Brief Communication

# Does hypoglycemia cause cardiovascular events?

**Sandeep Chopra, Aditya Kewal**

*Department of Cardiology, Christian Medical College and Hospital, Ludhiana, Punjab, India*

ABSTRACT

Hypoglycemia is a very common side effect of insulin therapy and, to a lesser extent, of treatment with oral hypoglycemic agents. Severe hypoglycemia can precipitate adverse cardiovascular outcomes such as myocardial ischemia and cardiac arrhythmia. These are mainly secondary to autonomic activation which results in hemodynamic changes, vasoconstriction and rise in intravascular coagulability and viscosity.

**Key words:** Cardiac arrhythmia, hypoglycemia, myocardial ischemia

## Introduction

Diabetes is a major risk factor for cardiovascular disease.[1] Patients with coronary artery disease (CAD) and diabetes have higher mortality and morbidity than patients without diabetes. Data from studies such as the UK Prospective Diabetes Study suggest that very good glycemic control is associated with fewer cardiovascular events.[2] However, tight glycemic control may increase the risk of hypoglycemia.

Hypoglycemia is a very common side effect of insulin therapy and, to a lesser extent, of treatment with sulfonylureas. Risk factors for severe hypoglycemia include age, duration of diabetes, strict glycemic control, sleep, impaired awareness of hypoglycemia, renal impairment, C-peptide negativity and previous history of severe hypoglycemia.[3,4]

Acute hypoglycemia provokes pronounced physiological responses, the important consequences of which are to maintain the supply of glucose to brain and promote hepatic production of glucose. Blood flow is increased to the myocardium, splanchnic circulation and the brain. Hypoglycemia and the rapid changes in blood glucose have been shown to increase counter-regulatory hormones such as epinephrine and nor-epinephrine, which may induce vasoconstriction and platelet aggregation, thereby precipitating myocardial ischemia.[5,6] Autonomic activation, principally of the sympatho-adrenal system, results in end-organ stimulation and the profuse release of epinephrine which precipitates hemodynamic changes like tachycardia, increased peripheral systolic blood pressure, decreased central blood pressure and increased myocardial contractility with an increased ejection fraction.[7,8] The increased activity of sympathetic nervous system and secretion of other hormones and peptides such as the potent vasoconstrictor endothelin have pronounced effects on intravascular coagulability and viscosity.[9] Increased plasma viscosity occurs during hypoglycemia because of an increase in erythrocyte concentration, while coagulation is promoted by platelet activation and an increment in factor VIII and von-Willebrand factor. Endothelial functions may be compromised during hypoglycemia because of an increase in C-reactive protein, mobilization and activation of neutrophils and platelet activation.

The catecholamine-induced increased myocardial contractility may induce ischemia in the myocardium in patients with CAD. The greater oxygen demand is not met because of not only the rigid vessels, but also endothelial dysfunction with failure to vasodilate.

Several studies have shown that the hypoglycemia is associated

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**Corresponding Author:** Dr. Sandeep Chopra, Department of Cardiology, Christian Medical College and Hospital, Ludhiana, Punjab, India. E-mail: drsandeepchopra@gmail.com

with a significant lengthening of the corrected QT interval ($QT_C$) in subjects with and without diabetes.[10,11] These changes are likely seen because of increased catecholamine release during hypoglycemia, and $QT_C$ prolongation, in particular, could lead to a high risk of ventricular tachycardia and sudden death.[12] Hyperinsulinemia and increased secretion of catecholamines may lead to hypokalemia during hypoglycemia, thus potentiating cardiac repolarizing abnormalities. These effects can be reversed by β-blockade and potassium replacements.[12]

Cardiovascular autonomic neuropathy or impairment is associated with increased mortality. Effects of antecedent hypoglycemia on cardiac autonomic regulation may contribute to the occurrence of adverse cardiac events. Abnormalities in high-frequency and low-frequency heart rate variability have been associated with hypoglycemia and increased catecholamine release.[13] However, other studies did not find any associations between heart rate variability, hypoglycemia and increased catecholamine release.[10]

Inflammation has been associated with cardiovascular disease and diabetes. Episodes of hypoglycemia have been found to be associated with rise in inflammatory cytokines including interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, C-reactive protein and endothelin-1.[14] These inflammatory cytokines result in endothelial injury and abnormalities in coagulation, resulting in rise of cardiovascular events. Inflammatory cytokines like IL-1 have also been shown to increase the severity of hypoglycemia, thus perpetuating a positive feedback cycle.[15] Studies have suggested that endothelial function may be compromised during acute hypoglycemia. Vessel wall stiffness was found to be increased during hypoglycemia in patients with type-1 diabetes of longer duration than those with shorter duration of diabetes.[16] Thus, hypoglycemia may increase the risk of cardiovascular events, especially in subsets of patients with longer duration of diabetes. Inflammation and endothelial dysfunction could potentially be the aggravating factors that contribute to increased cardiovascular risk with severe hypoglycemia, especially in the subset of patients with pre-existing cardiovascular disease, diabetes, and severe autonomic neuropathy.

A direct relationship between hypoglycemia and fatal cardiovascular event is difficult to demonstrate as blood glucose and cardiac monitoring are seldom performed simultaneously. In the ACCORD study, excess of deaths was noted in the intensive treatment arm, which led to discontinuation of study.[17] In the smaller study of veterans with type-2 diabetes, Veterans Affairs Diabetes Trial (VADT),[18] severe hypoglycemia was found to increase the risk of adverse events and deaths. There have been multiple case reports associating angina with hypoglycemia.[19] ECG changes, including ectopic activity, flattening of T-wave, ST depression, ventricular tachycardia, and atrial fibrillation, have been reported in cases of low plasma glucose.[20]

Sudden death during sleep has been described in patients with type-1 diabetes, the mechanism being a significant cardiac arrhythmia induced by nocturnal hypoglycemia.[21] Many of these patients have no evidence of severe hypoglycemia-induced neuronal damage at autopsy, implying that a cardiac arrhythmia had been triggered by hypoglycemia, resulting in sudden death. Despite the high frequency of nocturnal hypoglycemia in young patients with type-1 diabetes, sudden nocturnal death ("dead in bed" syndrome) is rare.

Evidence is accumulating that severe hypoglycemia can provoke adverse cardiovascular outcomes such as myocardial ischemia or cardiac arrhythmia. Episodes of severe hypoglycemia are common during intensive therapy in type-1 and type-2 diabetes in the out-patient as well as in-patient setting. Larger clinical trials are required to look specifically at the association between hypoglycemia and cardiovascular events and to determine the mechanism further. The challenge to the physicians is to lower blood glucose to normal values to decrease the risk for long-term complications and at the same time minimize hypoglycemia and hypoglycemia-associated morbidity and mortality.

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