Hypoglycemia and Vascular Disease
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Macrovascular and microvascular complications commonly occur in individuals with type 1 and type 2 diabetes. The mechanisms responsible for these complications remain the subjects of intense investigation. With regard to atherosclerosis specifically, there have been great strides in describing the pathophysiological connection between alterations in the diabetic metabolic state and altered endothelial, platelet, and vascular smooth muscle cell functions. Hyperglycemia and insulin resistance independently disrupt nitric oxide synthesis and signaling, induce the production of reactive oxygen species, and up-regulate inflammatory and thrombotic markers and mediators of vasoconstriction (1, 2).

Conversely, insulin per se has been shown to actually have vasodilatory and antiinflammatory effects independent of glycemia. Insulin exerts these beneficial effects via increased nitric oxide synthase production (thereby causing increased nitric oxide synthesis) and the suppression of reactive oxygen species, inflammatory mediators, and thrombotic markers (2).

To overcome the deleterious effects of hyperglycemia and insulin resistance, clinicians have increasingly used intensive glucose control for both type 1 and type 2 diabetes. Unfortunately, as glycemic control improves, rates of hypoglycemia increase. Multicenter randomized controlled trials to examine the effects of stricter glycemic control in both type 1 and type 2 diabetes have confirmed that not only do the total rates of hypoglycemia increase with improved glycemia, but the incidence of severe disabling hypoglycemia also increases.

Two recent large studies on glucose control and complications in type 2 diabetes mellitus [the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial and the Veterans Affairs Diabetes Trial] found no benefit of improved glycemic control on macrovascular complications. In fact, the ACCORD study found an increased mortality rate in the intensive glucose–control arm of the study, which was stopped earlier than planned. A major question that emanated from these studies was why intensive glycemic control did not produce beneficial effects. One speculative answer is that severe hypoglycemia overcame the benefits of improved glycemic control per se and caused increased macrovascular complications.

Hypoglycemia triggers an array of counterregulatory responses that function to return blood glucose to nonpathologic levels. Glucagon, epinephrine, norepinephrine, cortisol, pancreatic polypeptide, growth hormone, corticotropin, and the autonomic nervous system are all activated in response to hypoglycemia. In fact, the magnitude of the counterregulatory drive is directly proportional to the depth of hypoglycemia. In this way, the magnitude of counterregulatory responses doubles with each approximately 0.6-mmol/L (10-mg/dL) reduction in the plasma glucose concentration below approximately 3.9 mmol/L (70 mg/dL). Hypoglycemia is associated with considerable morbidity and even mortality. Case reports have linked hypoglycemia to acute severe myocardial and cerebrovascular events; however, the mechanisms responsible for hypoglycemia causing serious macrovascular events have not been fully elucidated.

More recently, additional studies have established associations between hypoglycemia and the development of cardiac and cerebral ischemia and cardiac arrhythmias (3). Furthermore, studies have identified several inflammatory, thrombotic, fibrinolytic, and oxidative-stress biomarkers that show significant, acute responses to hypoglycemia (3–5). Such changes, especially in the presence of a compromised vasculature (3), may further contribute to atherosclerotic processes.

Two very recent studies from independent laboratories add valuable evidence to support the theory that hypoglycemia, in addition to hyperglycemia and insulin resistance, can have adverse vascular effects (4, 5). Joy et al. and Wright et al. studied both patients with type 1 diabetes [mean (SE) hemoglobin A1c, 7.7% (0.2%) and 7.9% (0.9%), respectively] and nondiabetic control individuals. The hyperinsulinemic glucose clamp was used in both studies to establish euglycemia and hypoglycemia on separate occasions [5.2 mmol/L (94 mg/dL) and 4.5 mmol/L (81 mg/dL), respectively, during euglycemic clamps, and 2.9 mmol/L (52 mg/dL) and 2.5 mmol/L (45 mg/dL), respectively, during hypoglycemic clamps]. Samples were collected under baseline and experimental conditions, which lasted in the 2 studies for 120 minutes and 60 minutes, respec-
tively. Wright and colleagues tested for extended alterations in biomarker concentrations by sampling during the recovery period and at 6 and 24 hours after the start of the experimental period.

Joy et al. reported significantly different responses of circulating proinflammatory and proatherogenic vascular adhesion molecules to hypoglycemia and euglycemia. Soluble vascular cell adhesion molecule 1, soluble intercellular adhesion molecule 1, and soluble E-selectin all showed significant peak increases from baseline under hypoglycemic conditions in both healthy individuals and those with type 1 diabetes. Conversely, significant decreases in all 3 markers were observed in both groups during euglycemic clamps. Soluble P-selectin, plasminogen activator inhibitor 1, tissue plasminogen activator, von Willebrand factor, and platelet–monocyte aggregation were measured to assess platelet activation and fibrinolytic balance. Joy and colleagues found that soluble P-selectin (a marker of platelet activation) responded significantly differently to the 2 glycemic conditions in both the control and diabetic groups, with significant increases occurring during hypoglycemia and significant decreases occurring during normoglycemia. Wright et al. also found significant increases in soluble P-selectin at both 6 and 24 hours after the initiation of the hypoglycemic clamp in nondiabetics.

Plasminogen activator inhibitor 1, a major inhibitor of fibrinolysis, increased during hypoglycemia in both type 1 diabetes mellitus patients and healthy individuals. Plasma tissue plasminogen activator concentrations did not change, with the result that hypoglycemia induced acute reductions in fibrinolytic balance (4).

Wright and colleagues also determined that hyperinsulinemic euglycemia produced a significant decrease in von Willebrand factor from baseline in the diabetic group, indicating a vasculoprotective effect. In the same study, platelet–monocyte aggregation was significantly increased at 24 hours after hypoglycemia in the type 1 diabetes mellitus individuals.

Both laboratories also investigated changes in inflammatory markers. Joy et al. found that the responses of vascular endothelial growth factor to euglycemia and hypoglycemia were significantly different, with significant nadir and peak responses, respectively, in the 2 groups. Similar changes were reported for interleukin-6. These findings are in contrast to those of Wright et al., who reported increases in interleukin-6 for both groups under both study conditions. Joy and colleagues found that tumor necrosis factor α had a significant peak in response to hypoglycemia in type 1 diabetics and showed a significant reduction during hyperinsulinemic euglycemia in the healthy controls. Wright et al. noted a significant increase in CD40 ligand expression on monocytes from baseline during hypoglycemia in individuals with type 1 diabetes, although a significant confounding decrease in plasma CD40 ligand then occurred in the same group during recovery and at 6 hours.

Adiponectin, a cardioprotective and antiinflammatory adipokine, responded significantly differently to euglycemia and hypoglycemia in the control and diabetic groups. Hyperinsulinemic euglycemia elicited significant nadir values for adiponectin in the 2 groups. Adiponectin was not increased significantly during acute hypoglycemia (4). Further research is required to uncover the mechanism of action associated with the present novel observation.

A few conclusions and even more experimental hypotheses can be drawn from the findings described above. First, numerous inflammatory, thrombotic, and atherogenic biomarkers were shown to increase in response to hypoglycemia, results that highlight the possible relevance of hypoglycemia in the underlying causes for the increased prevalence of macrovascular complications in type 1 and type 2 diabetic patients. Importantly, these 2 studies established that hyperinsulinemia, under both experimental conditions, separated the confounding vasculoprotective effects of insulin from the independent effects of hypoglycemia. Indeed, the fact that several biomarkers decreased during hyperinsulinemic euglycemia is in agreement with and lends further support to the already substantial body of evidence demonstrating that insulin confers cardioprotective benefits.

Many research questions remain to be answered. Does the depth or duration of hypoglycemia affect the magnitude of the response of these biomarkers, and at what glycemic level do alterations begin to take effect? How long do such changes last? Wright et al. demonstrated that changes can continue for up to 24 hours after hypoglycemia has been corrected, a result that illuminates the importance of tracking changes after experimental conditions have been terminated. Another intriguing avenue of future research would be an investigation of whether repeated bouts of hypoglycemia blunt or even exacerbate the responses reported by Joy et al. and Wright et al.

Importantly, although these studies demonstrate an association between hypoglycemia and increases in inflammatory, thrombotic, and atherogenic markers, research is needed to identify the mechanisms by which low blood glucose could cause such changes. It is plausible that low glucose concentrations per se can elicit changes within endothelial cells, vascular smooth muscle cells, and platelets; however, with the extensive hormonal changes that occur during hypoglycemia, it is possible that catecholamines, cortisol, or other circulating hormones can induce extensive systemic changes as well.
In conclusion, patients with type 1 and type 2 diabetes have an increased risk of developing macrovascular and microvascular complications, which can lead to increased morbidity and mortality. Hyperglycemia and insulin resistance have been shown to mediate these risks, at least in part. The data summarized above suggest that hypoglycemia may also contribute to processes implicated in the development of acute and progressive vascular disease.

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References