Hypoglycemia From a Cardiologist's Perspective

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ABSTRACT

Hypoglycemia in people with diabetes mellitus (DM) has been potentially linked to cardiovascular morbidity and mortality. Pathophysiologically, hypoglycemia triggers activation of the sympathoadrenal system, leading to an increase in counter-regulatory hormones and, consequently, increased myocardial workload and oxygen demand. Additionally, hypoglycemia triggers proinflammatory and hematologic changes that provide the substrate for possible myocardial ischemia in the already-diseased diabetic cardiovascular system. Hypoglycemia creates electrophysiologic alterations causing P-R–interval shortening, ST-segment depression, T-wave flattening, reduction of T-wave area, and QTc-interval prolongation. Patients who experience hypoglycemia are at an increased risk of silent ischemia as well as QTc prolongation and consequent arrhythmias. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed an increase in all-cause mortality with intensive glycemic control, whereas the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study and Veteran's Affairs Diabetes Trial (VADT) showed no benefit with aggressive glycemic control. Women, elderly patients, and those with renal insufficiency are more vulnerable to hypoglycemic events. In fact, hypoglycemia is the most common metabolic complication experienced by older patients with DM in the United States. The concurrent use of medications like β -blockers warrants caution in DM because they can mask warning signs of hypoglycemia. Here we aim to elucidate the pathophysiology, review the electrocardiographic changes, analyze the current clinical literature, and consider the safety considerations of hypoglycemia as it relates to the cardiovascular system. In conclusion, in the current era of DM and its vascular ramifications, hypoglycemia from a cardiologist's perspective deserves due attention.

Introduction

Hypoglycemia is defined as an abnormally diminished concentration of glucose in the blood. This can manifest with tremulousness, diaphoresis, piloerection, hypothermia, and headache, and, when chronic and severe, it may cause central nervous system manifestations that in rare cases can even be fatal. Neuroglycopenia is defined as chronic hypoglycemia of a degree sufficient to impair brain function, resulting in personality changes and intellectual deterioration that may progress to convulsions, coma, and occasionally death.¹

For the classification of hypoglycemia, a plasma concentration of glucose <70 mg/dL is usually used as a cutoff. Types of hypoglycemia are categorized as (1) severe hypoglycemia (requiring assistance from another person for the

administration of carbohydrates or glucagon, or for taking corrective action); (2) documented symptomatic hypoglycemia (symptoms of hypoglycemia plus a glucose concentration <70 mg/dL); (3) asymptomatic hypoglycemia (no typical symptoms of hypoglycemia are noted but the plasma glucose concentration is <70 mg/dL); (4) probable symptomatic hypoglycemia (symptoms of hypoglycemia are not accompanied by plasma glucose determination, but it is presumed to be <70 mg/dL); and (5) pseudohypoglycemia (patient reports typical symptoms of hypoglycemia but the measured glucose concentration is >70 mg/dL).¹ In summary, hypoglycemia can produce a multiplicity of symptoms that mainly arise from the insufficient supply of glucose to the brain. In addition, hypoglycemia has also been linked with adverse cardiovascular events in patients with type 2 diabetes mellitus (T2DM) outside of hypoglycemic episodes themselves.²

Over the last decade, 3 large trials ($n = 22\,000$ patients combined), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and

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Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study, and the Veteran's Affairs Diabetes Trial (VADT), examined the effect of glucose lowering on cardiovascular events in patients with T2DM.^{3–5} All 3 trials found associations between episodes of severe hypoglycemia and an increased risk of adverse events. In the ACCORD trial, the risk of death in the intensive-strategy group increased nearly linearly from a glycated hemoglobin (HbA_{1c}) of 6.0 to 9.0. In addition, it appeared to be greater with intensive treatment than with standard strategy when the average HbA_{1c} was >7.0. They also noted that the higher the average HbA_{1c}, the greater the risk for death.⁶

Hypoglycemia is the most common metabolic complication experienced by older patients with DM in the United States and is related to a prolonged hospital stay at a greater medical cost. The vulnerability of the elderly to severe hypoglycemia may be secondary to a progressive age-related decrease in β -adrenergic receptor function.⁷ In patients with long-standing T2DM, such as elderly patients, the glucagon response to hypoglycemia is virtually absent.⁸ Therefore, in the elderly one should consider medications that are known not to cause hypoglycemia, such as incretins and newer agents. The recently published 2012 Beers list of prohibited medications in long-term care facilities lists the insulin sliding scale and glyburide as inappropriate.⁹ In this article, we will review the pathophysiology, electrocardiographic (ECG) changes, recent clinical-trial data, and legal considerations that pertain to hypoglycemia as it relates to the cardiovascular system.

Pathophysiology of Hypoglycemia

The pathophysiologic basis for the potential cardiovascular morbidity and mortality associated with acute hypoglycemia, especially in patients with long-standing DM, has been described by several authors^{10–12} (Figure 1). Acute hypoglycemia triggers activation of the sympathoadrenal system, leading to a release of epinephrine and other counter-regulatory hormones besides potent vasoactive peptides like endothelin. Consequently, there is increased cerebral, myocardial, and splanchnic blood flow with a decrease in blood supply to the skin and spleen.^{11,13}

From the cardiovascular hemodynamic standpoint, with hypoglycemia there is an increase in the myocardial workload and oxygen demand due to an increase in cardiac output, stroke volume, heart rate, and myocardial contractility. Furthermore, there is an increase in the peripheral systolic blood pressure, decrease in the peripheral arterial resistance with a widening of the pulse pressure, and a decrease in the central blood pressure.^{10,13} Interestingly, an increase in the circulating catecholamine levels causes a decrease in the peripheral arterial resistance by means of β -2 receptor-mediated vasodilation. In normal individuals, hypoglycemia causes increased elasticity of the arterial walls, causing return of the reflected wave during diastole. In patients with DM, the arterial walls are stiffer than normal, causing earlier return of the reflected wave during late systole; this adversely interferes with coronary perfusion, which primarily occurs during diastole.^{11,12} Additionally, hypoglycemic episodes have

been associated with activation of the coagulation system with increased amounts of factor VII, von Willebrand factor, and platelet activation. Also, there is an increase in C-reactive protein levels and inflammatory cytokines, including interleukin-6, interleukin-8, and tumor necrosis factor α , potentially leading to endothelial injury.¹⁴ Together, the above hemodynamic and hematologic changes provide the substrate for possible myocardial ischemia and cardiac dysrhythmias in an already-diseased diabetic cardiovascular system.¹³

β -Blockers must be used cautiously in patients with DM because they can mask the warning signs of hypoglycemia.¹⁵ By inhibiting the β -1 receptors, β -blockers can suppress tachycardia, which serves as one of the early warning signs of hypoglycemia. Hence, β -blockers may lead to hypoglycemic unawareness, which is well known to have deleterious outcomes. In addition, β -blockers, by virtue of blocking β -2 receptors in the muscle and liver, suppress glycogenolysis, which prevents correction of hypoglycemia.

Electrocardiographic Changes With Hypoglycemia

Hypoglycemia is known to trigger counter-regulatory adenosympathetic systems and thereby create cardiac electrical instability and electrophysiologic alterations.¹⁶ Atrioventricular conduction, ventricular depolarization, and repolarization are all affected by hypoglycemia. In the hyperinsulinemic-hypoglycemic clamp state, after obtaining a baseline plasma glucose level, a continuous infusion of insulin is started. Plasma glucose levels are measured at frequent time intervals and glucose is infused at a variable rate to achieve a target glucose concentration of ~50 mg/dL. Simultaneous ECG monitoring highlights the changes in atrioventricular conduction, ventricular depolarization, and ventricular repolarization in response to hypoglycemia. Laitinen and colleagues studied subjects using the hyperinsulinemic-hypoglycemic clamp state and reported statistical elevation of catecholamine levels along with multiple ECG alterations notable for P-R-interval shortening, ST-segment depression, T-wave flattening, reduction of T-wave area, and QTc-interval prolongation. Counter-regulatory norepinephrine release was associated with changes in ventricular depolarization and R-wave amplitude (impairment of euglycemic hyperinsulinemia induced R-wave amplification); and epinephrine release was associated with changes in ventricular repolarization and produced T-wave flattening.¹⁷ Multiple studies point toward T-wave flattening and increase in the R:T ratio as being one of the most characteristic, and perhaps even an ECG, indicator of hypoglycemia.^{17–19} The proarrhythmic effects of hypoglycemia in patients with DM are better understood with the hyperinsulinemic-hypoglycemic clamp state model. Hypoglycemia-induced silent myocardial ischemia has also been suggested by multiple authors.^{20,21} Desouza et al reported a statistically higher incidence of ECG and symptomatic ischemia during hypoglycemic episodes as compared with both hyperglycemia as well as normoglycemia in his study population.²² Several studies have reported a hypoglycemia-induced QTc-interval prolongation and subsequent proarrhythmia in both subjects with type 1 DM (T1DM) and T2DM.^{22,23} In a

The 5 Phases of Hypoglycemic Symptoms

Figure 1. The brain is unique in that it relies solely on carbohydrate metabolism for energy. The figure depicts the brain's response to hypoglycemia. These clinical manifestations rarely occur when the blood glucose level is >60 mg/dL. Each phase is related to a different anatomic portion of the brain, with the highest brain center being more susceptible and affected earliest. Adapted from Himwich, "A Review of Hypoglycemia, Its Physiology and Pathology, Symptomatology and Treatment."¹⁵ Abbreviations: RR, respiratory rate.

population-based study by Pappachan and colleagues, as well as in a case-control study by Whitsel et al, patients with DM in the upper quartile of QT index had a 3-fold higher risk of primary cardiac arrest as compared with patients with DM in the first quartile. This suggests a possible link between a prolonged QTc and sudden cardiac death in patients with DM.^{24–26} Another study examined the T1DM population data from the Europe and Diabetes Study (EURODIAB) cohort and reported that severe hypoglycemia was independently associated with prolongation of QTc interval in these patients.²⁷ Cardiac autonomic neuropathy is separately known to be a risk factor for QTc-interval prolongation and is reportedly twice as likely to be present in subjects with DM as in subjects without it.²⁶ Thus, the risk of QTc prolongation and consequent arrhythmia is exponentially increased in patients with DM who experience hypoglycemia. The ECG effect of hypoglycemia in patients with DM therefore warrants astute attention to allow early recognition and corrective action in this patient population, which is at baseline already predisposed to ischemia via accelerated coronary atherosclerosis and electrical instability through QTc-interval prolongation.

Recent Clinical Trials Pertaining to Hypoglycemia

Recent large trials reporting hypoglycemia have shown increased concerns due to significant adverse outcomes in patients. Whether hypoglycemia is a marker of increased cardiovascular risk or a risk factor continues to be a central concern for practicing physicians. Moreover, women, elderly patients, and those with increased comorbidities

are at higher risk for hypoglycemic events. In conclusion, both symptomatic severe and mild hypoglycemia have been associated with increased cardiovascular events and serious health outcomes.

Zoungas et al reported that in the patients with T2DM in the ADVANCE trial, hypoglycemia was associated with increased adverse events. Over a 5-year period, 231 patients (2.1%) had ≥ 1 severe hypoglycemic event; in the intensive glucose control arm, the rate was 2.7% (150/5571), and in the control arm it was 1.5% (81/5569). During the follow-up period, there was a 2.8 $\times$ increase in major macrovascular events and 2.6 $\times$ increase in death from cardiovascular causes. Independent risk factors for severe hypoglycemia were older age, longer duration of DM, higher creatinine levels, lower body mass index, lower cognitive function, use of ≥ 2 oral glucose-lowering drugs, history of smoking or microvascular disease, and assignment to the intensive glucose control arm ($P < 0.05$). However, the authors were unable to associate repeated episodes of severe hypoglycemia with death or vascular outcomes.²⁸

In both the ADVANCE study and the ACCORD study, yearly mortality in patients who reported severe hypoglycemia was higher in the group receiving standard treatment than in the group receiving intensive treatment. In addition, in the ACCORD trial, despite the higher rate of symptomatic severe hypoglycemia in the intensive treatment group, hypoglycemia was not considered to be a probable reason for the excess mortality associated with intensive control. In subjects who experienced ≥ 1 episode of hypoglycemia, the risk of death was lower in the intensive arm than in the standard arm.²⁹

Figure 2. The complex puzzle of the etiology of symptomatic hypoglycemia is far from settled. The figure reveals some of the complexity of symptomatic hypoglycemia's component parts. Abbreviations: CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; MVO₂, myocardial oxygen consumption.

Figure 3. There is serious concern for any hypoglycemic events in patients with type 2 DM. Clearly, severe hypoglycemia has a worse outcome, but even mild hypoglycemia results in reduced survival at 10 years. Unfortunately, this study did not report HbA_{1c} or blood-glucose information.³⁰ Abbreviations: DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin.

It remains unclear why the macrovascular event rate was not lowered in these trials with intensive blood sugar control when significant reductions were seen in microvascular event rates. Several possibilities exist for this anomaly, including the fact that older patients with a longer duration of DM, those patients who require multiple hypoglycemic agents to maintain glycemic control, and patients with a prior history of cardiovascular disease may represent a high-risk subset. Patients in the ADVANCE trial who were younger had a trend toward fewer events when intensively treated.⁵ In addition, the ACCORD trial found increased mortality in the patients randomized to the intensive arm who failed blood-sugar control.⁶ More research is needed to sort out the puzzle of symptomatic hypoglycemia and cardiovascular events in patients with T2DM treated with hypoglycemic agents (Figures 2–4).

Figure 4. Patients with severe or mild hypoglycemia have marked reduction in survival. As a comparison, patients who develop systolic HF have slightly better survival at 5 years. Although survival has improved, the absolute mortality rates for HF remain at approximately 50% within 5 years of diagnosis (Yancy CW et al).³⁸ Abbreviations: DM, diabetes mellitus; HF, heart failure.

Figure 5. Patients with severe hypoglycemia for the most part have increased cardiovascular risk factors. The significant increase in dyslipidemia in patients with type 2 DM but without hypoglycemia is very intriguing but remains unclear at present.³⁰ Abbreviations: DM, diabetes mellitus; HT, Hypertension.

Recently, Hsu et al presented a nationwide population-based study comprising 77 611 patients with newly diagnosed T2DM from the Taiwan National Health Research Institute from 1998 to 2009.³⁰ This study is of particular interest because the authors examine a population of patients from real-world outpatient clinical practice. Prior studies on hypoglycemia, for the most part from epidemiological analyses of clinical trials, related to acute myocardial infarction and included the Intense Metabolic Control By Means of Insulin in Patients With Diabetes Mellitus and Acute Myocardial Infarction (DIGAMI-2) and the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trials.^{31,32} Hsu and associates prospectively evaluated outcomes of patients with T2DM with hypoglycemic events against matched patients with T2DM without hypoglycemia. They investigated the interaction of hypoglycemia with total mortality and cardiovascular events. Other endpoints included stroke, coronary heart disease, cardiovascular diseases, and all-cause hospitalization. There were 1844 hypoglycemic events

reported, in which 500 patients were hospitalized; 1344 patients were outpatients among the 77 611 patients enrolled over 10 years. They found a 2-fold increase in adverse cardiovascular outcomes and hospitalization from any cause in T2DM with clinical hypoglycemia, even after adjusting for the propensity score. As noted from ACCORD, retrospective epidemiological analysis found a hazard ratio of 2.87 for all-cause mortality in patients with severe vs not-severe episodes of hypoglycemia in the standard treatment group.²⁹ Hypoglycemia may be a marker for vascular-disease severity in these typically treated patients with DM. These patients were more likely to be on insulin or a sulfonylurea with suspected difficulty controlling HbA_{1c}.

There may in fact be a window of opportunity to use aggressive blood-glucose control in patients newly diagnosed with DM. In the Diabetes Control and Complications Trial (DCCT), in patients with T1DM with a mean duration of 5.7 years and a mean age of 27 years, an intensive glucose-lowering therapy that dramatically increased the risk of severe hypoglycemia did not cause adverse cardiovascular outcomes.

In summary, in the ACCORD trial, intensive glucose-lowering when compared with standard therapy increased the risk of cardiovascular death. In contrast, in the ADVANCE trial and United Kingdom Prospective Diabetes Study (UKPDS), there was a neutral effect on cardiovascular death between intensive and standard glucose-lowering groups. To simplify these results, in patients with T2DM, strict glycemic control, which in turn increases the risk of severe hypoglycemia, reduces the risk of myocardial infarction, has a neutral effect on stroke, and has a mixed and rather uncertain effect on cardiovascular mortality.

Safety Considerations With Hypoglycemia

Hypoglycemia occurring in patients with DM has been linked to an increase in the risk of motor vehicle accidents (MVA). Driving is a complex task involving a composite interaction of visual-spatial, cognitive, and motor skills that can become impaired by the acute as well as chronic effects of the disease. Diabetic complications like retinopathy (proliferative and advanced nonproliferative) can result in loss of peripheral vision and visual acuity. Peripheral neuropathy may decrease proprioception in the lower extremities, impeding the appropriate use of pedals.³³ Acute complications like hypoglycemia and hyperglycemia may interfere with awareness and judgment. Numerous scientific studies have evaluated the relationship between complications of DM, including both hyperglycemia and hypoglycemia, and driving safety. A recent meta-analysis concluded that people with DM were at a 12% to 19% increased risk of MVA.³⁴ Studies focusing on patients with T1DM found that they had twice the number of collisions and increased moving-vehicle violations when compared with their spouses without DM.³⁵ A subsequent prospective study that included 452 patients with T1DM reported 52% hypoglycemia-related driving mishaps, with 5% of subjects reporting >6 mishaps.³⁶

Controlled trials have been performed in an attempt to identify factors associated with driving accidents in drivers with T1DM. One study revealed that drivers with a

history of driving mishaps (N = 16) required more dextrose infusion to maintain euglycemia, and during induced progressive hypoglycemia demonstrated less epinephrine release and greater driving impairments when compared with drivers without a history of driving mishaps (N = 22).³⁷ A subsequent prospective study confirmed the above findings and also demonstrated that drivers with a positive history for driving mishaps had fewer functional hypoglycemic symptoms, slower information-processing speed, and worse working memory.⁶ These studies together determine that at-risk drivers have greater insulin sensitivity and more frequent hypoglycemic episodes with a decrease in protective counter-regulatory mechanisms, even in the event of moderate hypoglycemia. In view of this growing body of ethical and legal evidence surrounding drivers with DM, the American Diabetes Association has released a statement recommending that “people with diabetes should be assessed individually, taking into account each individual’s medical history as well as the potential related risks associated with driving.” Drivers with potential risk factors for hypoglycemia should be counseled to the following: (1) test sugar before driving; (2) never begin an extended drive with low-normal blood glucose (eg, 70–90 mg/dL) without prophylactic carbohydrate consumption; (3) always carry a blood glucose meter and appropriate foods in the vehicle; (4) stop the vehicle as soon as any of the symptoms of low blood glucose are experienced; and (5) do not resume driving until their blood glucose and cognition have recovered.³³ In conclusion, complications of DM can impede motor skills essential for driving, therefore posing a higher risk of MVA. Clinicians have legal and ethical responsibilities to educate persons with DM in practicing safety and preventive measures.

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