Background: Ischemic stroke is a leading cause of death and long-term disability, and hyperglycemia is believed to aggravate cerebral ischemia.

Objectives: To review animal and human studies on the relationship between hyperglycemia and brain ischemia that elucidate some of the mechanisms for the deleterious effect of hyperglycemia. To discuss present and future clinical recommendations for glucose control.

Methods: Computerized data sources and published indexes and articles from 1976 through 2000 were searched for human studies that evaluated the association between stroke and hyperglycemia, and studies focused on experimental models of hyperglycemic animals with focal and global brain ischemia.

Results: Most human studies have shown that in acute stroke, admission hyperglycemia in patients with or without diabetes is associated with a worse clinical outcome than in patients without hyperglycemia. This association is more consistent in the nonlacunar type of stroke. Animal studies support these findings by showing both in global and in focal posts ischemic models that hyperglycemia exaggerates the following damaging processes: intracellular acidosis, accumulation of extracellular glutamate, brain edema formation, blood-brain barrier disruption, and tendency for hemorrhagic transformation. Insulin treatment of hyperglycemic animals was found to have a beneficial effect in focal and global brain ischemia, which may be mediated by the glucose-reduction effect or by a direct neuroprotection.

Conclusions: Most studies show the deleterious effect of early hyperglycemia, especially in patients with nonlacunar focal or global ischemia. Clinical trials of intensive insulin treatment are needed. Meanwhile simple measures to avoid excessive hyperglycemia are recommended.

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Diabetes Mellitus is associated with increased risk of stroke and coronary heart disease and remains an independent risk factor for both after adjusting for other known risk factors.1-3 Many studies have shown that patients with diabetes have a less favorable course than those without following myocardial infarction (MI).4,5 Furthermore, stress hyperglycemia in patients without diabetes was found to be associated with increased in-hospital mortality after MI.6 The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study has recently provided compelling evidence that achieving euglycemia during acute MI resulted in a significant reduction of long-term mortality.7 These results have revolutionized the standard care of patients with diabetes and acute MI.

Stroke, the most prevalent disabling disorder in western countries,6 and MI have many similarities. Hyperglycemia has also been associated with worse outcome of ischemic stroke in many human and animal studies. However the associations between diabetes, hyperglycemia, and hyperglycemic control and stroke outcome are still controversial issues. In addition, there are no established guidelines based on controlled studies that define optimal glucose control during acute brain ischemia. These issues will be discussed in this review.

Hyperglycemia vs Diabetes

Several studies9-12 showed that patients with diabetes who develop stroke have a less favorable outcome than those without; however, a few other studies did not confirm these findings.13,14 Interestingly, most studies, including large trials, have shown that admission hyperglycemia is a risk factor for poor outcome following focal and global cerebral ischemia.15-19 Weir
et al\(^1\) performed a long-term follow-up of 750 nondiabetic patients with acute stroke and, after adjusting for age, sex, type of stroke, smoking, and blood pressure, admission hyperglycemia remained a significant independent predictor of long-term higher mortality and morbidity. Data from a multicenter trial (ORG 10172 in acute Stroke Treatment [TOAST]) that included 1259 patients found that in patients with nonlacunar stroke, higher blood glucose levels were associated with worse outcome at 3 months.\(^2\) Adjustments for age, stroke severity on admission, other vascular risk factors, and diabetes mellitus did not alter this result. One possibility is that these studies may have included patients with undiagnosed diabetes, and some smaller studies support this possibility by performing additional laboratory tests for glycosylated hemoglobin showing that prestroke hyperglycemia was a predictor of worse outcome.\(^3\)\(^4\) Other studies, which did not confirm these findings, suggested that admission hyperglycemia is a marker of extensive brain damage leading to a greater increase in stress hormones resulting in hyperglycemia.\(^5\)\(^6\)\(^7\)\(^8\) However, van Kooten et al,\(^9\) who also found a significant association between hyperglycemia on admission and stroke outcome, did not find a correlation between catecholamine and glucose levels, implying that increased stress was not responsible for the hyperglycemia. In conclusion, although the association between admission hyperglycemia and worse outcome in acute stroke has been shown in most studies, it is still unclear whether it is related to diabetes (diagnosed or undiagnosed previously) or to a stress reaction.

A major difficulty in investigating the role of diabetes and hyperglycemia in acute stroke is the heterogeneous nature of diabetes/hyperglycemia in regard to the site of ischemia, the degree of vasculopathy, and the state of reperfusion. For example, in the TOAST trial, higher admission blood glucose levels were associated with worse outcome in nonlacunar strokes.\(^1\) In lacunar strokes, the relationship between hyperglycemia and outcome was inconsistent and differed between those who did and did not receive a low-molecular-weight heparinoid. These observations may be related to the findings in animal models of focal ischemia: in models with reperfusion, hyperglycemia increased infarct size, while in animals without reperfusion, hyperglycemia seemed to have no adverse effect and might even have been beneficial.\(^2\)\(^3\)\(^4\)\(^5\) These findings may be owing to less blood reaching the territory of the end arteries—insufficient blood to cause lactate accumulation and acidosis.\(^2\)\(^3\) Under these conditions hyperglycemia might even be beneficial in maintaining energy metabolism.\(^6\) End-artery infarctions resemble lacunar strokes, which are very common in patients with diabetes.\(^2\) Therefore, studies aimed at evaluating the effect of hyperglycemia on stroke outcome but that do not separate lacunar from nonlacunar strokes may be misleading.

The correlation between hyperglycemia and occurrence of hemorrhagic strokes or hemorrhagic transformations of ischemic strokes is also controversial. Some studies point toward lower frequency of intracerebral hemorrhages in patients with diabetes. In the Copenhagen Stroke Study,\(^7\) intracerebral hemorrhages were 6 times less frequent in patients with diabetes than in those without. Other smaller studies found that hyperglycemia and diabetes may be associated with an increased incidence of hemorrhagic transformation of ischemic infarcts.\(^8\)\(^9\) Hyperglycemia was found to be the only independent predictor of intracerebral hemorrhage in a study of 138 patients with ischemic stroke treated with tissue plasminogen activator.\(^10\) Serum glucose levels higher than 200 mg/dL (11.1 mmol/L) were associated with a 25% symptomatic hemorrhage rate.\(^11\)

**ANIMAL MODELS**

Animal studies have the advantage of controlling parameters such as timing of hyperglycemia, site of ischemia, and state of perfusion, and they provide strong evidence that acute hyperglycemia has a detrimental effect on ischemic brain damage.\(^12\)\(^13\)\(^14\)\(^15\) Mayer and Yamaguchi\(^16\) were the first to show that acute hyperglycemia in monkeys accentuated hypoxic-ischemic brain damage. In their study, the hyperglycemic animals suffered greater neurological deficit with extensive brain damage and widespread necrosis involving the cerebral cortex, basal ganglia, brainstem, and cerebellum than nonhyperglycemic animals.\(^17\) Pulsinelli et al\(^18\) described severe neuropathological changes with brain edema in ischemic brains of hyperglycemic rats. In another study of rats with experimental global brain ischemia, acute hyperglycemia was associated with extensive lesions in the neocortex and striatum compared with only mild damage in normoglycemic rats.\(^19\) Hyperglycemic rats had a marked reduction in neuronal counts compared with the normoglycemic animals, with prominent changes in the vascular endothelium and perivascular reactive microglia. These data suggest that the detrimental influence of hyperglycemia is initially mediated by an action on the vascular endothelium leading to widespread foci of infarction and neuronal loss.\(^20\) In animals with focal ischemia, the results are less consistent; however, hyperglycemia has been shown to increase brain damage in models with temporary ischemia and reperfusion.\(^21\)\(^22\)

Animal models elucidated some of the mechanisms of the deleterious effects of hyperglycemia on the brain. The most consistent finding in animal studies is the correlation between hyperglycemia and acidosis.\(^23\)\(^24\)\(^25\) During an ischemic event, local increase in anaerobic glycolysis leads to intracellular acidosis occurring shortly after the ischemic insult. Animals with acute hyperglycemia developed the most acidic mean cortical pH as well as higher cerebral lactate concentration, leading to an increase in neuronal and glial damage.\(^26\)\(^27\) Enhanced acidosis may exaggerate ischemic damage by mechanisms such as increasing free-radical formation, perturbing intracellular signal transduction, and activating endonucleases.\(^28\) A direct effect of lactic acid accumulation has been proposed, based on studies in which injection of lactic acid into the cerebral cortex led to histological changes resembling ischemic infarction.\(^29\)\(^30\)

The second mechanism that links hyperglycemia to increased brain damage is the effect of hyperglycemia on excitatory amino acids. It has been established that excitatory amino acids, notably glutamate, play a central role in neuronal death by activation of postsynaptic glu-
Hyperglycemia in animal models of brain ischemia was found to exaggerate edema formation, 44,45 blood-brain barrier injury, 44 and hemorrhagic transformation of the infarct. In a model of middle cerebral artery occlusion, a 5-fold increase in hemorrhagic infarct and a 25-fold increase in extensive hemorrhages were observed in hyperglycemic cats compared with the normoglycemic animals. 46

Hyperglycemia in patients with acute stroke and mild to moderate insulin and IGF-1 have a direct neuroprotective effect on the central nervous system parenchyma. In contrast to global ischemia, insulin therapy reduces ischemic brain damage and may be neuroprotective. 48-55 In a model of forebrain ischemia in rats, insulin not only reduced histological injury but improved neurobehavioral outcome. 9,50

It is still unclear whether this effect is due only to the effect of insulin on reducing glucose levels or is a direct effect. 48 In a global ischemic model, it was found that insulin has an effect in reducing neuronal necrosis in the major brain regions regardless of its effect on glucose levels. 51 In addition, insulin, and to a lesser extent insulin-like growth factor 1 (IGF-1), reduced ischemic damage when injected directly into the brain ventricles. 52 Therefore, it was suggested that in transient global ischemia, insulin and IGF-1 have a direct neuroprotective effect on central nervous system parenchyma. In contrast to global ischemia, in focal ischemia most of the neuroprotective effects of insulin are due to its effect on glucose levels, and administration of a glucose infusion concomitant with insulin abolished most of its effect. 53 In minimizing acute brain ischemia, insulin may also have a beneficial synergistic effect when, for example, used concomitantly with dizocilpine, a noncompetitive NMDA antagonist. 39,40 A study comparing treatment of diabetic rats during acute ischemic events with dizocilpine alone or with a combination of dizocilpine and insulin found an additive neuroprotective effect. 39

We do not yet have the results from controlled clinical trials evaluating the effect of insulin in stroke. Recently, a randomized clinical controlled trial (The Glucose Insulin in Stroke Trial [GIST]) was started. 55 This study is designed to determine whether glucose-potassium-insulin infusion and maintaining euglycemia in patients with acute stroke and mild to moderate hyperglycemia can improve outcome.

TREATMENT

The “ischemic penumbra” is the region surrounding a focal cerebral infarct showing selective neuronal damage with loss of electrical activity while retaining some metabolic viability. 56 This area might be rescued by improving the metabolic milieu and arresting the ischemic cascade. 57 An accumulating body of evidence derived from animal models shows that during acute focal and global ischemia, insulin therapy reduces ischemic brain damage and may be neuroprotective. 48-55 In a model of forebrain ischemia in rats, insulin not only reduced histological injury but improved neurobehavioral outcome. 9,50

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