

Proinflammatory and Prothrombotic Effects of Hypoglycemia

Hypoglycemia is known to be intrinsic to the treatment of diabetes because insulin is a powerful glucose-lowering agent and sulfonylureas exert their effect through insulin release by the pancreatic β -cells. Hypoglycemia occurs in association with these two common modes of therapy and was previously accepted as a part of the treatment of this condition. With the arrival of other modes of diabetes treatment, such as metformin, thiazolidinediones, α 2-glucosidase inhibitors, and incretins, which do not induce hypoglycemia except when administered in combination with insulin and sulfonylureas, the issue of hypoglycemia has to be assessed in the context of both the immediate risk related to neuroglycopenia and the possible long-term risk of diabetic vascular complications.

Vascular complications of hypoglycemia have to be tackled with greater urgency now because two recent trials of intensified diabetes treatment with insulin, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Veteran's Affairs Diabetes Trial (VADT), did not demonstrate a reduction in cardiovascular events (1,2). In fact, the intensified insulin treatment arm of the ACCORD trial had to be halted because of an increase in overall mortality, despite a reduction in acute myocardial infarction. The rate of hypoglycemia in both trials was significantly increased with intensified insulin treatment. Although the analysis of the ACCORD data did not support the hypothesis that the increased mortality in the study was a result of hypoglycemia, the fact that hypoglycemia may often be asymptomatic leaves us with the possibility that it may be responsible.

The fact that hypoglycemia results in platelet hyperaggregability (3) and an increase in several factors involved in the coagulation cascade has been known for over 2 decades. Activated partial thromboplastin time is shortened, fibrinogen and factor VIII increase, and platelet counts fall in association with hypoglycemia (4). More recently, two studies have shown that hypoglycemia induces proinflammatory changes including an in-

crease in the plasma concentration of interleukin (IL)-6 (5) and increases in other proinflammatory mediators, including leucocytosis, reactive oxygen species (ROS) generation, lipid peroxidation, and levels of tumor necrosis factor- α (TNF α), IL-1 β , and IL-8 (5). Two studies published in this issue of *Diabetes Care* confirm that hypoglycemia does, indeed, induce an increase in proinflammatory mediators and platelet activation, and has an inhibitory effect on fibrinolytic mechanisms. Wright et al. (6) and Gogitidze Joy et al. (7) both used an insulin infusion to gradually induce hypoglycemia and then clamped glucose at hypoglycemic levels of 2.5 and 2.9 mmol/L, respectively. The former maintained hypoglycemia for 60 min while the latter maintained it for 120 min. As is evident from the data, the effects of the longer duration of hypoglycemia in the study by Gogitidze Joy et al. are more impressive as reflected in the increase in proinflammatory mediators, in spite of the fact that glucose concentrations were not as low as those in the study by Wright et al. The increases in the indexes of inflammation and oxidative stress in the study by Razavi Nematollahi et al. (5) were even more impressive, probably because the mode of induction of hypoglycemia was by a bolus intravenous injection, which led to a rapid fall in blood glucose concentrations leading to a rapid release of catecholamines and the stimulation of the inflammatory response. In the study by Wright et al., hypoglycemia induced an increase in CD40 expression on mononuclear cells and plasma concentration of CD40L, as well as an increase in platelet-monocyte aggregates and P-selectin concentrations with a trend toward an increase in von Willebrand factor concentrations. In the study by Gogitidze Joy et al., hypoglycemia led to an increase in intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), P-selectin, and E-selectin, as well as plasminogen activator inhibitor-1 (PAI-1), TNF α , IL-6, and vascular endothelial growth factor (VEGF).

Both of these studies included control arms in which the effect of insulin infusions administered at the same rates as

above were investigated while maintaining glucose concentrations in the normal range through the appropriate titration of glucose infusion rates. Both studies confirmed the presence of an anti-inflammatory effect of insulin during infusions when euglycemia was maintained (8). Again, the anti-inflammatory effects of insulin were more impressive in the study by Gogitidze Joy et al. because they maintained the infusion of insulin for 120 min, whereas the study by Wright et al. infused insulin for only 60 min. Previous work has consistently shown impressive anti-inflammatory effects of insulin infused for 120 min or more (8). Thus, in situations where insulin infusions are used for the anti-inflammatory and cardioprotective actions of insulin, extreme care has to be exercised because hypoglycemia reverses the effects of euglycemic hyperinsulinemia. It is of interest that hypoglycemia exerts proinflammatory effects similar to those of hyperglycemia and glucose intake (9,10).

Clearly, hypoglycemia results in the induction of rapid inflammatory, platelet proaggregatory, antifibrinolytic, and prothrombotic responses. This effect of hypoglycemia overrides the anti-inflammatory, antiplatelet, and profibrinolytic effects of insulin observed under euglycemic conditions. In addition, there is also an increase in ROS generation and lipid peroxidation, reflecting oxidative stress. Although the hypoglycemic episodes are transient, repeated occurrences of such episodes may have cumulative effects that are detrimental to inflammation-based processes such as atherogenesis and its thrombotic complications. These detrimental effects would add to the previously demonstrated relationship between both silent and symptomatic hypoglycemia on cardiac angina. In one study involving diabetic patients with coronary heart disease who were continuously monitored for blood glucose concentrations and electrocardiographic changes, it was demonstrated that there was chest pain associated with hypoglycemia in 20% of the patients, of whom 40% had concomitant electrocardiogram (ECG) changes consistent with ischemia (11).

Asymptomatic hypoglycemia was also associated with ECG changes of ischemia in 14%. In this study, it was also observed that a rapid fall in glucose of >100 mg/dl per hour was more likely to be associated with chest pain and ECG changes of ischemia. This likely vasoconstrictor effect of hypoglycemia on coronary circulation is also probably attributable to catecholamines. This article does not comment on the occurrence of dysrhythmia; however, the sudden release of catecholamines is also conducive to the induction of abnormal cardiac rhythms. Collectively, therefore, hypoglycemia can trigger a sequence of events that may be extremely detrimental from the cardiac point of view.

It is important to note that the rapidity of the onset of hypoglycemia is also a major determinant of the proinflammatory changes. Further studies are necessary to increase our understanding of the pathophysiology of hypoglycemia and its relationship with inflammation, platelet aggregation, and thrombotic mechanisms. In addition, we also need further information on the effects of the severity, duration, and rapidity of hypoglycemia development. Such studies are even more important and urgent because insulin is now being used in the intensive care setting in very ill patients with profound and severe inflammation in association with the activation of thrombotic mechanisms. To add to these challenges, there are also the contrasting effects of spontaneous hypoglycemia, which carries a bad prognosis, whereas that induced by insulin does not, in patients with acute myocardial infarction (12,13).

Another important aspect of the pathophysiology of hypoglycemia is its effect on the brain. In addition to the obvious short- and long-term effects of neuroglycopenia, the brain is also vulnerable to systemic inflammation because cytokines from the circulation can potentially enter the brain, activate the microglia (the representatives of macrophages in the central nervous system), and activate a damaging, neurotoxic sequence of events (14). Whether hypoglycemia-induced catecholamine release also exerts a proinflammatory effect on microglia requires further investigation (15). It should be noted that repeated hypoglycemia and hypoglycemia-related deaths are associated with significant changes in the

hippocampus and the dentate gyrus (16,17).

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