The Case for: Hypoglycemia Is of Cardiovascular Importance

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Hypoglycemia, defined as a plasma glucose concentration <70 mg/dL, represents a major and potentially very dangerous side effect of glucose-lowering therapies in patients with diabetes, and it challenges the patient's ability to achieve and maintain optimal glycemic control (1–3). Statistically, the incidence of mild hypoglycemia in patients with type 1 diabetes is ~30 episodes/patient/year, whereas the incidence of severe hypoglycemia (i.e., requiring third-party assistance) may be as high as 3.2 episodes/patient/year (4). Furthermore, an estimated 2–4% of deaths of people with type 1 diabetes have been attributed to hypoglycemia. On the other hand, patients with type 2 diabetes experience hypoglycemia less frequently, with an incidence of mild and severe hypoglycemic episodes of 2–10/patient/year and 0.1–0.7/patient/year, respectively (4).

The occurrence of hypoglycemia, both in experimental and human settings even without diabetes or related metabolic changes, provokes substantial increase in counterregulatory hormonal secretion and affects the cardiovascular system and the brain, in turn affecting cognition, mood, and the level of consciousness. The secretion of counterregulatory hormones—of which glucagon and epinephrine are the most potent but also including norepinephrine, vasopressin, growth hormone, and cortisol—follows suppression of endogenous insulin secretion (5).

In addition, a specific response that occurs within the brain includes the activation of the central sympathetic nervous system, which promotes autonomic symptoms such as sweating, tremor, a pounding heart, hunger, and anxiety (6). Severe hypoglycemia is associated with significant morbidity such as cognitive impairment and can cause major neurological disability, including difficulty concentrating, drowsiness, and poor coordination. When blood glucose falls below 2.8 mmol/L, the majority of cognitive modalities are impaired. It is essential for a patient to be aware of these neuroglycopenic symptoms because they warn him/her that prompt action is required to treat the hypoglycemia and restore blood glucose to normal. In rare cases, prolonged severe hypoglycemia may cause permanent brain damage or can be fatal (7).

Hypoglycemia can induce a range of negative and potentially harmful effects on the cardiovascular system. A decrease in insulin and an increase in epinephrine levels mobilize free fatty acids from adipose tissue. Myocardial cells can use either fatty acids or glucose oxidation as their main energy fuel, which might lead to the shortage of energy substrate during severe hypoglycemia, especially occurring in the settings of altered vasculature, e.g., in diabetic patients (7).

During hypoglycemia, the attendant counterregulatory hormone response, mostly adrenergic, results in increases in heart rate and systolic blood pressure, which causes an augmented demand for coronary blood flow and oxygen consumption (7,8) and may result in arrhythmia, ischemia, and death. The failure of impaired coronary circulation in diabetic patients to respond to these challenges might cause cardiac rate and rhythm disturbances, including sinus tachycardia, sinus bradycardia (<40 bpm), and ventricular and atrial ectopy (9). In addition, ST wave changes with lengthening of the QT interval and ventricular repolarization abnormalities are found to be important features observed during episodes of hypoglycemia (10). Moreover, the "dead-in-bed" syndrome in diabetic patients is suggested to be linked to these abnormalities, while the tachycardia and the rise in blood pressure observed during a hypoglycemic episode might be important in destabilizing an atherosclerotic plaque (9,11).

Although it has long been suggested that major vascular events can be directly precipitated by the effects of severe hypoglycemia and hemodynamic changes on myocardial perfusion or of electrolyte disturbances causing arrhythmias, direct evidences for the existence of this relationship are still lacking or incomplete. Only a few reports have indicated that myocardial ischemia was directly precipitated by hypoglycemia (12). Electrocardiogram changes caused by hypoglycemia include T wave abnormalities and QT prolongation (13). These disturbances of cardiac rhythm are probably a consequence of the adrenergic response to hypoglycemia, which provokes a rapid fall in serum potassium concentration (9).

It is also often overlooked that hypoglycemia exerts profound effects on various constituents of the blood and that recurrent hypoglycemia may induce increasingly adverse effects on the vasculature, especially when it is already compromised by macro- and microangiopathies (2). In this regard, hypoglycemia induces the release of epinephrine leading to rises/increases in heart rate and systolic blood pressure with the occurrence of a small decrement in diastolic blood pressure via α and $\beta 2$ adrenoceptors. Catecholamines increase myocardial contractility, myocardial workload, and cardiac output. These effects can induce ischemia in the myocardium in patients with coronary artery disease. Furthermore, hypoglycemic events may trigger inflammation by

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inducing the release of C-reactive protein, interleukin-6, and vascular endothelial growth factor. Hypoglycemia also induces increased platelet and neutrophil activation. Underlying endothelial dysfunction leading to decreased vasodilatation may also contribute to cardiovascular risk (14).

Moreover, diabetic autonomic neuropathy is known to be associated with increased mortality, and resting QT intervals are generally found to be longer in patients with autonomic neuropathy. It has recently been demonstrated that brief periods of experimental hypoglycemia impair autonomic cardiovascular function for up to 16 h, which is additional evidence for clinically relevant interaction (15).

The use of continuous glucose monitoring has shown that hypoglycemia is more significantly associated with cardiac ischemia than normo- or hyperglycemia and that the same association is present in patients with considerable swings in blood glucose. In addition, in the same study, ambulatory electrocardiogram holter monitoring of ST-segment abnormalities in patients with coronary artery disease has shown that most ischemic events occur during daily activities accompanied by hypoglycemic events (16).

Moreover, the data coming from the large Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial have additionally supported the concept of the strong influence of hypoglycemia on the occurrence of ischemic events. In patients with ST-segment elevation myocardial infarction, the analysis of the relationship between the blood glucose levels at admission to the hospital and the subsequent mortality at 30 days has demonstrated the lowest level of mortality with euglycemia at admission but a comparably high mortality with either hypo- or hyperglycemia at admission, which suggested a high importance of hypoglycemia for inducing dangerous ischemic changes (17).

Although the previously mentioned trials have advocated for the existence of the direct influence of hypoglycemia on the occurrence of the ischemic event, the large trials comparing more versus less intensive strategies of glucose lowering, including the Diabetes Control and Complications Trial (DCCT) (18), UK Prospective Diabetes Study (UKPDS) (19), Action to Control Cardiovascular Risk in Diabetes (ACCORD) (20), Veterans Affairs Diabetes Trial (VADT) (21), and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (22), have brought some additional and more complex determinants into the relationship between hypoglycemia and cardiovascular ischemia.

The evaluation of all-cause mortality revealed the trend of the increases in the all-cause mortality in the intensive treatment groups of the ACCORD and the VADT in contrast to the ADVANCE study (23). The increase in all-cause mortality was parallel to the increase in cardiovascular mortality both in the VADT and ACCORD studies, which was opposite the decrease in both all-cause and cardiovascular mortality in the ADVANCE study (10).

In addition, in the ACCORD and VADT studies the intensive treatment groups exhibited significantly higher incidence of severe hypoglycemic episodes in contrast to the ADVANCE study (10). In the ACCORD trial, it has been demonstrated that a significant portion of hypoglycemic episodes were asymptomatic (24).

In this context, the results of the previous studies have suggested that the rapidity in blood glucose lowering and achieving the blood glucose targets might be important in provoking the risk of adverse events. In contrast to the ADVANCE study where the target glycemia was reached after 24 months, in the ACCORD and VADT studies the goals were achieved after 4 and 6 months, respectively (20–22).

In the ACCORD study, the analysis of the on-treatment factors associated with increased mortality has focused the attention on the reduction of HbA_{1c} and the incidence of severe hypoglycemia, as well as on the relationship between these two variables (25). In contrast to the findings in type 1 diabetes, where more frequent severe hypoglycemic events were found in patients with lower HbA_{1c} (18), in the individuals with type 2 diabetes participating in the ACCORD study more frequent severe hypoglycemic episodes were associated with higher HbA_{1c} in both intensive and standard treatment, i.e., in patients who failed to reduce the HbA_{1c} to the target values during the treatment (26).

Moreover, further analysis of the data from the ACCORD study has shown, evaluating the risk of mortality in the subjects having experienced a severe hypoglycemic episode, that lower mortality rate was found in the individuals showing higher incidence of mild-to-moderate hypoglycemic events in comparison with the subjects with lower incidence of nonsevere hypoglycemia (25,27). Thus, the higher incidence of mild-to-moderate hypoglycemic episodes could create an environment of "hypoglycemic preconditioning" in which the incidence of death of severe hypoglycemia was apparently decreased (hazard ratio 0.88 [95% CI 0.78–1.00]). The mechanisms underlying the beneficial effect of this preconditioning are still unclarified, although it has been hypothesized that absence of the preconditioning reflects the state of prolonged hyperglycemia in these individuals, accompanied by the failure of counterregulatory hormone response, which increases vulnerability to arrhythmias and other life-threatening cardiovascular events (25).

Altogether, we might hypothesize that hypoglycemia is of clinical relevance in more than one aspect. In some cases, it might directly cause myocardial ischemia in the context of an increased burden in the setting of altered coronary vasculature. However, especially in type 2 diabetic patients with long-lasting hyperglycemia resulting in clinical or subclinical changes to the cardiovascular system but also to other organs and tissues, an attempt to lower blood glucose rapidly to the therapeutic targets might be causing cardiovascular adverse events or death occurring on the background of the multiorgan impairments that previously remained undetected.

In conclusion, severe hypoglycemia could increase the risk of cardiovascular death in individuals with underlying cardiovascular disease. This risk might be further confounded by the development of impaired awareness of hypoglycemia, particularly in patients with coexisting autonomic neuropathy, a strong risk factor for sudden death. In diabetic patients, the long-standing hyperglycemia with an aggressive approach to reach therapeutic glucose targets can significantly increase the cardiovascular risk during severe hypoglycemic episodes.

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