Until recently, few authors have emphasized the difference between hyperglycemic and hypoglycemic brain damage as each relates to strokelike symptoms.\(^1\)\(^-\)\(^4\) In addition, although it is generally recognized that diabetes is associated with increased risk and worse prognosis from stroke, few pathological reports have defined the vascular pathology of diabetes-related stroke. Hyperglycemia as a metabolic derangement may predispose to cerebral infarction in the presence of ischemia or anoxia and a worse prognosis from these injuries. Subgroups of patients with stroke may be differentially vulnerable to the insults of elevated blood glucose. Current knowledge about the relationship between glucose and stroke will be reviewed.

**Hypo- Versus Hyperglycemia**

Elevated blood glucose has been implicated both as a risk factor for stroke and for a worse prognosis from cerebral ischemia and hemorrhage. Hypoglycemia may be associated with strokelike symptoms.\(^1\)\(^-\)\(^3\) Hypoglycemic brain damage and the poorly understood mechanisms that cause transient attacks of hemiplegia and aphasia are not the same as those seen in cerebral ischemia.\(^3\)\(^-\)\(^4\) When permanent pathological changes of brain tissue are due to hypoglycemia, there is a selective loss of neurons of more than one type in the superficial and paraventricular layers of the cerebral cortex and hippocampus, especially the dentate gyrus of the latter.\(^3\) Ischemia, on the other hand, causes selective loss of one type of neuron, depending on the brain region involved (for example, the pyramidal cell in the deeper middle cortex layers 3, 5, and 6 and in the CA1 region of the hippocampus). However, brain cell death is not limited to the neurons as in hypoglycemia; glial and endothelial cells also die in ischemic infarcts.

During hypoglycemia brain lactate does not rise, and tissue pH does not fall. Also, the drop in ATP energy is not as significant as that seen in ischemia because fuels other than glucose are used.\(^3\) Blood supply is not a critical determinant of cell death in hypoglycemia.\(^5\) The structural damage of hypoglycemia is greatest in the cerebrum, whereas in ischemia cerebellar Purkinje cells are also prominently damaged. Hypoglycemia disrupts dendritic trees but, unlike ischemia, spares axons. Neuronal death occurs as membranes disrupt at the perikaryon. In ischemia lactic acidosis occurs, and ATP levels drop in cerebral tissues. Cerebral blood flow is intimately related to tissue survival. The blood–brain barrier is disrupted, cell membranes lose their gated pumps, cells become acidic and die, and tissue edema forms. Both hypoglycemic and ischemic cell death are affected by excitotoxin release and ultimate calcium entry into the cell. However, the cell receptors involved, their location, and the specificity and origin of excitotoxins released have yet to be definitively identified. Hyperglycemia accentuates ischemic cerebral tissue damage.\(^4\)\(^,\)\(^6\) Since rapid correction of blood glucose during hypoglycemia might promote hypoperfusion and an elevation of brain lactate to above-normal levels, Auer\(^3\) has suggested that stroke might occur in this setting secondary to lactic acid-induced infarction. It remains to be determined if and how often this occurs. Under such circumstances it would be impossible to distinguish clinically and pathologically whether infarction or hypoglycemia was the initiating insult leading to brain damage.

Since hypoglycemia does not cause stroke, the rest of this discussion will focus on the relationship of hyperglycemia and cerebral infarction and hemorrhage.

**Hyperglycemia and Intracerebral Hemorrhage**

Little has been written about the association of elevated blood glucose with intracerebral hemorrhage. In an attempt to correlate the clinical course, computed tomographic (CT) findings, and 30-day mortality, Mohr et al reported that in the NINCDS Pilot Stroke Data Bank series of acute stroke patients, elevated blood glucose levels during the first 7 days after the onset of stroke from hematoma were associated with greater incidence of mortality at 30 days. Similarly, Melamed\(^8\) showed a correlation between hyperglycemia in hemorrhagic stroke (intracerebral, intraventricular, subarachnoid), clinical severity (coma), and poor prognosis (mortality). In a large number of necropsies, Kane and Aronson\(^9\) found a lower incidence of intracerebral hemorrhage and arteriolar necrosis in diabetics with hypertension than in people with hypertension and no diabetes. Peress et al\(^10\) reported an autopsy...
series in which there was a decreased frequency of cerebral hemorrhage in diabetics. Cerebral hemorrhage occurred more commonly in nondiabetics in the necropsy group of Alex et al. Therefore, although elevated blood glucose at the time of intracerebral hemorrhage may correlate with poor prognosis for the patient, long-term hyperglycemia, defined as diabetes mellitus, does not appear to affect the occurrence of intracerebral hemorrhage. In patients with cerebral hemorrhage, increased catecholamine release could cause an increase in blood sugar. Hyperglycemia then would be the epiphenomenon of the hemorrhage, not the cause.

Hyperglycemia and Infarction in Diabetes

Much more is known about the relation between elevated blood glucose and cerebral infarction. In large necropsy series an increased incidence of cerebral infarction has been found among diabetics. Diabetes is an independent risk factor for atherothrombotic brain infarction at all ages. Although there is a strong relationship between diabetes and hypertension and although diabetics are predisposed to coronary artery disease, the increased occurrence of ischemic strokes in diabetics is not fully accounted for by these facts. The type and topography of diabetes-related cerebral infarction may differ from brain infarcts in nondiabetics. Diabetes may be a risk factor for lacunar infarction.

Kane and Aronson found that diabetics had more lacunar lesions, especially in the distribution of "parasagittal perforating arteries" feeding the basal ganglia, thalamus, pons, and cerebellum. Peress et al also found that the frequency of these infarcts was greater in diabetics and increased as they aged. Like Kane and Aronson, Peress et al found that cerebral hemispheric lesions in diabetics showed more "diencephalic" involvement in paramedian tissues supplied by short small perforators. Diabetics also had more infratentorial infarcts, again increasing as they became older. Most infarcts in diabetics of all ages occur in the pons in tissue supplied by paramedian perforators off the basilar artery.

While Alex et al found a higher frequency of all types of cerebral infarction in diabetics, the incidence of small lesions and of proliferative vascular disease of small intraparenchymal cerebral vessels was particularly high. Histologically, the lesions consisted of proliferation of the endothelium with periodic acid-Schiff (PAS)-positive fine fibrillary structures interwoven between the endothelial cells of small intracerebral arteries, veins, and meningeal veins. Reske-Nielsen et al studied the brains of diabetics who were presumably free of long-standing hypertension and other maladies in an attempt to define cerebral changes specific to diabetes. The diabetic "angiopathy" described by these authors was similar to the vascular lesion found more frequently in the diabetics of the autopsy series of Alex et al.

Vascular lesions consisted of two types. The changes seen in large and medium-sized vessels and in smaller arteries and arterioles differed from capillary pathology. Large, medium-sized, and smaller arteries and arterioles showed changes indistinguishable from atheroma; the smaller vessel findings were consistent with microatheroma and were characterized by fibrils in the walls that stained PAS-positive, correlating, where heavy, with occlusion. Capillaries showed diffuse and focal thickening of the basement membrane. Some smaller arteries had walls totally transformed to lipid, few to hyalin. Furthermore, the diabetic angiopathic lesions correlated with areas of tissue necrosis at sites corresponding to clinical focal neurological deficits in life. Dejong found advanced atheromatous changes in the pial cortical vessels of a young diabetic patient with hemiplegia as well as thickened capillaries and deep white matter atheromatous arteriolar disease; in some instances there was hyalinization of arteriolar walls. Caplan and coworkers reported a preponderance of diabetics among patients with intracranial atheroma of the vertebral arteries and proximal middle cerebral artery (MCA) in patients with intracranial disease of the carotid artery. However, diabetes may not be an independent risk factor for extracranial carotid disease as it would appear to be for atheroma at other body sites. Diabetics may be predisposed to intracranial atheroma of large, medium-sized, and smaller vessels as well as to microangiopathy of arterioles and capillaries.

Although the increased incidence of stroke and poor outcome in diabetics might be explained by the intracranial lesions just described, which could lead to intracranial vascular thrombosis and occlusion with poor collateral circulation, other abnormalities of questionable impact on incidence and prognosis from stroke have been noted in diabetics. Poor prognosis in diabetics with stroke may be related to an increased incidence of cardiac death. Diabetics have chronic impairment of cerebral blood flow and autoregulation, lower white and red blood cell deformability, hyperviscosity, endothelial cell dysfunction, hypercoagulability, impaired prostacyclin synthesis that increases platelet adhesiveness, and possible dysfunction of cortical arteriolar smooth muscle and endothelium, which are important for collateral flow. Alternatively, hyperglycemia, when present at the time of ischemia, may play a key role in infarct production and the outcome from ischemia in diabetics.

Hyperglycemia in Nondiabetics and Diabetics

Hyperglycemia may predispose to infarction when present at the time of ischemia and to poor recovery from stroke. Recent evidence suggests that its role may be more important for a particular subgroup of stroke types, thus explaining current disagreement about the prognostic significance of elevated blood glucose for stroke outcome.
Hyperglycemia commonly precedes stroke in those with previously undiagnosed diabetes. Davis et al45 reported that recent onset of hyperglycemia was a more important risk factor for stroke than long-standing diabetes and that there is a short median time between the onset of diabetes and stroke. Candelise et al44 found larger lesions and worse neurological deficits by CT in nondiabetic patients with elevated blood glucose at the time of stroke. Pulsinelli et al39 reported that both diabetics and nondiabetics who were hyperglycemic at the time of stroke, as measured by admission blood glucose, did worse. Berger and Hakim43 noted more profound cerebral edema on CT and worse clinical outcome in both diabetic and nondiabetic patients with elevated blood glucose during the first 10 days after the onset of nonlacrural anterior circulation infarction. However, Mohr et al7 and Adams et al41 deny the prognostic significance of elevated admission blood glucose (above normal range) at ischemic stroke onset, but they included all vascular territories and stroke types in their analyses. Interestingly, Berger and Hakim43 did not find any impact of a history of diabetes on stroke-related edema or outcome. Likewise, Cox and Lorains,38 excluding brainstem infarcts, reported that hyperglycemia at the time of the ischemic stroke is more important for prognosis than a history of diabetes as indicated by elevated glycosylated hemoglobin (HbA1c). Cox and Lorains38 also reported a death in a patient given intravenous glucose during the acute stroke period. Helgason40 reported that hyperglycemia with elevated glycosylated hemoglobin and elevated fasting admission glucose levels, when present in the same patient at the time of ischemic stroke, correlated with poor outcome, whereas a history of diabetes or sole elevation of glucose poststroke did not.

Hyperglycemia in Laboratory Animals

Animal models of hyperglycemia at the time of cerebral infarction have shown larger infarcts and worse prognosis due to increased tissue and cellular acidosis and lactate levels. In the laboratory hyperglycemia induced after brain ischemia has occurred appears to have no adverse effect.46 Ginsberg et al47 found no correlation between elevated glucose levels and outcome or edema from infarct, but they used an animal model that caused stroke at an end-artery site, presumably where collateral circulation and a graded ischemic penumbra are absent. Edema and acidosis may be most important for tissue survival in the face of continued blood supply, metabolism, and anaerobic glycolysis because glucose arrives via collaterals and promotes lactic acidosis. There is evidence that after ischemia in non-end-artery territories, the damage is worse the higher the arriving glucose levels.48,49 However, it appears that if the infarct rim receives markedly reduced blood supply, hyperglycemia is detrimental, but if the blood supply is just slightly reduced, then glucose may be beneficial.47,50 In end-artery infarction the amount of glucose arriving at the hypoxic ischemic infarct edge is minimal and, therefore, may not be detrimental for edema formation or necrosis. End-artery infarction may be analogous to lacunar infarcts in man.

Site, Size, and Type of Infarct and Meaning of Hyperglycemia

The discrepancies in the relationship of hyperglycemia and stroke outcome might be explained by the different cerebral sites analyzed in clinical studies. It may be that lacunar infarcts fare better in the face of hyperglycemia. Because the NINCDS Pilot Stroke Study7 and the series of Adams et al41 looked at all infarct patients, including those with lacunes, hyperglycemia appeared less detrimental than if only MCA infarcts, for example, were studied. The strokes of Berger and Hakim43 involved large or medium-sized vessels and were in the MCA or anterior cerebral artery territories where collaterals and glucose supply to the ischemic penumbra are important. Further patient studies differentiating the cerebral vascular distribution of infarction are needed to assess the importance of hyperglycemia for prognosis in stroke of certain types and in occlusion in different vascular territories.

Hyperglycemia may be a response to stroke or may be caused in the setting of acute stroke by intravenous infusions or preexisting hyperglycemia. Berger and Hakim43 claim that lesions were similar in all patients on initial CT, and they argue that large infarcts and edema were ultimately the result and not the cause of acute stroke hyperglycemia. Cerebral site and type of stroke may play some role in the production of what may be “stress hyperglycemia.” Melamed8 found more elevated blood glucose levels in hemorrhagic stroke and brainstem infarcts than in strokes in other locations, and Longstrength et al51 suggest that in patients who do poorly after cardiopulmonary resuscitation, the amount of hyperglycemia is a reflection of the severity of brain ischemia and not its cause. Again, analysis of infarct location and correlation with poststroke glucose levels will define the importance of cerebral site for “stress hyperglycemia.”

Therapeutic Implications

Although diabetics may have increased intracranial atheroma and microvascular disease, it has not yet been shown that better control of blood glucose levels decreases the incidence of the cerebral lesions or improves the prognosis for stroke in these patients. No final conclusion can be made regarding the cause of hyperglycemia in patients with acute stroke, whether due to new-onset diabetes, stroke site or type, catecholamine release, or the use of medications (intravenous glucose). The prognostic significance of elevation of blood glucose in acute stroke may differ for different stroke types. Thus, with large and medium-sized vessel
apply to lacunar strokes. 47 Likewise, when hypo-

Thus, the interplay between hyperglycemia and collateral flow in the ischemic penumbra may be poor. However, if collateral flow is good, glucose might be needed in the penumbra.49-50 Lowering therapies in acute stroke (Figure 1).


Figure 1. Possible interrelationship between hyperglycemia and stroke.

References
5. Auer R, Hall P, Ingvar M, Siesjo BK: Hypotension as a complication of hyperglycemia leads to enhanced energy failure but no increase in neuronal necrosis. Stroke 1986; 17:442-448

dermacy infarcts where collaterals are of prime importance for tissue survival, perhaps hyperglycemia from the addition of intravenous glucose should be avoided, and treatment with insulin to maintain glucose in modest ranges should be instituted if collateral flow is poor. However, if collateral flow is good, glucose might be needed in the penumbra.49-50 Thus, the interplay between hyperglycemia and collateral flow in the ischemic penumbra may be significant for tissue survival. Different rules may apply to lacunar strokes.47 Likewise, when hypotension or vessel occlusion is present during surgery, intraoperative ischemic complications might be diminished by avoiding hyperglycemia from glucose infusions or use of anesthetic agents that accentuate hyperglycemia.48 Future studies are needed to define the roles played by ischemic neuroanatomical site and vascular occlusion type as each relates to elevated glucose levels, collateral flow measurement, and outcome from stroke. Until these issues are clear, no definite recommendations can be made about the use of glucose or glucose-lowering therapies in acute stroke (Figure 1).
Blood glucose and stroke.
C M Helgason

Stroke. 1988;19:1049-1053
doi: 10.1161/01.STR.19.8.1049

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/19/8/1049.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/