Review Article

Hypoglycemia and coronary events: A reason for concern

Dilip Gude, Intensivist, Physician and Research Coordinator Department of Internal Medicine/Critical care, Princess Durr-e-Shehvar Children’s and General Hospital, Purani Haveli, Hyderabad, India. Email: letsgo.dilip@gmail.com


Key Words: Hypoglycemia, coronary artery disease, myocardial infarction

Abstract

Hypoglycemia is increasingly associated with increased cardiovascular mortality. Apart from the counter regulatory hormone response perturbing the myocardial oxygen demand/supply ratio, there are other mechanisms at interplay. Clinicians need to have their antennas up in watching for coronary events in every patient experiencing hypoglycemia. We discuss a case of hypoglycemia triggered coronary event and review the pertinent literature

Introduction

Neuroglycopenia is known to promote secretion of counterregulatory hormones, primarily the adrenomedullary adrenaline and norepinephrine (along with glucagon, growth hormone and glucocorticoids), which have relevant cardiovascular effects. We would like to share our experience about a patient with documented hypoglycemia developing an acute coronary event.

Case

A 52 year old male patient [normotensive and nonsmoker with symptoms corresponding to class I New York Heart Association (NYHA) and Class I Canadian cardiovascular Society (CCS)] of long standing diabetes presented with unresponsiveness for about half an hour. His blood sugar was found to be 32 mg/dl. His blood pressure was 100/70 mm in right upper limb. ECG showed bradycardia, ST depressions and T inversions in inferior leads (II, III and aVF). Twenty five percent dextrose was administered and his sensorium improved. Immediate anticoagulation, fluids and statin were given and patient was taken up for angiography and subsequent right coronary artery stent placement was done.
Discussion

Our patient who is a nonsmoker and normotensive and with Class I NYHA and CCS developed acute coronary syndrome probably owing to the hypoglycemic episode. Another similar instance was reported in a patient but without significant coronary stenosis. We review the incidence/prevalence and pathophysiological mechanisms of hypoglycemia-induced coronary events.

In long standing diabetics the brain may shift glucose thresholds of hypoglycemia-symptom responses to higher levels masking most of the mild hypoglycemia episodes (until blood glucose decreases to levels ≤50 mg/dl). The resultant hypoglycemia unawareness increases the risk of prolonging the duration and increasing the frequency of hypoglycemia. A detrimental vicious cycle evolves that worsens hypoglycemia coupled with brain dysfunction precipitating cardiovascular morbidity.

Older age, longer duration of diabetes, exercise, alcohol, insulin treatment at baseline, previous cardiovascular events, renal dysfunction (high albumin-to-creatinine ratio), infection, low BMI, decreased intake, and dementia, depression, and psychiatric illnesses compound one’s risk for hypoglycemia. Severe hypoglycemia apart from causing bradycardia, atrial fibrillation and ventricular arrhythmias is associated with a prolongation of QT interval (which in turn increases propensity to ischemia/infarction).

Mechanisms:
The counter-regulatory stress response secondary to hypoglycemia response decreases pancreatic β-cell insulin secretion, increases pancreatic α-cell glucagon secretion and increases secretion of ACTH/glucocorticoids. Hypoglycemia also affects inflammatory cytokine secretion, endothelial function, coagulation, and fibrinolysis.

Inflammation:
Hypoglycemia is proven to augment the release of C-reactive protein (CRP), IL-6, IL-8, TNF-α, endothelin-1 and vascular endothelial growth factor (VEGF) and increase platelet and neutrophil activation. Cytokines such as IL-1 have been shown to increase the severity of hypoglycemia sustaining a positive feedback cycle. The heightened sympathoadrenal response may precipitate arrhythmias and increase myocardial contractility, myocardial workload, and cardiac output and in conjunction with endothelial dysfunction may trigger ischemia/infarction.

Coagulation:
Hypoglycemia is also linked with platelet function abnormalities and activation of the fibrinolytic system (as documented by raised plasma coagulation factors). The sympathoadrenal activation directly increases platelet activation and aggregation, leukocyte mobilization, and blood coagulability. In an observation Factor VIII was increased 2-fold after 30 minutes of hypoglycemia.

Endothelial dysfunction:
Endothelin-1 (ET-1) levels in patients with type 1 DM are believed to rise by 70% above baseline values 1 hour after insulin-induced hypoglycemia. Vessel wall
stiffness is found to be increased during hypoglycemia in patients with type 1 diabetes of longer duration than those with a shorter duration of diabetes. Underlying endothelial dysfunction in patients with coronary artery disease contributes to decreased vasodilatory responses to nitric oxide further heightening cardiovascular risk.

**Autonomic neuropathy:**
Cardiovascular autonomic neuropathy or impairment which worsens from antecedent hypoglycemic attacks is known to contribute to the occurrence of adverse cardiac events and increase mortality. Likewise abnormalities in heart rate variability have been associated with hypoglycemia and increases in catecholamine release.

**Altered metabolism:**
Longstanding hypoglycemia has a detrimental effect on cardiac metabolism owing to the inability of the heart during acute ischemia to use glucose (the preferred substrate), instead of fatty acids, after exhaustion of myocardial glycogen reserves.

The above factors are closely interdependent and contribute synergistically to increased cardiovascular risk. This risk is amplified exponentially especially in those with preexisting cardiovascular disease, longer duration of diabetes, and severe autonomic neuropathy.

**Evidence in support:**
Acute coronary syndromes when coupled with hypoglycemia in the acute phase of their presentation are expected to have worse short- and long-term outcomes. In diabetics with acute coronary syndromes hypoglycemia within 48 hours of their admission was associated with a 2-fold increase in all-cause mortality. Fasting hypoglycemia was independently associated with a 3-fold increased risk in cardiovascular mortality (CVM) after a mean follow-up of 8 years. Patients with ST-segment–elevation myocardial infarction, with a Thrombolysis in Myocardial Infarction (TIMI) risk score >4 and concomitant hypoglycemia had a >11-fold increased risk of death within 30 days compared with those with normal glucose levels. Hypoglycemia has also been shown to increase the size of a myocardial infarct (by >40% as evidenced in animal studies). Patients receiving insulin therapy on admission to intensive care (who had 13-fold increased prevalence of severe hypoglycemia compared to those on conventional therapy) sported a 16% increase in the relative risk of CVM. Also in patients after myocardial infarction, spontaneous hypoglycemia was associated with a 2-fold increase in in-hospital mortality.

Hypoglycemia has a direct relationship with angina. It was associated with one third of all episodes of angina and corresponding ischemic ECG changes in patients with DM and coexisting coronary artery disease.

The hypothesis that hypoglycemia decreases the myocardial blood flow reserve (MBFR) was supported in a study. It showed that insulin-induced hypoglycemia decreases the myocardial blood flow reserve in both patients with type 1 DM and healthy subjects (measured via myocardial contrast echocardiography).
Hypoglycemia is also associated with longer term complications. In elderly patients who sustained an acute myocardial infarction fasting hypoglycemia was associated with a 33% increase in 3-year mortality rates.\textsuperscript{21}

**Weaker evidence:**
In the Veterans Affairs Diabetes Trial (VADT) type 2 diabetics were grouped under either intensive treatment or conventional treatment. Even though there was increased incidence of severe hypoglycemia in the intensive treatment group, there was no significant difference in cardiovascular events between the two treatment arms.\textsuperscript{22}

Similarly Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study that randomized participants to an intensive glycemic control arm(with higher incidence of hypoglycemia) and a standard glycemic control arm found no association between hypoglycemia and cardiovascular mortality. Nevertheless there was a discrepancy of having extremely low number of patients (<3%) who had severe hypoglycemia in the intensive treatment arm.\textsuperscript{23}

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial the risk of major cardiovascular events did not significantly differ in the insulin-provision group than in the insulin-sensitization group despite higher frequency of severe hypoglycemia in the former.\textsuperscript{24}

**Conclusion**
We reiterate that one needs to have a high index of suspicion for coronary catastrophes in dealing with patients presenting with hypoglycemia. Knowledge about the mechanisms by which hypoglycemia precipitates such events bolsters appropriate approach and management. Further large scale studies are warranted to reinforce and unequivocally establish the association between hypoglycemia and coronary events.

**References**


