in hospitalized patients. Here, we review landmark trials in patients in ICUs that resulted in changes in clinical practice and revisions of professional societies’ recommendations for glycemic targets in hospitalized patients.

The Leuven Surgical ICU study was the pioneer of trials that promoted intensive glucose control in ICU settings. In this study, 1548 patients in surgical ICUs were randomized to conventional blood glucose control with a target of 180–200 mg/dL (10–11.1 mmol/L) or the intensive therapy group with a target of 80–110 mg/dL (4.4–6.1 mmol/L). A total of 63% of these patients were cardiac surgery patients and 13% had pre-existing diabetes, and almost all patients received early parenteral nutrition after surgery. The patients in the intensive glycemic targets group compared to patients with the conventional blood glucose targets had significantly less bacteremia, lower ventilator dependency, and shorter ICU stays, and had an overall 34% reduction in mortality \[38\]. However, subsequent studies did not confirm these findings and the majority of them reported that lower glucose targets were associated with more hypoglycemic events and even increased mortality in patients in ICUs \[39,40\].

In the Glucontrol trial, a seven-country randomized clinical trial (RCT), 1101 medical and surgical patients in ICU were randomized to tight glycemic targets of 80–110 mg/dL
(4.4–6.1 mmol/L) vs. conventional glycemic control of 140–180 mg/dL (7.8–10 mmol/L). No statistically significant difference in mortality was detected in either group (15.3% vs. 17.2%). However, the risk of hypoglycemia was increased in the intensive tight glycemic group (8.7% vs. 2.7% \( p < 0.0001 \)) [39]. In the Efficacy of Volume Substitution and Insulin Therapy in Sepsis (VISEP) trial from Germany, 600 patients with sepsis in ICUs were randomized to conventional glucose control of 180–200 mg/dL (10–11.5 mmol/L) vs. intensive glucose control with a target of 80–110 mg/dL (4–6.1 mmol/L). This trial was stopped early as no significant difference between 28- and 90-day mortality rates was detected in either group (21.6% vs. 21.9% and 29.5% vs. 32.8%, respectively); however, those in the intensive group had a significantly higher rate of hypoglycemic events (12.1% vs. 2.1%) [41].

In the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial, 6104 patients in ICU were randomized to the conventional glycemic control with a target of blood glucose < 180 mg/dL (10 mmol/L) or intensive glucose control with a target of 81–108 mg/dL (4.4–5.7 mmol/L) [42]. Data from the NICE-SUGAR trial reported that hospital mortality was not significantly different in both groups but the mortality rate at 90 days was significantly higher in the intensive group (24.9% vs. 27.5% \( p = 0.02 \)), with a higher incidence of hypoglycemia events (0.5% vs. 6.8%) in the intensive group [42]. A subsequent analysis of data by the NICE-SUGAR investigators also reported that patients with hypoglycemia had a two-fold increase in mortality compared to patients without hypoglycemic events [43].

Additionally, many studies have documented the significant negative impact of hypoglycemia in the hospital outcomes of cardiac surgery patients. A retrospective study of 409 cardiac surgery patients showed that every 20 points above a blood glucose of 100 mg/dL (5.6 mmol/L) is associated with a 30% increase in adverse outcomes, including pulmonary and renal complications and mortality [44]. A meta-analysis of five randomized clinical trials (RCTs) in 706 cardiac surgery patients showed that intensive glycemic control was associated with a decreased rate of infections (risk ratio = 0.50; 95% confidence Interval [CI] = 0.29–0.84; \( p = 0.009 \) but was not associated with a decreased mortality (95% confidence interval [CI] = −0.01 to 0.03; \( p = 0.25 \)) [45].

In the GLUCO-CABG trial, 302 post-CABG patients with stress hyperglycemia with diabetes and without diabetes were assigned to computerized intensive blood glucose control with a target of 100–140 mg/dL (5.6–7.8 mmol/L) and conservative blood glucose control with a target of 141–180 mg/dL (7.8–10 mmol/L) [46]. In this trial, the intensive group had a 20% reduction (nonsignificant) in perioperative complications (42% vs. 52%; \( p = 0.08 \)) [46]. In addition, no significant difference in the rate of complications and mortality among patients with diabetes in both groups was detected (49.3% vs. 45.8%; \( p = 0.65 \)) [46]. However, in patients with stress hyperglycemia and without pre-existing diabetes, the rate of complications (including sternal wound infections, bacteremia, respiratory failure, pneumonia, acute kidney injury, stroke, cardiac arrhythmia, and heart failure) was significantly lower in the intensive group than in the conservative glucose control group (35% vs. 58%; \( p = 0.006 \)) [46]. Hospitalization costs were also significantly lower in patients with stress hyperglycemia in the intensive group compared to the conservative glucose control group (USD 36.681 vs. USD 40,913; \( p = 0.04 \)). The rate of mild hypoglycemia was significantly higher in the intensive group (9% vs. 3%; \( p = 0.09 \)); however, it was still lower than the reported hypoglycemic events in patients in the ICU. The lower rate of mild hypoglycemia events in this study was attributed to the use of computerized insulin infusion protocols. In this trial, no severe hypoglycemia less than 40 mg/dL (2.2 mmol/L) was reported in patients in the intensive and conventional glycemic groups [46]. These findings suggest that in selected patients in ICUs, such as cardiac surgery patients, lower glycemic targets in experienced centers while avoiding severe hypoglycemia may be beneficial.

Based on a large number of observational studies and randomized trials including the above-mentioned studies, many professional societies including ADA (the American Diabetes Association), AACE (the American Association of Clinical Endocrinologists), and the Endocrine Society recommend glycemic targets of 140 to 180 mg/dL (7.8–10 mmol/L) for the
majority of patients in ICUs and a lower glucose target of 110–140 mg/dL (6.1–7.8 mmol/L) for selected patients in ICUs (including post-cardiac-surgery patients in medical centers with expertise) [8,19,30]. Glucose levels above 180 mg/dL (10 mmol/L) and lower than 110 mg/dL (6.1 mmol/L) are not recommended in ICU patients [19,30]. Additionally, the Society of Critical Care Medicine recommends blood glucose targets of lower than 180 mg/dL (10 mmol/L) in patients in ICUs and recommends initiation of treatment when glucose is above 150 mg/dL (8.3 mmol/L) [47].

4.2. Treatment of Hyperglycemia in the ICU Settings

Intravenous (IV) insulin infusion is the preferred method for achieving blood glucose targets in ICU patients as it offers flexibility in the care of critically ill patients in ICUs with their need for treatment adjustments in response to frequent changes in their blood glucose and nutritional intake [48]. There is no ideal protocol or clear evidence that supports the benefit of one protocol over any others [49].

A proper insulin infusion protocol offers the ability to adjust the infusion rate based on the current and previous glucose values and the rate of glucose changes and the ability to closely monitor blood glucose changes with hourly glucose measurements and adjustments [50]. In some institutions, software-based or computerized algorithms have been used for IV insulin infusion protocols. Proportional–integral–derivative (PID) models are mostly used in software-based protocols. In these models, previous glucose levels are used to titrate the insulin infusion rate by using a dynamic multiplier responsive to insulin sensitivity and changes in glucose levels for a given insulin dose [51]. Recent randomized clinical trials (RCTs) and retrospective cohorts have reported more rapid and tighter glycemic control and lower glycemic variability with computerized algorithms than the standard paper protocol [52,53]. In a recent study, 61 patients in ICUs in a computerized protocol group were compared to 51 patients in ICUs with similar demographics that were assigned to the standard insulin protocol, and it was reported that the computerized group had a greater percentage of glucose measurements that were within the target range compared to the standard insulin protocol group (68.4% vs. 36.5%, p < 0.001) [53]. The computerized group also had a shorter time-to-target [median (interquartile range) 5 h (3–8 h) vs. 7 h (4–10 h); p = 0.02] and lower severe hypoglycemic events (26 vs. 6, p < 0.0001) [53]. However, these findings were not confirmed by other studies, including a multicenter study which evaluated a computerized insulin protocol and standard insulin infusion protocol in 1300 patients in 34 French ICUs [54]. This study reported no statistically significant difference between the computerized vs. standard insulin infusion protocols, and reported more hypoglycemic events in the computerized insulin protocol [54].

5. Glycemic Targets and the Management of Hyperglycemia in Noncritically Ill Patients

For noncritically ill medical and surgical patients, ADA and AACE recommend a target of premeal blood glucose lower than 140 mg/dL (7.8 mmol/L) and random blood glucose lower than 180 mg/dL (10 mmol/L) in non-ICU settings [19,30]. Subcutaneous insulin is the treatment of choice for noncritically ill patients. However, the use of sliding-scale insulin alone for hospitalized patients with diabetes is not recommended [19,30]. For hospitalized patients with type 1 diabetes, the use of basal insulin plus short- or rapid-acting insulin for meal coverage is recommended [30]. Many recent studies have reported that the use of subcutaneous basal insulin plus short- or rapid-acting insulin prior to meals (basal/bolus) is the most appropriate and safe treatment for the management of hyperglycemia in hospitalized patients with type 2 diabetes [19,30,55]. In a prospective randomized multicenter trial, the Randomized Study of Basal Bolus Insulin Therapy (RABBIT-2) Medicine, 130 patients with type 2 diabetes were assigned randomly to a basal/bolus insulin regimen vs. sliding-scale alone. This study showed that 66% of patients in the basal/bolus regimen group achieved blood glucose lower than 140 mg/dL (7.8 mmol/L) compared to 38% of patients in the sliding-scale group (p < 0.05) [56]. In the RABBIT-2 trial, the incidence of hypoglycemia
was the same in both groups (<5% of patients) [56]. In another similar study, a randomized
multicenter trial (Randomized Study of Basal Bolus Insulin Therapy (RABBIT-2) Surgery),
212 surgical patients with type 2 diabetes were assigned randomly to the sliding-scale
insulin regimen vs. basal/bolus insulin regimen. In this study, blood glucose lower than
140 mg/dL (7.8 mmol/L) was achieved in 55% of patients in the basal/bolus insulin group
vs. 31% of patients in the sliding-scale group (p < 0.001) [57]. Additionally, the rate of com-
plications such as wound infection, pneumonia, acute kidney injury, and acute respiratory
failure was reduced in the basal/bolus insulin regimen group vs. the sliding-scale group
(8.6% and 24.3%; odds ratio 3.39 (95% confidence interval [CI]: 1.50–7.65); p = 0.003) [57].
However, hypoglycemia with blood glucose lower than 70 mg/dL (3.9 mmol/L) was seen
in 23.1% of patients in the basal/bolus group vs. 4.7% of patients in the sliding-scale insulin
group (p < 0.001) [57]. Due to the higher risk of hypoglycemia in the basal/bolus insulin
group in surgical patients, a subsequent study was performed to evaluate the treatment
protocols of basal insulin plus a lower insulin scale defined as a correction scale (basal plus)
vs. basal/bolus insulin vs. sliding-scale insulin regimens in insulin-naïve hospitalized
patients on only oral agents at home or in patients with very minimal insulin usage at
home (<0.4 units/kg/day) and in patients with poor oral intake in the hospital [58].
In this study, 375 patients with diabetes were randomly assigned to basal plus (basal insulin
plus correction scale) vs. basal/bolus vs. sliding scale. Both basal/bolus and basal plus
groups had less treatment failure than the sliding-scale group (0% vs. 2% vs. 19%, respectively;
p < 0.001) [58]. The incidence of hypoglycemia with blood glucose lower than 70 mg/dL
(3.9 mmol/L) was higher in both the basal/bolus and basal plus groups (16% vs. 8%,
p = 0.48) than in the sliding-scale group (3%) (p < 0.05) [58]. However, the incidence of
severe hypoglycemia with blood glucose lower than 40 mg/dL (2.2 mmol/L) was not
significantly different among the three treatment groups (1% vs. 1% vs. 0%, respectively;
p = 0.76) [58]. Therefore, for surgical patients with poor nutritional intake or at higher risk
of hypoglycemia and patients on low doses of insulin at home, it is recommended to use
the basal insulin plus correction scale with short-acting insulin rather than using meal
boluses or the sliding-scale alone.

The recommended dose of insulin for most people with type 2 diabetes admitted to
the hospital is 0.3–0.5 units/kg/day. However, the starting dose in elderly patients and
patients with impaired renal function should be lower to decrease the risk of hypoglycemia
in these high-risk groups [59].

The use of noninsulin therapies in hospitalized patients with type 2 diabetes is not
recommended [30]. ADA and AACE recommend against using metformin in hospitalized
patients due to the presence of dehydration and acute kidney injury in many patients [19,30].
Sulfonylurea can increase the risk of severe hypoglycemia and is not recommended for in-
patient settings [30]. Glucagon-like peptide-1 (GLP-1) agonists are also not well tolerated in
hospitalized patients due to gastrointestinal side effects including nausea and vomiting [30].
However, recent studies have shown that Dipeptidyl Peptidase IV (DPP-IV) inhibitors
alone or with basal insulin may be a safe and effective choice in noncritically ill patients [30].
However; among DPP-IV inhibitors, saxagliptin and alogliptin are contraindicated in pa-
tients with congestive heart failure [30,60,61]. Sodium Glucose cotransporter-2 (SGLT-2)
inhibitors are not recommended by the FDA for inpatient glycemic control due to the
increased risk of euglycemic diabetic ketoacidosis (e-DKA), and they should be held for
3–4 days prior to any elective surgery [30].

6. Medical Nutrition Therapy in Hospitalized Patients with Diabetes

It has been recommended that all surgical patients, patients with diabetes, and hospi-
talized patients with stress hyperglycemia with blood glucose > 140 mg/dL (7.8 mmol/L) have a nutrition assessment in the first 24 h of hospital admission [19,30]. The daily energy
intake requirement for patients with diabetes is usually met with 25–35 calories/kg/day,
while critically ill patients may require less with the target of 15–25 calories/kg/day [62]. Enteral nutrition is the second-best option after oral nutrition as it is associated with a lower risk of complications, a lower risk of gastric mucosa atrophy, and a lower risk of infection and thrombosis compared to parenteral nutrition [63,64]. Standard enteral formulas provide lower amounts of lipids (30% of total calories) combined with higher carbohydrate content (55–66% of total calories); however, diabetic specific formulas (DSFs) have replaced some carbohydrates with monosaturated fatty acids (up to 35% of total calories), fibers (10–15% of total calories), and fructose (up to 30% of total calories) [64,65]. It has been reported that the postprandial spike in blood glucose was reduced by 18–29 mg/dL (0.8–1.7 mmol/L) with the use of DSF in noncritically ill patients, with no significant increase in LDL cholesterol or increase in the risk of lactic acidosis [65].

For continuous enteral feeding, the use of basal insulin with short- or rapid-acting insulin boluses per sliding scale every 4–6 h is recommended [30]. Basal insulin is calculated based on patients’ total daily dose plus additional insulin for enteral feeding which is calculated as 1 unit of insulin for each 10–15 g of carbohydrates in the enteral feeding formula. If enteral feeding is interrupted, the immediate use of IV dextrose (D10) at 50 mL/h is recommended to avoid hypoglycemia [30]. For bolus enteral feedings, the use of 1 unit of regular insulin for each 10–15 g of carbohydrates in the enteral feeding formula plus correctional insulin before each feeding is recommended. For nocturnal tube feeding, the use of insulin NPH given at the start of feeding is appropriate [30,62,63]. In critically ill patients, the use of parenteral nutrition is recommended with intravenous insulin infusion for the management of hyperglycemia [30,62,66]. To reduce hyperglycemia, glucose content in parenteral nutrition should be limited to 150–200 g/day. The addition of regular insulin at 1 unit for each 10 g of dextrose in a parenteral nutrition bag is also recommended by the ADA for patients with diabetes to avoid hypoglycemia with an interruption of parenteral nutrition [30].

7. The Management of Steroid-Induced Hyperglycemia in Hospitalized Patients

The use of steroids in the hospital settings is very common. A single-center study reported that 12.8% of patients were administered glucocorticoids during each admission [67]. The most common form of administration is the daily morning use of prednisone or prednisolone, which usually results in hyperglycemia in the late afternoon and in the evening. The goal of treatment with insulin is to treat hyperglycemia while avoiding nocturnal hypoglycemia. Therefore, the use of basal insulin NPH with a morning dose of prednisone or prednisolone is recommended in addition to the patients’ daily basal/bolus insulin regimen [68]. For longer-acting steroids, such as dexamethasone, the use of basal analogue insulin is suggested [68]. Standard diabetes education and follow-up with outpatient providers in one week after discharge are recommended for all patients being discharged on steroids [68].

In Tables 1 and 2, we summarize the above-mentioned glycemic targets and treatments in different hospital settings.
Table 1. Summary of glycemic targets in hospitalized patients.

<table>
<thead>
<tr>
<th>Practice Changing Trials</th>
<th>ICU Patients</th>
<th>Non-ICU Patients</th>
<th>Pre-OP *</th>
<th>PACU/OR **</th>
<th>Medical Nutrition Therapy</th>
<th>Steroid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—Leuven Surgical ICU: intensive glucose targets [38]</td>
<td>1—RABBIT-2 Medicine: Target fasting Blood Glucose (BG) &lt; 140 mg/dL (7.8 mmol/L) and random BG &lt; 180 mg/dL (10 mmol/L); recommends the use of the basal/bolus regimen over sliding scale [56]</td>
<td>1—ADA/AACE: Target fasting Blood Glucose (BG) &lt; 140 mg/dL (7.8 mmol/L) and random glucose &lt; 180 mg/dL (10 mmol/L) [19,30]</td>
<td>No RCTs for Pre-Op meds. ADA.</td>
<td>No RCTs, only expert opinion.</td>
<td>No RCTs available.</td>
<td>No RCT is available.</td>
</tr>
<tr>
<td>2—Glucontrol, VISEP: no benefit in intensive targets [39,41]</td>
<td>2—RABBIT-2 Surgery: Target of fasting BG &lt; 140 mg/dL (7.8 mmol/L) and random BG &lt; 180 mg/dL (10 mmol/L); recommends the use of the basal/bolus regimen over sliding scale [57]</td>
<td>2—Endocrine Society: Target BG: 140–180 mg/dL (7.8–10 mmol/L). In terminal illness, there is an increased risk of hypoglycemia with limited life expectancy; target &lt; 200 mg/dL (11.2 mmol/L) [66]</td>
<td>Check glucose hourly; start treatment if BG &gt; 180 mg/dL (10 mmol/L) [30]</td>
<td>ICU settings: Target BG: 140–180 mg/dL (7.8–10 mmol/L). Non-ICU settings: fasting BG &lt; 140 mg/dL (7.8 mmol/L) and random BG &lt; 180 mg/dL (10 mmol/L) [30]</td>
<td>ICU settings: Target BG: 140–180 mg/dL (7.8–10 mmol/L) Non-ICU settings: fasting BG &lt; 140 mg/dL (7.8 mmol/L) and random BG &lt; 180 mg/dL (10 mmol/L) [30]</td>
<td></td>
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<tr>
<td>3—NICE-SUGAR: intensive targets increase mortality at 90 days [42]</td>
<td>3—Basal Plus trial: recommends the use of the basal-plus correction scale in surgical patients with a higher risk of hypoglycemia [58]</td>
<td>3—Endocrine Society: Target BG: 140–180 mg/dL (7.8–10 mmol/L). In terminal illness, limited life expectancy BG &lt; 200 mg/dL (11.2 mmol/L) [30]</td>
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<tr>
<td>4—GlucocABG: a target blood glucose (BG) of 110–140 mg/dL (6.1–7.8 mmol/L) in some cardiac patients may be beneficial [46]</td>
<td>4—RABBIT-2 Medicine: Target fasting Blood Glucose (BG) &lt; 140 mg/dL (7.8 mmol/L) and random BG &lt; 180 mg/dL (10 mmol/L); recommends the use of the basal/bolus regimen over sliding scale [56]</td>
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* Pre-Op: preoperation period. ** PACU: Post-Anesthesia Care Unit/OR:Operating room.
Table 2. Summary of treatment of hyperglycemia in hospitalized patients.

<table>
<thead>
<tr>
<th>ICU Patients</th>
<th>Non-ICU Patients</th>
<th>Pre-Operation</th>
<th>Post-Anesthesia Care Unit or Operation Room</th>
<th>Medical Nutrition Therapy</th>
<th>High Dose Steroid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Options:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Poor intake or NPO [58]</td>
<td>Basal insulin (0.1–0.15 units/kg) Plus correction scale</td>
<td>Basal insulin (0.2–0.25 units/kg) Plus correction scale</td>
<td>Basal insulin (0.3 units/kg) plus correction scale</td>
<td>2-Surgery &gt;4 h, Hemodynamic changes: Temp changes: Start IV insulin infusion [14]</td>
<td>Critically Ill pts on steroid: IV insulin infusion [30]</td>
</tr>
<tr>
<td>Normal intake [56,57]</td>
<td>Basal insulin (0.1–0.15 units/kg), meal bolus insulin and correction scale</td>
<td>Basal insulin (0.2–0.25 units/kg), meal bolus insulin and correction scale</td>
<td>Basal insulin (0.3 units/kg), meal-bolus insulin and correction scale</td>
<td>Hold short-acting insulin on the day of surgery, use 80% of am dose of glargine insulin on the day of surgery and 50% of insulin 70/30 in am if BG &gt; 120 mg/dL (6.7 mmol/L) and Hold if BG &lt; 120 mg/dL (6.7 mmol/L)</td>
<td>3-Nocturnal enteral feed: Use NPH insulin at the start of feed [14]</td>
</tr>
<tr>
<td>On Low doses of insulin [61,62]</td>
<td>Basal insulin (0.1–0.15 units/kg) plus DPP-IV inhs</td>
<td>Basal insulin (0.2–0.25 units/kg) plus DPP-IV inhs</td>
<td>Basal insulin (0.3 units/kg) plus DPP-IV inhs</td>
<td>Longer acting steroid; dexamethasone: basal insulin plus correctional scale [30]</td>
<td>4-Parenteral nutrition: Use IV insulin infusion in ICU. In non-ICU: use Regular insulin [30]</td>
</tr>
</tbody>
</table>
8. The Use of Glucose-Monitoring Devices and Closed-Loop Insulin Pumps in the Hospital Settings

The recent Endocrine Society guideline recommends the use of continuous glucose monitoring (CGM) devices in patients at higher risk of hypoglycemia including those aged > 65; with a BMI < 27 kg/m²; on a total daily dose of insulin > 0.6 units/kg; with a history of CKD stage 3 or higher, liver failure, active malignancy, pancreatic disorder, or congestive heart failure; and patients with a history of recurrent hypoglycemia with impaired awareness [66]. However, if there are situations with an interference with CGM, such as volume depletion, the use of vasopressor therapy, hypoperfusion, temperature changes, and the use of high-dose acetaminophen or vitamin C, the use of CGM is not recommended [66,69]. Recent observational studies have shown that the use of CGM can increase the detection of hypoglycemia in hospitalized patients compared to point-of-care (POC) testing [30,66]. Currently, the results of studies that compare the accuracy and efficiency of different CGM methods in hospitalized patients are not available. Due to the lower accuracy of CGM readings for very high or low glucose values, it is recommended to confirm those readings of CGM with POC testing in hospitalized patients prior to any insulin changes [66]. CGM calibration with POC testing is recommended for the first 12 h of application of new CGM sensors [69].

Recent studies have reported that the use of closed-loop insulin pumps in hospitalized patients in ICU and non-ICU settings is associated with a longer time in glycemic targets and lower mean daily glucose values without increasing the risk of hypoglycemia [70,71]. However, an insulin pump is not recommended in the treatment of diabetes ketoacidosis or hyperosmolar hyperglycemic state and if the patient is not able to appropriately use the pump due to severe illness or an altered mental status [66].

9. Diabetes Consultation and Discharge Planning

It has been shown that inpatient diabetes education and endocrinology/diabetes consultation may shorten the length of hospital stay and reduce the rate of readmission, especially in patients on medicine wards; therefore; ADA, AACE, and Endocrine Society guidelines recommend the use of diabetes-specific team consultations if available [19,30,66]. It has also been recommended to consult diabetes specialists when patients are placed on high-dose steroids and immunosuppressants, when parenteral or enteral feeding is initiated, when persistent hypoglycemia and/or hyperglycemia exists despite dose adjustments, and if admission HbA1c is >8% or adjustments of home medications are needed [19,30,66].

Based on ADA and AACE recommendations, discharge education for patients with diabetes should include the self-monitoring of diabetes care, when to contact providers, and the recognition and treatment of hypoglycemia and hyperglycemia [19,30]. Sick-day management should be also reviewed with patients prior to their discharge [30]. Most patients need to be seen by outpatient healthcare providers within 1–2 weeks after discharge, especially if blood glucose levels during the admission were elevated or changes were made to their home medications at discharge [19,30].

Readmission within 30 days of discharge is reported in about 14–20% of discharged patients with diabetes, which is almost twice the readmission rate of patients without diabetes [19]. Factors contributing to readmissions are older age, male gender, a longer duration of hospital stay, multiple comorbidities, and lower socioeconomic and educational status [30]. It has been shown that timely outpatient follow-up, inpatient diabetes education, and scheduled home health visits can significantly reduce readmissions [72].

10. Updates in the Management of Hyperglycemic Emergencies

Diabetes ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most serious and life-threatening hyperglycemic emergencies in patients with diabetes [73]. The frequency of DKA has increased by 30% during the past decade, with more than 140,000 hospital admissions per year being reported in the US in 2021 [30]. However, mortality has decreased in the US and is currently less than 1% in patients with DKA and
between 5 and 16% in patients with HHS [30,73]. The treatment of hyperglycemic crisis represents a substantial part of diabetes care costs, with an estimated total annual hospital costs of USD 2.4 billion [73]. Treatment protocols for the management of DKA/HHS have been associated with decreased costs and improved patient safety [30,73]. It has been shown that in mild-to-moderate DKA (pH > 7.0 and bicarb >10 mEq/L with no altered mental status), subcutaneous short-acting insulin can be used instead of intravenous insulin treatment to reduce the costs of care [74]. A recent Cochrane review showed that there was no significant difference in outcomes in patients treated with intravenous insulin vs. subcutaneous short-acting insulin with frequent blood glucose checks and fluid replacement [75]. Therefore, ADA and AACE recommend that in uncomplicated DKA, patients can be treated with subcutaneous insulin in protected settings with frequent monitoring [30].

Euglycemic DKA (when blood glucose is <200–250 mg/dL (11.9–13.1 mmol/L), pH < 7.3, and bicarb < 18 mEq/L) has been reported more commonly with the increased use of SGLT-2 inhibitors in patients with diabetes. It has also been reported in hospitalized patients with recent surgery, prolonged starvation, pregnancy, and infection. Treatment is similar to DKA with the addition of glucose-containing fluid replacement [76].

11. Summary

Diabetes has become the most prevalent metabolic disease, affecting more than 537 million people worldwide, and the prevalence of diabetes in hospital settings has been reported to be as high as 22–30% of all noncritically ill hospitalized patients [1,2]. In this review, we discussed historical and most recent studies that reported an increased risk of adverse outcomes in hospitalized patients with hyperglycemia with pre-existing diabetes and in patients with stress hyperglycemia without pre-existing diabetes. We reviewed landmark trials including the Leuven Surgical ICU trial, which was the premier study in advocating for tight glycemic control in ICU settings [38]. In this trial, a tight glycemic target resulted in an overall 34% reduction in mortality. However, follow-up studies were not able to confirm these findings, including the Leuven Medical ICU trial in which 1200 medical ICU patients were randomized to a tight blood glucose target of 80–110 mg/dL (4.4–6.1 mmol/L) vs. a conventional blood glucose target of 180–200 mg/dL (10–11.1 mmol/L). In this study, the tight blood glucose target did not significantly reduce hospital mortality (37.3 vs. 40%, p = 0.33) [77]. We also reviewed the Glucontrol trial, a seven-country, multicenter, randomized clinical trial, and the VISEP study, a multicenter trial from Germany [39,41]. In both trials, intensive glycemic targets were not associated with a reduction in mortality of patients in the ICU. We then reviewed a practice-changing landmark trial, NICE-SUGAR, which reported increased 90-day mortality in the intensive glycemic group [42]. These findings resulted in the revision of many different professional societies’ recommendations to avoid intensive glucose targets in critically ill patients. Therefore, ADA, AACE, and Endocrine Society guidelines consequently recommend a target of 140–180 mg/dL (7.8–10 mmol/L) for most patients in ICU settings [19,30,66]. We then reviewed the recent Gluco-CABG study, which suggested the possible benefits of using a lower glycemic target of 110–140 mg/dL (6.1–7.8 mmol/L) in patients undergoing cardiac surgery without a history of diabetes and with stress hyperglycemia [46]. Studies on intravenous insulin infusion protocols vs. a computerized protocol in the treatment of hyperglycemia in patients in ICUs were discussed in this review [51–53]. Due to the lack of compelling evidence and the considerable costs of computerized protocols, ADA and AACE have not yet made any recommendations [30]. Subsequently, data that pertained to recent recommendations for glycemic targets and insulin treatment in non-ICU settings, including basal/bolus and basal plus regimens, were reviewed [56–58]. We summarized updates in medical nutrition therapy in hospitalized patients with diabetes and steroid-induced hyperglycemia, discharge planning for patients with diabetes, and recent recommendations for the use of continuous glucose monitors and closed-loop insulin pumps in hospitalized
patients [62–72]. Finally, hyperglycemic emergencies and treatment updates were reviewed here, with a focus on cost-saving approaches [73–76].

12. Conclusions and Future Directions

In summary, glycemic control in hospitalized patients is a collective effort and requires a team of diabetes educators, pharmacists, nurses, PAs, CNPs, and endocrinologists to improve the quality of care and hospitalization outcomes for patients with diabetes. The most acceptable target for inpatient glycemic control is blood glucose in the range of 140–180 mg/dL (7.8–10 mmol/L) [19,30,66]. Computerized glycemic algorithms, continuous glucose monitors, and closed-loop insulin deliveries in hospitalized patients should be the focus of further research as they can shape the future of inpatient glycemic management.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References


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