Chapter 41
Hypoglycemia and its Impact in Diabetes

SM Sadikot

INTRODUCTION

Hypoglycemia is defined as plasma glucose values less than 70 mg/dL. The incidence of hypoglycemia is not uniform due to the lack of standardization of definition and classification. The true incidence of hypoglycemia is complicated by the occurrence of hypoglycemia unawareness.1 According to Bailey et al. severe hypoglycemia annually affects approximately 10–30% of type 1 diabetic patients, less than 5% of insulin-treated type 2 diabetic patients and less than 1% of type 2 diabetic patients receiving sulfonylurea. Hypoglycemia is one of the most common diabetic emergencies in ambulatory care; however, most patients do not require hospitalization as they usually respond to treatment.2 The UK Hypoglycemia Study Group reported an incidence of severe hypoglycemia of 110 episodes per 100 patient years.3 Ginde et al. analyzed data from 1993 to 2005 in National Hospital Ambulatory Medical Care Survey, which showed that there were 5 million emergency department visits for hypoglycemia out of which 25% resulted in admission. It was seen that visit rates were higher in patients less than 45 years of age, females, in blacks and in Hispanics.4

Hypoglycemia can be a major barrier to optimal glycemic control.5 Glycemic control can be inhibited by iatrogenic hypoglycemia and leads to:6

- Recurrent morbidity in most people with type 1 diabetes mellitus and advanced type 2 diabetes mellitus
- Compromise in physiological and behavioral defenses against hypoglycemia leading to recurrent episodes of hyperglycemia
- Hindrance for the maintenance of euglycemia

Although the risk of hypoglycemia is lower in type 2 diabetes compared with type 1 diabetes, its frequency increases with increased duration of the condition and insulin treatment.1 Hypoglycemia has a substantial clinical impact and can cause dementia and myocardial infarction in diabetic patients. Hypoglycemia is associated with lower quality of life, lower treatment satisfaction and increased fear of hypoglycemia and avoidance symptoms. The impact of hypoglycemia on work productivity leads to increased costs and economic burden. Hypoglycemia should be kept in mind during clinical decision as it impacts patients’ health, quality of life and causes economic burden.5

DIABETIC RETINOPATHY

Animal studies have shown that reduced blood glucose values lead to diplopia, dimness of vision, blurred vision and loss of contrast sensitivity. Khan et al. assessed effects of acute hypoglycemia on retinal function. The results showed decrease in retinal response in type 1 diabetes with reduced amplitude of response in central macular retina.6

Cardiovascular Complications

Bonds et al. conducted a retrospective epidemiological analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which showed that symptomatic, severe hypoglycemia predisposed patients to increased risk of death in conditions such as cardiovascular disease, evidence of subclinical disease or presence of two additional cardiovascular risk factors.7 Frequent and unrecognized hypoglycemia in intensive group versus standard group did not show huge statistical difference in the hazards ratio (HR) for mortality including frequency of hypoglycemic episodes, which was 0.93 (95% CI 0.9–0.97; P < 0.001) for participants in the intensive group and 0.98 (0.91–1.06; P = 0.615) for participants in the standard group.8 Severe hypoglycemia is associated with significant morbidity including major vascular events, such as myocardial infarction and stroke. Earlier studies did not find any association between hypoglycemia and myocardial infarction due to the lack of continuous electrocardiography (ECG) monitoring and lack of knowledge that type 1 diabetic patients often have silent myocardial ischemia.9 It has now been shown that following myocardial infarction, spontaneous hypoglycemia is associated with a twofold increased risk of mortality. The possibility of decrease in myocardial blood flow reserve may lead to cardiovascular mortality in hypoglycemic patients.10 Kosiborod et al. evaluated mortality risk in patients with myocardial infarction due to spontaneous hypoglycemia.11 Boucai et al. also demonstrated that hypoglycemia was associated with increased inhospital mortality in patients with spontaneous hypoglycemia.12 Wright et al. discuss recent studies that have shown a positive association between hypoglycemia and all-cause mortality risk. Acute hypoglycemia has caused changes in ECG, especially T-wave abnormalities and QT prolongation; there is no evidence for proarrhythmic effect of hypoglycemia.9 Hypoglycemia may increase the risk of ischemia and sudden death in individuals with type 2 diabetes.13 Veterans Affairs Diabetes Trial showed that severe hypoglycemic event was an important predictor for cardiovascular death (HR 3.79; 95% CI 3.37–4.15; P < 0.001) and all-cause mortality (HR 6.37; 95% CI 2.57–15.8; P = .0001). However, in Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial there was no increase in all-cause or cardiovascular (CV) mortality with severe hypoglycemia. Although the trials provided different results, severe hypoglycemia is strongly associated with increased cardiovascular risks.14

DIABETIC NEPHROPATHY

Intensive glycemic control has been shown to reduce incidence and progression of microvascular outcomes; however, intensive therapy is associated with severe hypoglycemia, raising concerns in patients...
with renal dysfunction. Hence, individual target glycemic goals are recommended in patients with reduced glomerular filtration rate.\textsuperscript{15} Insulin resistance can lead to metabolic syndrome in association with renal disease, called cardio renal syndrome.\textsuperscript{16}

A recent review by Ensling et al. correlates hypoglycemia-induced increase in nonesterified fatty acids to lipid abnormalities. This review concluded that lipid abnormalities can lead to insulin resistance and may contribute to cardio renal syndrome. However, further studies are needed to validate the possible link between hypoglycemia and cardio renal syndrome.\textsuperscript{16}

Moen et al. showed that the incidence of hypoglycemia was higher in patients with chronic kidney disease (CKD) than in patients without CKD. The same study showed that among patients with diabetes, the rate was 10.72 versus 5.33 per 100 patient-months without diabetes and the odds of 1 day mortality were increased at all levels of hypoglycemia but attenuated in CKD. The authors concluded that CKD is a risk factor for hypoglycemia.\textsuperscript{17}

**Neurologic Complications**

Hypoglycemic events lead to impaired nutrient delivery to the brain and may cause impaired cognitive functioning in children and young adults with type 1 diabetes. The role of hypoglycemia in dementia in elderly is not studied. A recent study by Whitmer et al. evaluated the same and found statistically significant association between hypoglycemia and dementia.\textsuperscript{18}

**IMPACT OF HYPOGLYCEMIA ON THE QUALITY OF LIFE**

The well-being of a patient may be directly affected by hypoglycemia and indirectly due to fear of recurrence. This in turn can lead to compromise of antidiabetic therapy. Recent study data from the United States on patients on antidiabetic drugs suggest that treatment-related side effects, including hypoglycemia, can lead to decreased treatment satisfaction and health-related quality of life (HRQoL). Marrett et al. used HRQoL (assessed using the EuroQol-5D Questionnaire [EQ-5D] US-weighted summary score [utility] and Worry subscale of the Hypoglycemia Fear Survey [HFS]) to evaluate the severity and frequency of hypoglycemia on quality of life. The level of severity is classified as mild, moderate, severe and very severe. It was seen that after adjusting for age, gender, weight gain, HbA1c, microvascular complications and selected cardiovascular conditions, the utility decrement was 0.045 (by level of severity: 0.009, 0.055, 0.131, 0.208), and the HFS increase was 9.6 (by severity: 5.3, 12.4, 17.6, 23.2). Health-related quality of life further decreased with greater frequency of hypoglycemic episodes.\textsuperscript{19} Alvarez-Guisasola et al. evaluated patient-reported hypoglycemic symptoms with ratings of their HRQoL state (EuroQol visual analogue scale, EQ-5D VAS), and patient-reported adverse events. It was seen that patients reporting hypoglycemic symptoms had significantly lower EQ-5D VAS scores, indicating worse patient-reported quality of life. Greater hypoglycemic symptom severity reduced quality of life.\textsuperscript{20} Elderly patients are at an increased risk for geriatric syndromes (i.e. depression and falls), pharmacotherapy-related hypoglycemia and diabetes complications leading to complicated care management. Care planning is also complicated due to limited life expectancy and high rates of comorbidity and functional disability. Laiteerapong et al. have shown that geriatric syndromes [25.3 (95% CI 25.8 – 24.8), \(P < 0.001\) and diabetes complications [23.5 (24.0 – 22.9), \(P < 0.001\)] were associated with lower physical HRQoL. Hypoglycemia was associated with lower mental HRQoL [24.0 (27.0 – 21.1), \(P = 0.008\)]. Prevention of hypoglycemia is needed to improve quality of life.\textsuperscript{21} Parents are usually responsible for administration of treatment in young children, especially in type 1 diabetes.

Parents have the sole responsibility until children are 8 years of age, combined responsibility between 8 years and 11 years of age and usually responsibility is transferred from parents to children during adolescences. Diabetes management may have a negative effect on parents’ well-being. Hypoglycemia avoidance behavior in parents may lead to poor glycemic control due to fear and anxiety of occurrence of hypoglycemic episode. Barnard et al. demonstrated that HFS with the parent version (HFS parent) was commonly used as outcome measure. The Patton 2008 study showed that mothers experienced greater fear of hypoglycemia than fathers of young children. Greater paternal pediatric parenting stress was correlated with fathers’ psychological resources including lower self-efficacy about diabetes management. The author concludes that parents of children with type 1 diabetes reported considerable parental fear of hypoglycemia, affecting both parental health and quality of life.\textsuperscript{22}

**Employment**

The American Diabetes Association (ADA) 2012 guidelines recommend that any person with diabetes whether on insulin or not should be eligible for any employment for which the person is otherwise qualified. A healthcare professional with expertise in treating diabetes should perform an individualized assessment in case of medical fitness questions.\textsuperscript{23} A single episode of severe hypoglycemia should not per se disqualify an individual from employment; however, recurrent episodes of severe hypoglycemia, which may hamper patients’ productivity or affect the safety of others, might need further evaluation. A detailed patient history, determination of factors leading to severe hypoglycemia and job duties need to be carefully examined to minimize hypoglycemic events. It is also recommended that job accommodation should be tailored for individual patients for effective and safe performance of job responsibilities.\textsuperscript{24}

**Driving**

Impaired consciousness or cognition due to diabetes, during driving, may lead to loss of employment or restriction on person’s license, as people with diabetes are also subject to licensing requirements. Hypoglycemic episodes may lead to impaired consciousness, causing motor vehicle accidents. Epidemiologic and simulator data have suggested that patients on insulin have small increase in risk of motor vehicle accidents due to hypoglycemia and decreased awareness of hypoglycemia.\textsuperscript{25} The ADA position statement on driving, recommends that there should be no restriction of driving, based on diabetes. Health professional assessment should be taken into account in case of restrictions. A detailed physician evaluation is needed in patients with severe hypoglycemia for appropriate therapy. Patients with suspended license due to diabetes can be reinstated after few months with correction of the problem.\textsuperscript{26}

**Physical Exercise**

Fear of hypoglycemia is the biggest barrier to exercise in diabetic patients especially, in type 1 diabetes.\textsuperscript{26,27} American Diabetes Association recommends a graded exercise test in individuals with diabetes aged over 35 years or those with type 2 diabetes for over 10 years and type 1 diabetes for over 15 years.\textsuperscript{26} In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. American Diabetes Association 2012 recommends added carbohydrates if pre-exercise glucose levels are less than 100 mg/dl (5.6 mmol/L).\textsuperscript{21} Patients should not exercise during periods of hypoglycemia and should be avoided for 24 hours after an episode of hypoglycemia.\textsuperscript{28} Taplin et al. showed that reducing basal
insulin dose can prevent postexercise nocturnal hypoglycemia in type 1 diabetes patients.

CONCLUSION

- Hypoglycemia affects morbidity and mortality in type 2 diabetes with diabetic complications.
- Hypoglycemia decreases quality of life, further reduced by increased severity and frequency.
- Hypoglycemia may affect daily life, including driving, employment and physical activity.
- American Diabetes Association-position-statement recommends against blanket restriction of diabetic patients in relation to driving and employment.

REFERENCES