Hypoglycemia is a common finding in both daily clinical practice and acute care settings. The causes of severe hypoglycemia (SH) are multi-factorial and the major etiologies are iatrogenic, infectious diseases with sepsis and tumor or autoimmune diseases. With the advent of aggressive lowering of HbA1c values to achieve optimal glycemic control, patients are at increased risk of hypoglycemic episodes. Iatrogenic hypoglycemia can cause recurrent morbidity, sometime irreversible neurologic complications and even death, and further preclude maintenance of euglycemia over a lifetime of diabetes. Recent studies have shown that hypoglycemia is associated with adverse outcomes in many acute illnesses. In addition, hypoglycemia is associated with increased mortality among elderly and non-diabetic hospitalized patients. Clinicians should have high clinical suspicion of subtle symptoms of hypoglycemia and provide prompt treatment. Clinicians should know that hypoglycemia is associated with considerable adverse outcomes in many acute critical illnesses. In order to reduce hypoglycemia-associated morbidity and mortality, timely health education programs and close monitoring should be applied to those diabetic patients presenting to the Emergency Department with SH. ED disposition strategies should be further validated and justified to achieve balance between the benefits of euglycemia and the risks of SH. We discuss relevant issues regarding hypoglycemia in emergency and critical care settings.

Key Words: Hypoglycemia, hyperglycemia, diabetes mellitus, emergency medicine, intensive care unit, anti-diabetic agents, insulin

INTRODUCTION

Hypoglycemia is a common finding in both daily clinical practice and acute care settings. The prevalence of hypoglycemic episodes remains high following the prevalence of diabetes. The causes of severe hypoglycemia (SH) are multi-factorial and the major etiologies are iatrogenic, infectious diseases with sepsis, tumor or related to autoimmune diseases. Reduction of blood glucose levels among patients with diabetes mellitus (DM) has been shown to reduce cardiovascular complications. The advent of aggressive lowering of HbA1c values causes an increased risk of hypoglycemic episodes in these patients. Iatrogenic hypoglycemia
Hypoglycemia occurs frequently in both patients with type 1 DM (T1DM) and type 2 DM (T2DM). It significantly affects patients’ daily lives, and increases risk of serious injury, and is often a limiting factor in achieving physiologic glucose levels with diabetic therapy. Hypoglycemia should be proven by fulfillment of the Whipple’s triad: 1) symptoms consistent with hypoglycemia; 2) a low plasma glucose concentration measured with a precise method; and 3) relief of the presenting symptoms after the plasma glucose level is raised.

**Definition of hypoglycemia**

The lower limit of the fasting plasma glucose concentration is normally approximately 70 mg/dL. Generally, the biochemical threshold for hypoglycemia is about 70 mg/dL. Mild hypoglycemia can be defined as an episode that can be self-treated. SH is defined as event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. A serum glucose cut-off value of 40-50 mg/dL has been used to define SH.

**Incidence**

Patients with T1DM could experience an average two episodes of symptomatic hypoglycemia per week. In general, SH appears to be less frequent in insulin-treated patients with T2DM than with T1DM. The incidence of hypoglycemia episodes in insulin-treated patients with T2DM was 0.44 episodes per patient year; 16.5 of patients had experienced at least one event. The annualized rate of hypoglycemia was 2.7% to 3% in patients treated with intensive insulin therapy targeting HbA1c of 6-6.5%, compared to 1% to 1.5% with standard treatment. Approximately 7% of patients admitted to the Emergency Department (ED) with complaints of altered mental status have hypoglycemia. Up to 20% of patients with diabetes treated with insulin or anti-diabetic agents (ADAs) had hypoglycemia-related symptoms that required ED evaluation and treatment.

**Clinical presentations**

Hypoglycemic symptoms in adults can be divided into autonomic, neuroglycopenic and non-specific groups. Clinical presentations of hypoglycemia are listed in Table 1. Autonomic symptoms tend to occur first at blood glucose levels of around 59-65 mg/dL; neuroglycopenic symptoms occur at blood glucose levels of about 47-54 mg/dL; finally, cognitive functions deteriorate at a slightly lower blood glucose levels. Symptoms of hypoglycemia may differ with increasing duration of diabetes but can also be affected by a period of recent metabolic change. Hypoglycemic symptoms can be nonspecific, including weakness, unsteadiness, sleepiness, faintness, and a feeling of tense-tiredness. Many people feel sad and unhappy with overt pessimism and negative feelings. Blurred vision and reading difficulties are common during insulin-induced hypoglycemia in normal subjects and in insulin-treated patients. Hypoglycemic symptoms are also age-specific; neurological symptoms are predominant in elderly patients, whereas features of behavioral changes are more common in children. History of morning headache or hangover, poor sleep quality, vivid dreams or nightmares, profuse sweating in bed and restless behavior (found by their spouses or partners) during sleep are symptoms that may suggest...
Alcohol consumption can cause prolonged, unexpected hypoglycemia in people with T2DM, particularly in those taking ADA. Non-islet cell tumor hypoglycemia is a rare but well-recognized phenomenon. Hepatocellular carcinoma can present with SH. In critically ill patients, female gender, diabetes, mechanical ventilation, continuous veno-venous hemodialysis and prolonged intensive stays are associated with increased risk of hypoglycemia. Risk factors for the development of hypoglycemia in patients with diabetes are listed in Table 2.

**Insulin and insulin secretagogues**

The use of peakless insulin analogues can reduce the incidence of hypoglycemia. Reducing the insulin dose by combining it with another ADA can lead to a lower incidence of hypoglycemia than insulin treatment alone. About 20% of patients prescribed sulphonylureas experience one or more episodes of hypoglycemia, and each year more than 1% will have an episode of SH. The metabolites of glyburide are metabolically active and can accumulate in patients with renal insufficiency. In contrast, the metabolites of glypizide and glimepiride are largely inactive. Thus glyburide is associated with the highest risk of hypoglycemia and can cause episodes to be prolonged, while there is a lower risk of hypoglycemia in patients treated with glimepiride and glypizide. Polypharmacy with additional drugs increases the risk for drug interactions. Renal insufficiency and deficiencies of diabetes care are commonly neglected crucial contraindications of sulphonylureas and contributed to risk of SH in geriatric patients.

**Other anti-diabetic agents**

Metformin, thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors appear to be appropriate oral options for minimizing the risk of hypoglycemia. Metformin acts by increasing insulin sensitivity and reducing hepatic glucose output and does not increase plasma insulin levels, thereby posing a low risk of hypoglycemia when used as monotherapy; however, the risk of hypoglycemia may be significantly increased when metformin is added to exogenous insulin or insulin secretagogues. Glitazones work by activating peroxisome proliferator-activated receptor γ and sensitizing tissues such as the liver, skeleton muscle and adipose tissue to insulin. Glitazone monotherapy and glitazone-metformin

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**Table 1. Clinical Presentations of Hypoglycemia**

| Symptoms       | Complaints            |
|----------------|-----------------------|
| Autonomic      |                       |
| Hunger         |                       |
| Pallor         |                       |
| Palpitation    | Pounding heart, rapid heartbeat |
| Shaking        | Trembling             |
| Sweating       |                       |
| Confusion      | Slowed thinking       |
| Drowsiness     | Lightheaded, visual disturbance, blurred or double vision |
| Diplopia       |                       |
| Hemiparesis    |                       |
| Incoordination | Poor concentration    |
| Odd behavior   | Restlessness          |
| Speech difficulty | Slurred speech      |
| Seizure        |                       |
| Non-specific/behavioral/miscellaneous | Anger, irritability, denial, sleepwalking |
| Behavioral     |                       |
| General malaise|                       |
| Headache       | Nocturnal headache    |
| Nausea         |                       |
| Nervous tense  |                       |
| Tingling lips  |                       |

**Table 2. Risk Factors for Hypoglycemia**

| Advanced age | Intercurrent illness |
|--------------|---------------------|
| Alcohol consumption | Malnutrition |
| Autonomic neuropathy | Polypharmacy |
| Adrenergic-blocking agents | Renal insufficiency |
| Cognitive impairment | Sedative |
| Endocrine deficiencies | Secretagogues/insulin |
| Hypoglycemia unawareness | Tight glycemic control |
| Hepatic dysfunction | Hypothyroidism |

Risk factors

**Patients**

Impaired hypoglycemia awareness, old age, longer duration of diabetes and insulin therapy increase the risk of hypoglycemia. Infection or its sequelae may also increase the risk of SH. For insulin-treated patients, exercise increases the risk of hypoglycemia. This risk may either be immediate, mean-
combination have a lower risk of hypoglycemia than sulphonylureas monotherapy or sulphonylureas-metformin combinations.\textsuperscript{56,57} DPP-4 increases glucagon-like peptide 1 levels and lowers blood glucose levels via stimulation of insulin, only at meals or in the presence of elevated blood glucose concentrations and inhibition of glucagon secretion. The risk of hypoglycemia is much lower than with sulphonylureas.\textsuperscript{58} Monotherapy with α-glucosidase inhibitor has not been reported to cause hypoglycemia, but caution is warranted in concurrent use of prandial insulin or insulin secretagogues. Mismatching between peak serum glucose levels and peak prandial insulin levels may occur due to delayed carbohydrate absorption from the gut secondary to the effects of α-glucosidase inhibitor.\textsuperscript{59}

Other drug-induced hypoglycemia
The most commonly reported medications to be associated with hypoglycemia are quinolones, pentamidine, quinine, angiotensin-converting enzyme inhibitors and beta-adrenergic blockers.\textsuperscript{60} Severe hypoglycemia with inappropriately high levels of insulin and c-peptide has been found in patients treated with quinolones with or without sulphonylureas.\textsuperscript{61,62} Beverages such as tonic water can contain quinine and have been reported to cause hypoglycemia.\textsuperscript{63} Gatifloxacin, quinine and disopyramide can stimulate insulin release by inhibiting the pancreatic β-cell ATP sensitive K channels.\textsuperscript{64-66} In users of glipizide or glyburide; drug-drug interactions are evident with ciprofloxacin (in glyburide users only), clarithromycin, co-trimoxazole, fluconazole, and levofloxacin.\textsuperscript{67} Trimethoprim can induce CYP2C8 inhibition, thus increasing the plasma concentration of repaglinide.\textsuperscript{68} Concurrent use of sibutramine and sedatives was reported to have caused SH in a young woman with low body mass index.\textsuperscript{69} Medications that can potentiate the development of hypoglycemia are summarized in Table 3.

Who should have blood glucose checked and when?
In patients who have altered consciousness, focal neurologic deficit or seizure attack, blood glucose level should be checked immediately. Hypoglycemia is one of the most common stroke mimics.\textsuperscript{70} Determination of blood glucose is one of the key procedures in the acute management protocol of acute ischemic stroke.\textsuperscript{71} Therefore, all patients presenting with stroke symptoms should have their glucose measured to exclude hypoglycemia. Although debate remains, hypoglycemia is one of the differential diagnoses of the “6H/6T” for pulseless electrical activity/asystole and refractory ventricular dysrhythmia.\textsuperscript{72,73}

Who should be admitted to the hospital?
The patients’ response to treatment, etiology of hypoglycemia, existing comorbid conditions and social situation are factors that need to be considered when determining disposition.\textsuperscript{74} However, recommendations regarding disposition of patients with diabetes presenting with SH are generally based on retrospective studies, practice patterns, anecdote, and medical “common sense”; these suggestions lack support from validated studies.\textsuperscript{75} A single massive overdose of insulin glargine or sulphonylurea can cause unexpected prolonged hypoglycemia. Sulphonylurases can cause refractory and prolonged hypoglycemia and are the primary ADA associated with hypoglycemia. Higher admission rates are also observed in patients with abnormal laboratory findings including hypokalemia, hyperkalemia, leukocytosis, pyuria and either newly diagnosed or pre-existing renal failure.\textsuperscript{75} The accumulated recurrent hypoglycemia rates have been identified as ranging from 6.1% to 14.7%, depended on the study population and settings.\textsuperscript{77,78} Nearly 32% of patients who were admitted to the hospital for SH developed recurrent hypoglycemia (RH). Patients with T2DM who presented at the ED with SH as well as certain risk factors, including loss of a recent meal, coronary artery disease, infection, and poor renal function were associated with increased risk of developing RH.\textsuperscript{77} A ‘response-to-treatment’-based strategy was indicated to be useful in determining the ED disposition of diabetic patients presenting with SH. In one study, the initial serum glucose levels, therapeutic responses to glucose replacement and changes in serum glucose over time (mg/dL/hour) were retrospectively evaluated.\textsuperscript{77} Therapeutic responses to glucose replacement and changes in serum glucose levels over time can differentiate patients with RH and overshoot hyperglycemia (OH) from those with fa-

### Table 3. Drugs that can Potentiate the Development of Hypoglycemia

| Drug                |
|---------------------|
| Beta-blockers       |
| Disopyramide        |
| Pentamidine         |
| Quinine             |
| Quinolone           |
| Sulphonylurea       |
| Salicylates         |
| Sulfonamide         |
| Sibutramine         |
| Trimethoprim        |

YONSEI MED J HTTP://WWWONEYMJORG VOLUME 52 NUMBER 6 NOVEMBER 2011
vorables glucose patterns during the first 48 h after presentation in the ED with SH. Using a cut-off value of 14.6 mg/dL/hr for changes in serum glucose levels over time, the sensitivity and specificity values for the development of RH were 78.9% and 64.4%; for the development of OH, using a cut-off value of 28.7 mg/dL/hr achieved sensitivity and specificity values of 85.5% and 78.8%. Nearly 24% of diabetic patients who presented to the ED with SH actually had OH during hospitalization. These patients still required intensive serum glucose monitoring and ADA adjustment and had a similarly prolonged stay in the hospital. This is presumably due to multiple factors. Such factors include underlying complex interactions between triggering events, stress responses and the effects of counter-regulatory hormones. Additional potential contributing elements to prolonged hospital stay include recently increased dosages of ADA for poorly controlled hyperglycemia, severe infections, evolutionary chronic renal insufficiency, heart failure and polypharmacy. However, this ‘response-to-treatment’ disposition strategy should be further validated in prospective studies. Without further study, we still recommend that a longer ED observation or admission is needed for patients who have increased risk of RH, including unsatisfactory response to treatment, multiple comorbidities, the use of sulphonylureas or long-acting insulin preparations, poor oral intake, and those with concurrent infection or impaired renal or liver function.

Management
Self-treatment by ingestion of glucose tablets (the commonly recommended dose of glucose in adult is 20 g) or carbohydrate containing juices, soft drinks, candy, snacks or a meal can effectively ameliorate asymptomatic (detected by self-monitoring of blood glucose) or mild-moderate symptomatic hypoglycemia within 15-20 minutes. Parenteral treatment is necessary when a hypoglycemic patient is unwilling or unable to take carbohydrates orally. Initial management of hypoglycemia consists of administration of 1 g/kg body weight dextrose, as D50W in adults. This can be followed by infusion of D5W or D10W at a rate maintaining serum glucose above 100 mg/dL in certain circumstances. Repeat bedside glucose determination should be performed every 30 min for the first two hours, to detect RH. Glucose replacement should be given intravenously in patients treated with α-glucosidase inhibitors.

Glucagon can cause glycogenolysis but also insulin release; thus it is most useful in T1DM rather than T2DM patients. It can be given 1 mg intramuscularly or subcutaneously. The effect is transient and patients should be instructed to eat to restore glycogen stores.

Administration of glucose or glucagon in patients with sulphonylurea-induced hypoglycemia may be unsatisfactory because these antidotal approaches are associated with further exacerbation of insulin release by glucose and glucagon, leading to only temporary beneficial effects and later RH. Octreotide can be safely and effectively used in treatment of sulphonylurea-induced hypoglycemia in patients with congestive heart failure and renal failure by adhering to dosing guidelines and close monitoring.

Acute coronary syndrome
Hyperglycemia is associated with increased mortality rates in patients who are diagnosed upon admission with acute myocardial infarction (AMI) and unstable angina. However, in healthy individuals and patients with T1DM, acute hypoglycemia can result in complex vascular effects including activation of prothrombotic, proinflammatory, and pro-atherogenic mechanisms. Moderate hypoglycemia acutely increases the circulating levels of plasminogen activator inhibitor, vascular endothelial growth factor, vascular adhesion molecules, interleukin-6, and markers of platelet activation. In T2DM patients with coronary artery disease, hypoglycemic episodes are associated with depressed heart rate variability; however, beta-blocking agents are able to contrast this relationship. Hypoglycemia is associated with increased short-term mortality in patients hospitalized with AMI, but this risk is confined to patients who develop hypoglycemia spontaneously. Hypoglycemia that occurs after initiation of insulin therapy is not associated with a higher risk of mortality and may not be a direct mediator of adverse outcomes in AMI patients.

Hypertension, cardiac dysrhythmia and QT prolongation
By using continuous glucose monitoring system and 24-hour electrocardiographic monitoring, a close temporal relationship can be found between hypoglycemia and elevated blood pressure; nocturnal hypoglycemia is found to be associated with QTc prolongation and cardiac rate/rhythm disturbances in ambulant patients with T1DM. Since cardiovascular disease and all-cause mortality is closely linked
to elevated blood pressure, increased blood pressure variability and recurrent rises blood pressure post-hypoglycemia episode may be of concern.\textsuperscript{91}

**Ampulla cardiomyopathy**
Ampulla cardiomyopathy after hypoglycemic coma was reported in a young female who had anorexia nervosa. Hypoglycemia-associated cardiomyopathy can cause reversible ventricular dysfunction that requires mechanical support.\textsuperscript{92,93}

**Sudden death and “dead in bed” syndrome**
Sudden nocturnal death in patients with T1DM is thought to be due to nocturnal hypoglycemia-related QT prolongation with subsequent ventricular tachyarrhythmia.\textsuperscript{89} Potential factors contributing to the increased risk of sudden cardiac death observed in patients with DM include silent myocardial ischemia, autonomic nervous system dysfunction, abnormal cardiac repolarization, hypoglycemia, a hypercoagulable state secondary to DM, diabetic cardiomyopathy, and impaired respiratory response to hypoxia and hypercapnia.\textsuperscript{94} An estimated 2-4\% of deaths of patients with T1DM had been attributed to hypoglycemia.\textsuperscript{95}

**Noncardiogenic pulmonary edema**
Pulmonary edema was a well-known complication of insulin-shock therapy for schizophrenia in the past but has become an “ignored complication” in recent years. Severe hypoglycemia can cause noncardiogenic pulmonary edema as a result of: 1) massive sympathetic nervous system activation and its associated hemodynamic alterations; 2) disrupted integrity of the alveolar epithelium and pulmonary capillary endothelium and 3) acute effects of insulin on the cardiovascular system and capillary permeability.\textsuperscript{100-102}

**Pneumonia**
Hypoglycemia was independently associated with increased in-hospital, 30-day and 1-year mortality, and with further need for mechanical ventilation and inotropic support in patients presenting with community-acquired pneumonia.\textsuperscript{96,97}

**Critical care medicine**
Hyperglycemia during critical illness is common and is associated with increased mortality. Hyperglycemia is a potentially harmful but correctable metabolic derangement in intensive care unit (ICU) patients.\textsuperscript{86} Even mild or moderate hypoglycemia (<81 mg/dL) are associated with increased mortality in ICU patients, and hypoglycemia is independently associated with increased risk of death, cardiovascular death, and death due to infectious disease.\textsuperscript{98} Intensive glucose control in ICU patients has been shown to lower rates of mortality in past studies. However, recent systematic review and meta-analysis conclude that there is no evidence to support the use of intensive insulin therapy in general-surgical ICU patients who are fed according to current guidelines. Tight glycemic control (between 80-109 mg/dL) is associated with a high incidence of hypoglycemia and an increased risk of death in patients not receiving parenteral nutrition.\textsuperscript{13,23} Female gender, diabetes history, length of ICU stay, and necessity of mechanical ventilation and renal replacement are risk factors for the development of hypoglycemia.\textsuperscript{12} Insisting glycemic control and targeting a blood glucose level of less than 150 to 180 mg/dL is suggested.\textsuperscript{23,99}

**NEUROLOGY**

Hypoglycemia is known to cause neurologic deficits ranging from reversible focal deficits to irreversible coma. The associated neurologic deficits can be attributed to acute brain injury, selective neuronal vulnerability, cerebral vasospasm and asymmetric cerebral blood flow.\textsuperscript{103-106} Hypoglycemia causes neuronal damage only when the electroencephalography becomes flat; this usually occurs after serum glucose levels at less than 18 mg/dL for some period. Hypoglycemia often differs from ischemia in its neuropathologic distribution. White matter is more sensitive to hypoglycemia and there is no specific association between the pattern of injury and clinical outcomes whether the cerebral cortex, deep gray matter, and/or white matter are affected. Involvement of the dentate gyrus of the hippocampus can occur. Diffuse and extensive injury observed on the diffusion-weighted images predicts a poor neurologic outcome in patients with hypoglycemic injuries.\textsuperscript{107} However, the cerebellum and brainstem are usually universally spared in hypoglycemic brain damage.\textsuperscript{108} Central pontine myelinolysis can be caused by hypoglycemia.\textsuperscript{109} Avoiding treatment-induced hyperglycemic overshoots may minimize hypoglycemic brain injury. Maintaining a normal serum glucose concentration during treatment is recommended for treating ischemic brain injury.\textsuperscript{110} Following hypertension and atrial fibrillation, DM
Other endocrinological emergencies
Severe hypoglycemia can be the initial clinical presentation in patients with thyrotoxicosis. In a state of hyperthyroidism, facilitated glucose utilization in the presence of hyperinsulinemia is not appropriately counter-regulated.\textsuperscript{114-116} Hypoglycemia is one of the key features of adrenal insufficiency. The clinical presentations of adrenal insufficiency can range from altered consciousness, hypotension, hypothermia, malaise and nausea/vomiting, and cardiac arrhythmia.\textsuperscript{117}

Electrolyte imbalances
Insulin increases skeletal muscle potassium uptake by activating membrane Na\textsuperscript{+}/K\textsuperscript{+} ATPase.\textsuperscript{118} Insulin can also regulate phosphorus and magnesium balance.\textsuperscript{119} Hypoglycemia can be complicated by hyponatremia, hypokalemia, hypophosphatemia, and hypomagnesemia.\textsuperscript{81,120,121} Thus serum electrolytes should be carefully monitored in patients with severe and prolonged hypoglycemia.

Acute steatosis
Elevated liver enzymes and acute steatosis have also been reported to be associated with hypoglycemia. Excessive carbohydrate and insulin administration can lead to triglyceride accumulation in the hepatocytes and steatosis as a consequence of insufficient exportation of lipids from the liver.\textsuperscript{122,123}

CONCLUSION
Clinicians should have high clinical suspicion of subtle symptoms of hypoglycemia and provide prompt treatment. Clinicians should be aware that hypoglycemia is associated with considerable adverse outcomes in many acute critical illnesses. To reduce hypoglycemia-associated morbidity and mortality, a timely health education programme and close monitoring should be applied to those diabetic patients presenting to the Emergency Department with SH. ED disposition strategies should be further validated and justified to achieve balance between the benefits from euglycemia and the risks of SH.

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