



The clinical impact of inpatient hypoglycemia

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ABSTRACT

Hypoglycemia is common in hospitalized patients and is associated with poor outcomes, including increased mortality. Older individuals and those with comorbidities are more likely to suffer the adverse consequences of inpatient hypoglycemia. Observational studies have shown that spontaneous inpatient hypoglycemia is a greater risk factor for death than iatrogenic hypoglycemia, suggesting that hypoglycemia acts as a marker for more severe illness, and may not directly cause death. Initial randomized controlled trials of intensive insulin therapy in intensive care units demonstrated improvements in mortality with tight glycemic control, despite high rates of hypoglycemia. However, follow-up studies have not confirmed these initial findings, and the largest NICE-SUGAR study showed an increase in mortality in the tight control group. Despite these recent findings, a causal link between hypoglycemia and mortality has not been clearly established. Nonetheless, there is potential for harm from inpatient hypoglycemia, so evidence-based strategies to treat hyperglycemia, while preventing hypoglycemia should be instituted, in accordance with current practice guidelines.

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1. Introduction

Hospitalized patients with and without diabetes have frequent dysglycemia, and both hyperglycemia and hypoglycemia are associated with poor outcomes. Inpatient hyperglycemia is associated with increased mortality and in-hospital complications (Umpierrez et al., 2002). However, while initial small studies of aggressive glycemic control with intensive insulin therapy (IIT) showed improved clinical outcomes (Van den Berghe et al., 2006, 2001), subsequent large-scale trials reported high rates of hypoglycemia and even suggested harmful effects of intensive glucose lowering (Brunkhorst et al., 2008; NICE-SUGAR Study Investigators, 2009; Preiser et al., 2009). It is now clear that patients with both spontaneous and iatrogenic hypoglycemia are also at particularly high risk of complications, including longer and more expensive hospital stays and increased mortality rates (Boucai, Southern, & Zonszein, 2011; Garg, Hurwitz, Turchin, & Trivedi, 2013; Turchin et al., 2009). Hospitalized patients who are elderly or severely ill are especially vulnerable to the adverse effects of inpatient hypoglycemia (Boucai et al., 2011). In addition, most inpatient studies of IIT have been conducted in the intensive care unit

setting, with very little evidence to guide optimal treatment of patients admitted to the general medical wards. Therefore, in this review we stress the importance of safely avoiding dysglycemia in hospitalized patients, and offer strategies to prevent hypoglycemia. We also highlight the distinction between iatrogenic and spontaneous hypoglycemia, and present evidence that hypoglycemia is a marker of more severe illness, rather than a direct cause of poor outcomes.

2. Definition of hypoglycemia

The definition of hypoglycemia has been a topic of debate, since the range of “normal” glucose levels and the threshold for symptoms vary between individuals. In the outpatient setting, true hypoglycemia is often defined as the threshold at which counterregulation occurs. In relatively healthy outpatient populations, counterregulatory hormonal responses, with release of epinephrine and glucagon, can begin to occur when blood glucose levels fall below ~70 mg/dL. With progressive hypoglycemia growth hormone and cortisol release are also triggered (Mitrakou et al., 1991; Schwartz, Clutter, Shah, & Cryer, 1987). Sympathoadrenal activation, which causes catecholamine and acetylcholine release, leads to *autonomic symptoms* of hypoglycemia, including palpitations, tremor, arousal, sweating and hunger (Cryer, 2013; Mitrakou et al., 1991; Schwartz et al., 1987; Service, 1995). These symptoms are usually precipitated by blood glucose levels ~55 mg/dL or lower, and lead to a behavioral response of increased carbohydrate ingestion which further protects against hypoglycemia. If blood glucose levels continue to fall below ~50 mg/dL individuals can develop symptoms of neuroglycopenia (i.e. dizziness, confusion, tiredness, seizure and/or coma) due to insufficient glucose delivery to the brain

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(Cryer, 2013; Mitrakou et al., 1991; Schwartz et al., 1987; Service, 1995). While it is likely that hypoglycemia induces some of the same physiologic changes in sick, hospitalized patients, using thresholds of counterregulation derived from outpatient studies in an inpatient population is problematic because inpatients may have impaired counterregulation. Based on outpatient studies, it is also clear that there is large interindividual variability in counterregulatory responses and symptom development due to patient age, gender, duration of diabetes, comorbidities, and the presence of antecedent hypoglycemia (Dagogo-Jack, Craft, & Cryer, 1993; Matyka et al., 1997; Merimee & Fineberg, 1973; Santiago et al., 1984). In addition, hospitalized patients may only manifest neuroglycopenic symptoms of hypoglycemia, without preceding autonomic symptoms due to a variety of factors including polypharmacy, multi-organ dysfunction, and presence of longstanding diabetes (Shorr, Ray, Daugherty, & Griffin, 1997). Therefore, rather than using glycemic thresholds of counterregulation or symptoms, it is recommended to use only the glycemic level to categorize hospitalized patients as hypoglycemic or normoglycemic, with ≤ 70 mg/dL as a safe cutoff. This threshold was recently endorsed by a consensus statement published by the American Diabetes Association and the Endocrine Society working group (Seaquist et al., 2013).

3. Incidence of inpatient hypoglycemia

Among patients with and without diabetes admitted to general medical wards, the incidence of hypoglycemia (defined as blood glucose levels ≤ 70 mg/dL) ranges from 3.5% to 10.5% (Boucai et al., 2011; Cook et al., 2009). In patients with diabetes, hypoglycemia can occur in 12%–18%, with even higher rates reported when more aggressive antihyperglycemic therapy is used (Wexler, Meigs, Cagliero, Nathan, & Grant, 2007). For example, hypoglycemia defined as a point-of-care glucose ≤ 70 mg/dL was reported in 23% of surgical patients with type 2 diabetes (T2DM) receiving a basal-bolus insulin regimen (Umpierrez et al., 2011). Based on the largest observational study that included data from 126 hospitals, among patients admitted to ICUs, the incidences of hypoglycemia and severe hypoglycemia (defined as blood glucose ≤ 40 mg/dL) were 10% and 1.9%, respectively (Cook et al., 2009). Not surprisingly, interventional studies of IIT in the ICU have reported much higher rates of hypoglycemia, with the incidence of blood glucose ≤ 40 mg/dL ranging from 5% to 18.7% in the tight control groups (Brunkhorst et al., 2008; NICE-SUGAR Study Investigators, 2009; Preiser et al., 2009; Van den Berghe et al., 2006, 2001). Thus, although rates of hypoglycemia vary appreciably according to patient group, setting and treatment, overall hypoglycemia is a common problem among hospitalized patients.

4. Risk factors for hypoglycemia

Multiple factors contribute to the development of hypoglycemia in hospitalized patients. Although diabetes and use of glucose lowering medications are the most common risk factors, only about one half of hypoglycemic events occur in patients with diabetes or receiving insulin treatment (Boucai et al., 2011; Kagansky et al., 2003; Krinsley & Grover, 2007). Spontaneous hypoglycemia, which occurs without a clear precipitant, must be distinguished from drug-induced or iatrogenic hypoglycemia, because it has a worse prognosis and a distinct pathogenesis as will be discussed below. In patients with diabetes, outpatient studies have shown that recurrent antecedent hypoglycemia is an important risk factor for subsequent hypoglycemia due to the development of hypoglycemia associated autonomic failure (HAAF) in which counterregulatory hormone responses become impaired (Cryer, 2013). Although studies on counterregulation in sick patients are not available, it is likely that HAAF is also a risk factor for severe hypoglycemia in many hospitalized patients with diabetes. Longer duration of diabetes and severe or recurrent antecedent hypoglycemia

are further contributors to development of HAAF (Donnelly et al., 2005; Segel, Paramore, & Cryer, 2002). In addition, while clinicians are usually aware of HAAF in individuals with type 1 diabetes (T1DM), they may be less attuned to this issue in patients who are elderly or severely ill, or those who have T2DM, in whom counterregulation may also be abnormal (Matyka et al., 1997; Segel et al., 2002). Therefore, it is critical to measure blood sugar often in such patients, particularly those with changes in behavior or level of consciousness.

Risk factors for spontaneous hypoglycemia include septic shock, renal failure, severe critical illness, heart failure, liver failure and malignancy (Boucai et al., 2011; Fischer, Lees, & Newman, 1986; Kagansky et al., 2003; Krinsley & Grover, 2007). During hospitalization, patients undergo constant changes in insulin sensitivity and alterations in counterregulatory hormonal responses due to illness, procedures and medications (Smith, Winterstein, Johns, Rosenberg, & Sauer, 2005; Umpierrez et al., 2012; Van der Crabben et al., 2009). Furthermore, older patients often have age-related organ dysfunction affecting insulin sensitivity and drug metabolism, which potentiates hypoglycemic events (Shorr et al., 1997). They also develop symptoms at a significantly lower mean glucose threshold (54 ± 3.6 mg/dL) compared to younger patients, in whom symptoms manifest at higher mean glucose levels (65 ± 1.8 mg/dL) (Matyka et al., 1997). Elderly patients or those with impaired cognition may lack the ability to communicate their symptoms.

Many other risk factors contribute to development of inpatient hypoglycemia. Treatment with insulin is the most common risk factor for inpatient hypoglycemia (Boucai et al., 2011). Other risk factors include use of sulfonylurea therapy, failure to adjust insulin to nutritional intake, and changes to hospital routine (Varghese et al., 2007; Vriesendorp et al., 2006). Interruptions in usual nutritional intake and changes in medications frequently occur during hospitalization, and can precipitate hypoglycemia when hypoglycemic agents are used (Smith et al., 2005; Umpierrez et al., 2012). Aside from insulin and oral hypoglycemic agents, certain medications that are frequently administered in the hospital can also cause hypoglycemia directly, including quinolones, heparin, beta blockers, and trimethoprim-sulfamethoxazole (Murad et al., 2009). The risk of inducing iatrogenic hypoglycemia is further increased by drug-to-drug interactions in the setting of polypharmacy, a common occurrence in hospitalized patients. Thus, epidemiologic studies support a multifactorial etiology of hypoglycemia in hospitalized patients. It is important to highlight that the majority of hospitalized patients with hypoglycemia are either ill or exposed to medications that can cause hypoglycemia, whereas primary hypoglycemic disorders, such as those caused by tumors or endocrine deficiencies, are rare in this setting (Service, 1995). Finally, it is crucial to differentiate iatrogenic hypoglycemia, defined as hypoglycemia caused by the treatment provided to inpatients, from spontaneous hypoglycemia, an idiopathic event that can occur with or without medications, as will be discussed in more detail below.

5. Acute consequences of hypoglycemia

Hypoglycemia can cause acute inflammatory, cardiovascular and neurologic changes. In experimental models, hypoglycemia causes an increase in catecholamine levels and inflammatory markers, platelet activation and endothelial dysfunction (Gogitidze Joy et al., 2010; Schwartz et al., 1987; Wright et al., 2010). Hypoglycemia in healthy controls and subjects with T1DM causes an increase in platelet monocyte adhesion and markers of platelet activation (P-selectin) and inflammation (monocyte CD-40, IL-6 and hsCRP) (Wright et al., 2010). In adults with and without T1DM, mild hypoglycemia also results in increases in atherogenic vascular adhesion molecules (VCAM-1, ICAM-1, E-selectin) (Gogitidze Joy et al., 2010). Other studies have demonstrated an acute increase in leukocyte mobilization and clotting factors due to acute hypoglycemia (Collier et al., 1990; Corral, Webber, & Frier, 1980). Interestingly, some of the prothrombotic and inflammatory effects of acute hypoglycemia may be diminished by beta blockade, suggesting that the changes are induced by sympathoadrenal activation and may not occur in those with impaired

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