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Hypoglycemia in Diabetes: Challenges and Opportunities in Care

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ABSTRACT

Optimal glycemic control, an A1c < 7% for most patients, is necessary to reduce the risk for diabetes complications. However, tight glucose control carries a risk for hypoglycemia. Hypoglycemia can be a frightening aspect of living with diabetes, causing harmful effects to the cardiovascular system and a decrease in quality of life. This article reviews the important aspects of hypoglycemia management from both the patient and provider perspective. Nurse practitioners (NPs) should understand the physiology behind glucose homeostasis and lead evidence-based discussions regarding medication timing and dose, physical activity/exercise, alcohol consumption, symptom management, treatment, and prevention of low blood glucoses. The management of special populations such as older adults, those with renal impairment, and pregnant women is included. In light of mounting evidence that hypoglycemia is harmful and should be avoided at all costs, NPs are well positioned to assist patients in identifying, managing, and preventing hypoglycemia.

Keywords: cardiovascular risk reduction, diabetes, hypoglycemia, low blood glucose, patient education

Hypoglycemia in those with type 1 and type 2 diabetes is generally defined as a blood glucose (BG) level low enough to cause signs and symptoms or have the potential to cause harm.[1] Although there is no standard definition, for many patients this generally occurs with a BG concentration less than 70 mg/dL. Studies suggest that individuals with type 1 diabetes (T1DM) have between 115 and 320 episodes of severe hypoglycemia, defined as a BG event that requires the assistance of another individual, per 100 patient years, whereas individuals with type 2 diabetes (T2DM) have severe hypoglycemia at a rate of 30 to 70 per 100 patient years.[2] Additionally, up to 10% of deaths in patients with T1DM may be related to hypoglycemia.[3] Patients with diabetes often fear hypoglycemia because the symptoms can be debilitating and frightening. Many patients who desire to obtain well-controlled BG often have difficulty reaching lower targets because tight glucose control often leads to more frequent hypoglycemia. In 2013, the American Diabetes Association and the Endocrine Society published a report with evidence linking hypoglycemia and adverse outcomes in children, adults, and older patients.[1] In addition, a new work group on hypoglycemia through the American Diabetes Association has been established to provide clinical guidance regarding hypoglycemia. Nurse practitioners (NPs) are well positioned to assist patients with identifying hypoglycemic episodes, recommending appropriate treatment, and eliminating hypoglycemic episodes through appropriate medication regulation and patient education.

GLUCOSE HOMEOSTASIS

In individuals with diabetes, hypoglycemia is generally the result of excess insulin or the inability to raise BG through endogenous or exogenous methods. The regulation of BG requires a complex interplay between the liver, kidneys, muscle, adipocytes, pancreas, and neuroendocrine system. Glucose influx

into the circulation is primarily through the ingestion of carbohydrates and the production of endogenous glucose by the liver and kidneys. The brain uses glucose as an exclusive energy substrate, using up to 25% of the total glucose in the body. In addition to the brain, glucose efflux is driven by use by muscle, fat, liver, and kidneys.[4] Proper functioning of both the hepatic and renal systems is vital for an appropriate hypoglycemia response. The liver is responsible for approximately 80% of endogenous glucose release, whereas the kidneys produce approximately 20%.[5] Therefore, individuals with diabetes who have concomitant liver or renal disease often have more frequent or more troubling hypoglycemic episodes because of the loss of the innate protective mechanisms.

A physiologic chain of events occurs once the BG level approaches lower physiologic levels (80-85 mg/dL) in an attempt to restore normal glucose concentration. The first counter-regulatory measure is the halting of insulin production. As BG falls to 65 to 70 mg/dL, the second counter-regulatory response occurs as the alpha cells of the pancreas begin to release glucagon, an endogenous hormone that raises BG levels. In addition, the body releases epinephrine, cortisol, and growth hormone, all designed to increase BG. Finally, as BG drops to < 55 mg/dL, the body produces exogenous glucose from the liver to facilitate glycemic improvement.[4] This chain of events is dependent on the proper functioning of the pancreatic alpha cells and liver and kidneys, both of which are responsible for gluconeogenesis.

There is substantial research to support the idea that individuals with diabetes who have repeated hypoglycemia lose protective mechanisms. Repeated hypoglycemic episodes fail to trigger the same sympathoadrenal responses over time as the threshold for activation of the sympathetic nervous system decreases. Frequent hypoglycemia can cause hypoglycemia-associated autonomic failure (HAAF), which includes impaired counter-regulation and loss of hypoglycemia awareness.[6] The loss of the HAAF mechanism is further evidence to support addressing and eradicating hypoglycemia early and often in the disease course.

REVIEW OF THE LITERATURE

It is a well-established fact that glycemic control reduces the risk for vascular disease. However, achieving glycemic control comes with limitations and risks. Hypoglycemia may cause recurrent morbidity in those with T1DM as well as in those with advanced T2DM.[7]

Recent literature has confirmed that hypoglycemia in the outpatient setting can cause short-term deleterious effects to those with diabetes and should be avoided. An increasing number of studies have suggested that hypoglycemia is linked to higher cardiovascular risk and all-cause mortality.[6] Furthermore, studies in patients with T1DM suggest that rapid falls in BG levels lead to increases in heart rate, blood pressure, myocardial contractility, stroke volume, and cardiac output.[8] These effects are consistent with a *fight or flight* response caused by surges of epinephrine and norepinephrine. In addition to increased stress on cardiac function, hypoglycemia can cause prolonged QT changes and may be related to some of the sudden death cases seen in young patients with T1DM.[8] Moreover, iatrogenic hypoglycemia may contribute to the development of atherosclerotic vascular disease in diabetes through impaired vascular and endothelial function.[9] The physiologic changes caused by hypoglycemia may not affect patients acutely, but the effect over time of repeated hypoglycemic stress may cause altered cardiac function. A history of hypoglycemia is also correlated with a cognitive decline in older adults with diabetes, even after controlling for other risk factors of vascular disease, causing long-term cognitive impairment.[10]

HYPOGLYCEMIA RISK FACTORS/PRECIPITANTS

Hypoglycemia in both T1DM and T2DM diabetes is often iatrogenic, with insulin, insulin secretagogues, and glitinides acting as the most common precipitants. These medications raise insulin levels and lower the plasma glucose concentration.[6] Other common precipitants of hypoglycemia include physical activity/exercise, gastroparesis, alcohol consumption, a mismatch of insulin dose and food, and missed meals. Providers should be aware that some nondiabetes drugs are associated with an