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Cerebrovascular Disorders

Diabetes Mellitus, Acute Hyperglycemia, and Ischemic Stroke

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Opinion statement

Acute brain ischemia is a dynamic process susceptible to multiple modulating factors, such as blood glucose level. During acute ischemic brain injury, hyperglycemia exacerbates multiple deleterious derangements. Timely and sufficient correction of hyperglycemia during acute brain ischemia may limit the brain injury and improve clinical outcomes. The clinical efficacy of such intervention remains to be proven. Although results from animal and clinical observational studies suggest that hyperglycemia during acute brain ischemia may exacerbate the brain injury, there is no evidence from randomized treatment trials that rapid correction of the hyperglycemia improves outcomes. Given the excess effort, cost, and risk involved in rapid and safe correction of hyperglycemia during acute stroke, less aggressive treatments with subcutaneous insulin seem appropriate at this time. Subcutaneous insulin protocols can maintain blood glucose levels below 200 mg/dL a majority of the time in most patients, especially if basal insulin is added. When available, an endocrinology consultant can optimize the acute treatment and help the transition to long-term care. Given the multiple reports linking admission hyperglycemia with symptomatic hemorrhagic conversion of ischemic stroke treated with thrombolytic drugs, it may be best to rapidly lower severe hyperglycemia in such patients. For example, if the admission blood glucose is approximately 300 mg/dL and the patient is a candidate for thrombolytic therapy, consider giving an intravenous bolus of regular insulin 8 units. Somewhat lower or higher insulin doses may be best for lesser or greater hyperglycemia. Such a bolus will start lowering the blood glucose in about 5 min. A temporary continuous intravenous insulin infusion may then be used in most patients to maintain the glucose closer to normal levels (eg, below 180 or 140 mg/dL).

Introduction

Blood glucose regulation involves intestinal absorption, release into the bloodstream from glycogen stores (glycogenolysis), synthesis (gluconeogenesis) and release into the bloodstream, transport from blood into interstitial spaces and cells throughout the body, and urinary excretion. Levels of blood glucose fluctuate more rapidly and to a greater extent than levels of any other metabolite. Such glucose fluctuations are greater in patients with insulin resistance and during acute illness. Either excessively low or high blood glucose levels have well-known complications. This review focuses on hyperglycemia.

Although the complications of chronic hyperglycemia and acute hyperosmolar severe hyperglycemia are well known, the complications of acute (stress) moderate hyperglycemia are not. Approximately 40% of patients with acute ischemic stroke have admission hyperglycemia (>130 mg/dL) [1,2], and the majority of such patients have diabetes mellitus. The hyperglycemia during acute stroke reflects both a spectrum of acute stress and a spectrum of insulin resistance. Our ability to correct glucose deviations rapidly may have important clinical implications in patients with acute ischemic stroke. Here we summarize the data about hyperglycemia during acute ischemic stroke and how it relates to outcomes. We also offer suggestions for treating hyperglycemia during acute stroke.

Diabetes and risk of stroke

Diabetes mellitus, through chronic hyperglycemia, has been linked with accelerated development of both microvascular disease and atherosclerosis throughout the body. Consequently, diabetes mellitus increases the combined risk of stroke and myocardial infarction by about 2.5 times [3] and the risk of stroke alone 1.7 to 2.1 times [4,5], compared with otherwise similar patients without diabetes. Diabetes also increases the risk of stroke after a transient ischemic attack (TIA), as it represents one of the Ds in the $ABCD^2$ score, which includes age (0 or 1), blood pressure level (0 or 1), clinical stroke symptoms (0, 1, or 2), duration of the TIA symptoms (0, 1, or 2), and diabetes (0 or 1) [6]. Risk of stroke increases with increasing $ABCD^2$ score, within the range from 0 to 7.

Thus it is reasonable to expect that better control of chronic hyperglycemia may reduce the incidence of vascular events. This hypothesis was tested in five randomized clinical trials totaling 33,040 patients: strict glycemic control lowered the hemoglobin A1C by 0.9% (from 7.5% to 6.6%) compared with standard therapy [7]. In these five clinical trials, strict glycemic control lowered the rate of coronary events, but not stroke or death. A reason for these findings is not readily apparent.

Elevated fasting glucose or diabetes mellitus in combination with other, interrelated vascular risk factors has been defined as the *metabolic syndrome* [8]. Because of the coexistence of multiple vascular risk factors, patients with the metabolic syndrome have a higher risk for vascular outcomes than those with a single risk factor. The International Diabetes Federation has defined the metabolic syndrome as central obesity plus two of the following four additional derangements: 1) elevated triglycerides, 2) decreased HDL cholesterol, 3) elevated blood pressure, and 4) elevated fasting plasma glucose. Thus, although all patients with the metabolic syndrome have central obesity, they are somewhat heterogeneous with respect to the other risk factors. Consequently, treatment for the metabolic syndrome is individualized and not

specific to the syndrome. It appears that each risk factor within the metabolic syndrome should be identified and treated as indicated, and that classification into this syndrome offers no clear advantage.

Can animal stroke hyperglycemia studies lead to optimized clinical trials?

Although animal studies usually precede clinical trials, there is a risk that positive findings in animals will not translate to similar clinical results [9]. In most animal studies, acute hyperglycemia immediately before or during ischemia exacerbates the ischemic brain injury [10–13]. Compared with normoglycemic animals, animals with ischemic stroke and hyperglycemia tend to have more brain edema, hemorrhagic transformation of infarcts, brain herniation, and death. However, not all animal studies confirm such observations. The exacerbated damage with hyperglycemia is usually seen in animal ischemic stroke models with reperfusion and occurs less with permanent occlusion [12,14]. This finding suggests that reperfusion of ischemic brain may be an important factor leading to increased brain damage by hyperglycemia [13].

Relatively few animal interventional studies have looked at the effects of hyperglycemia correction in focal brain ischemia [11,15–17]. Some animal interventional studies show a benefit related to reduction of the acute hyperglycemia. Unfortunately, many of the animal studies do not seem clinically relevant because the models involved global and not focal brain ischemia, the glucose levels were unusually high, or the hyperglycemia was corrected around the time that the ischemia began. In some studies using insulin, the animals became severely hypoglycemic (<45 mg/dL), had seizures, and died. One such study reported a *U*-shaped curve indicating optimal outcome at a glucose level of about 126 mg/dL and worsening outcomes below and above this level [17].

In an acute ischemic stroke interventional study in rats, one group of 10 rats was made hyperglycemic (555 mg/dL) for 2 h before and 2 h after permanent middle cerebral artery (MCA) occlusion, another group of ten was made diabetic (blood glucose, 542 mg/dL) 4 days before the MCA occlusion and was not treated, another group of ten was made diabetic and was treated with insulin since 2 days before the MCA occlusion (blood glucose, 176 mg/dL), and 15 rats were used as controls (blood glucose, 156–176 mg/dL) [15]. Infarct volumes were larger with acute hyperglycemia (161 mm^3) and with untreated diabetes (190 mm^3) than with insulin-treated diabetes (131 mm^3) or in controls (121 mm^3). However, a therapeutic effect cannot be translated to clinical acute stroke, as insulin treatment was started 2 days before the MCA occlusion, and blood glucose levels at the time of MCA occlusion were similar to those in the control group.

Unfortunately, the animal studies so far have not established a clear relation between the degree of hyperglycemia and extent of acute ischemic brain injury. Is the relationship linear, as suggested by some clinical studies? Also, a therapeutic time window for hyperglycemia correction has not been established. Is it crucial (as with thrombolytic therapies) to inter-

vene as early as possible for best results? If so, how far does this therapeutic window extend?

Can nonstroke acute hyperglycemia correction clinical trials be extrapolated to stroke?

Randomized trials have studied aggressive correction of hyperglycemia in multiple acute illnesses, with varied results. The most convincing positive trial was the surgical intensive care unit (SICU) trial, in which postsurgical ventilated patients were randomized to aggressive or standard correction of hyperglycemia while in the SICU [18, Class I]. Patients treated aggressively had considerably lower mean glucose levels (by about 50 mg/dL) and better clinical outcomes than patients under standard care. Significant benefits associated with aggressive hyperglycemia correction included decreased mortality, shorter time on ventilator, fewer bloodstream infections, and less critical-illness polyneuropathy. A similar trial with patients in the medical intensive care unit (MICU) showed less convincing results, without a statistically significant difference in the primary outcome (mortality) [19, Class I]. However, mortality among patients who stayed in the MICU for at least 3 days (secondary outcome) was significantly reduced in the aggressive insulin treatment group. The mean blood glucose difference between the treatment groups in that trial was about 51 mg/dL.

In the latest ICU trial of hyperglycemia correction, 6104 patients were randomized to intensive or standard treatment for three or more days [20, Class I]. The mean blood glucose was about 35 mg/dL lower in the intensive group than in the standard group. The primary outcome, death, was more common in the intensive treatment group (27.5%) than in the standard treatment group (24.9%; $P=0.02$). This treatment effect was similar among medical and surgical ICU patients. Severe hypoglycemia (<40 mg/dL) occurred in 6.8% of patients in the intensive group and 0.5% of those in the standard group.

One trial tested the efficacy of aggressive hyperglycemia correction in patients with sepsis [21]. The mean glucose levels were 39 mg/dL lower in the aggressive-treatment group than in the usual-care group. That trial was stopped early because of safety concerns about excess severe hypoglycemia (<40 mg/dL) in the aggressive-treatment group (17.0% vs 4.1% in the control group). The severe hypoglycemia in the aggressively treated group was associated with a significantly higher rate of serious adverse events (10.9% vs 5.2% in the control group).

Three randomized clinical trials of hyperglycemia correction in acute myocardial infarction have been reported [22–24]. Only the first trial showed significant benefit from aggressive insulin treatment [23]. In that trial, the mean glucose levels were 38 mg/dL lower in the aggressive-treatment group than in the control group, and mortality at 1 year (18.6%) was significantly reduced versus the control group (26.1%). In the two later randomized trials, the mean glucose differences between the treatment groups were smaller (12–16 mg/dL), which may have contributed to a neutral (no benefit) result.

Two randomized trials studied the effects of aggressive hyperglycemia correction during coronary artery bypass surgery [25,26]. The smaller trial (N=141), in patients with diabetes mellitus and with a mean blood glucose difference between the two treatment groups of 122 mg/dL, showed a benefit related to the aggressive intervention [26]. However, the larger trial (N=400), in patients mostly without diabetes and with a mean glucose difference between the two treatment groups of 43 mg/dL, did not show a benefit [25].

These nonstroke illnesses involve considerably different pathophysiologic processes than acute brain ischemia and therefore are not comparable to stroke. The effects of hyperglycemia on acutely ischemic myocardium are likely to be much different than its effects on acutely ischemic brain cells. Also, much of the benefit from aggressive hyperglycemia reduction in the SICU trial could be attributed to reductions in critical-illness polyneuropathy and bloodstream infections, which are not applicable to most patients with acute stroke.

Observational acute stroke hyperglycemia studies

Human studies have largely been observational, and most of them show an association between hyperglycemia and inferior clinical outcomes from acute ischemic stroke [10,27•,28,29]. The higher the glucose level during acute ischemic stroke, the worse the outcomes are. Some studies suggest a linear decrease in favorable outcomes as blood glucose increases [30,31]. One study found that during the initial 48 h of acute ischemic stroke, maximum glucose of 155 mg/dL was the best cutoff for predicting outcome [32]. In that study, however, the area under the receiver operating characteristic curve was only 0.66 (closer to 0.5 than to 1.0), indicating that this is not a distinct cutoff. Some findings suggest that patients with acute lacunar strokes (small subcortical infarcts caused by occlusion of small penetrating arterioles) have better outcomes with hyperglycemia [30,33•]. This result may be important and deserves further study.

One study analyzed the relation between acute hyperglycemia and recanalization in 139 patients with MCA occlusion treated with intravenous tissue-type plasminogen activator (tPA) [34]. The MCA occlusion was documented and followed with transcranial Doppler. After adjusting for stroke etiology and risk factors, poor recanalization was associated with admission hyperglycemia (>158 mg/dL, P=0.03), proximal MCA occlusion (P=0.03), and platelet count greater than 219,000/mL (P=0.03). However, chronic hyperglycemia determined by hemoglobin A1C and fructosamine had no relation to recanalization. The investigators attributed the decreased recanalization associated with hyperglycemia to antifibrinolytic and hypercoagulable effects of hyperglycemia. The favored explanation was that glycation of the regulatory protein annexin II increases the formation of plasminogen/tPA/annexin complexes, which interfere with fibrinolysis. The investigators also considered that hyperglycemia increases plasminogen activator–inhibitor concentrations.

We studied the relation between admission hyperglycemia and recanalization in 53 consecutive patients with proximal MCA occlusion treated with endovascular procedures by the University of California at Los Angeles

(UCLA) Stroke Service between 2004 and 2009. Recanalization was classified by the Thrombolysis In Myocardial Infarction (TIMI) method: poor (no or incomplete poststenotic arterial filling, TIMI 0–1) or adequate (slow, but complete, or normal poststenotic arterial filling, TIMI 2–3) using serial magnetic resonance arteriograms. Patients with poor recanalization had somewhat higher admission blood glucose (154 vs 139 mg/dL; $P=0.66$, Mann-Whitney test) and a higher rate of hyperglycemia (>140 mg/dL) (44% vs 23%; $P=0.10$, chi-square test) than patients with adequate recanalization. Our findings are consistent with the previous similar studies; our sample size is likely too small to show statistical significance.

Another important observation is the association between hyperglycemia and hemorrhagic transformation of infarcts. Patients with higher admission glucose levels are more likely to have a hemorrhagic conversion of their infarct [29,31,35,36]. We studied the relation between hyperglycemia and serious hemorrhagic transformation of infarcts in the same 53 consecutive patients just discussed. Serious hemorrhagic transformation was determined by serial MRI as confluent parenchymal hemorrhage with some mass effect within 24 h after stroke onset. Patients with serious hemorrhagic transformation had somewhat higher admission glucose levels (159 versus 140 mg/dL; $P=0.19$, Mann-Whitney test) and a higher rate of hyperglycemia (>140 mg/dL) (50% vs 24%; $P=0.09$, chi-square test) than patients without serious hemorrhagic transformation. This finding is also consistent with previously published observations in patients treated with thrombolysis, and this complication also has been reported in animal studies [37,38].

In addition to clinical outcomes, there is MRI evidence of ischemic stroke worsening with hyperglycemia [39–42]. Higher blood glucose levels have been associated with greater acute infarct growth compared with lower glucose levels, based on acute and delayed diffusion and perfusion MRI. However, one study found that in a small subgroup ($N=11$) of acute stroke patients with persistent arterial occlusion, treatment of hyperglycemia with intravenous insulin was associated with greater infarct growth [43]. Additional studies are needed to clarify these interesting observations.

How might hyperglycemia exacerbate ischemic brain injury?

The reproducible associations reported between hyperglycemia and poorer outcomes suggest a potential causal relationship. Multiple physiologic mechanisms have been proposed for how hyperglycemia might exacerbate ischemic brain injury (Table 1). The relative importance of the various injury-exacerbating mechanisms has not been established.

Much attention has been devoted to the study of brain lactate accumulation and brain acidosis due to hyperglycemia, but lactate has not been shown to exacerbate acute ischemic brain injury in animal studies [27•] or in a pilot clinical stroke trial [43].

Another potential mechanism by which hyperglycemia may exacerbate ischemic brain injury occurs at the level of microcirculation. Hyperglycemia can induce a variety of detrimental changes in cerebral endothelial cells within hours [13]. Acute hyperglycemia can impair cerebrovascular autoregulation, resulting in deleterious reperfusion predisposing to hemorrhagic

Table 1. Derangements exacerbated by hyperglycemia during brain ischemia in animal studies, clinical studies, or both[a]

Brain acidosis and increased lactate
Cytotoxic brain edema
Hemorrhagic transformation of infarcts
Impaired thrombolysis
Blood-brain barrier disruption
Cytotoxicity, slowed calcium recovery
Impaired ATP/energy recovery
Accumulation of free radicals
Impaired vascular reactivity
Stimulated inflammatory reactions

[a]The relative importance of these derangements has not been established
ATP—adenosine triphosphate

transformation of infarcts. Hyperglycemia can also stimulate inflammation through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to upregulation of intracellular adhesion molecule 1, vascular cellular adhesion molecule 1, and E-selectin [13]. The adhesion molecules promote leukocyte adhesion to post-capillary venule walls, obstructing flow [44].

Hyperglycemia can also increase levels of plasminogen activator inhibitor 1 (PAI-1) by post-translational modification of proteins [13]. PAI-1 interferes with the actions of tPA, reducing the chance of early brain reperfusion. Another apparently important exacerbating mechanism of acute ischemic brain injury with hyperglycemia is the accumulation of free radicals. One study showed that glucose donates electrons to form superoxide radicals that exacerbate the injury during acute brain ischemia [45].

Randomized clinical trials in acute stroke with hyperglycemia

The supporting data outlined above have inspired five randomized pilot clinical trials of rapid hyperglycemia correction in acute ischemic stroke [43,46–49]. These pilot trials have demonstrated the relative safety and feasibility of rapid hyperglycemia lowering with intravenous insulin as compared with subcutaneous insulin during acute stroke. These small pilot trials were not intended to show clinical efficacy of the intravenous insulin intervention.

One efficacy trial in acute stroke with hyperglycemia has been completed, the GIST-UK (Glucose Insulin Stroke Trial—United Kingdom) [50•, Class I]. In this trial, 933 acute stroke patients without previous insulin treatment were randomized within 24 h after stroke onset to infusions of normal saline or insulin for 24 h. The mean admission glucose level was similar in the two treatment groups (137–141 mg/dL), and during treatment the difference in mean glucose between the two groups was only 10 mg/dL. The only worrisome complication was an increase in mortality associated with the largest drops in blood glucose levels in the insulin-treated group. There were no significant differences in clinical outcomes, including mortality, neurologic def-

icit, and handicap, between the two treatment groups. Although insulin infusion and hyperglycemia lowering may not be beneficial during acute stroke, additional potential reasons for the neutral results of the GIST-UK trial include delayed initiation of insulin infusion and the relatively small difference in glucose levels between the treatment groups.

Additional clinical efficacy trials are needed to address the uncertainty about the benefit of rapid hyperglycemia correction during acute stroke. These trials should differ from the GIST-UK trial by initiating the insulin infusion sooner and enrolling patients with higher glucose levels to achieve a greater difference in glucose between the treatment groups. If proven beneficial, a substantial proportion of acute stroke patients could be treated more effectively with a relatively inexpensive drug (insulin) that is familiar to health care providers. If this treatment proves ineffective, our efforts can be redirected toward other promising acute stroke therapies.

Another reason why additional randomized clinical trials are needed involves the costs of the treatment. Using intravenous insulin to rapidly control hyperglycemia (near 100 mg/dL) during acute illness requires admission to a specialized hospital unit that is prepared to administer it—either an ICU or, in some hospitals, an intermediate unit (also termed a transitional, progressive, or stepdown unit). Consequently, safe intravenous insulin infusion therapy necessitates a greater personnel effort and eventually greater cost. To justify such additional effort, costs, and risk, we should await convincing evidence of efficacy from randomized clinical trials.

Treatment

Lowering hyperglycemia during acute stroke

Subcutaneous insulin

Subcutaneous insulin protocols usually can maintain blood glucose levels below 200 mg/dL in most patients, especially if basal insulin is added.

Subcutaneous regular insulin sliding scales are familiar to health care providers and seem safe because they typically lower blood glucose levels over a period of several hours and rarely result in hypoglycemia. The most simple sliding scales call for regular insulin doses based on the recent glucose levels.

More sophisticated treatment protocols include additional insulin doses for meals and long-acting basal insulin [51]. When available, an endocrinology consultant can optimize the acute treatment and help the transition to long-term care.

Daily insulin needs are likely to change rapidly during acute illness. The subcutaneous insulin sliding scales do not require admission to specialized hospital units or frequent glucose monitoring and appear to be the current standard of care in most clinical settings. However, it seems unreasonable that subcutaneous insulin treatment will rapidly

and safely lower hyperglycemia to near 100 mg/dL and maintain such good control during acute stroke.

Intravenous insulin

At this time, the only effective method to lower hyperglycemia to near 100 mg/dL within 4 to 5 h and to keep it near that level is to use intravenous insulin.

For ischemic stroke treated with thrombolytic drugs, it may be best to rapidly lower severe hyperglycemia. For example, if the admission blood glucose is approximately 300 mg/dL and the patient is a candidate for thrombolytic therapy, consider giving an intravenous bolus of regular insulin 8 units. Somewhat lower or higher insulin doses may be best for lesser or greater hyperglycemia. This bolus will start lowering the blood glucose in about 5 min. A temporary continuous intravenous insulin infusion may then be used in most patients to maintain the glucose closer to normal levels (eg, below 180 or 140 mg/dL).

There are multiple protocols that rapidly correct hyperglycemia in ICU patients. Some protocols have trade names [52,53] and some do not [46]. Some academic institutions use protocols developed by local experts; some of these are available on their institutional websites, and many are publicly accessible on the Web [54]. Differences between these protocols that do not appear to be crucial at this time include whether to add potassium and/or a small amount of glucose to the solution. These protocols consider recent blood glucose levels but differ somewhat in the formulas used to determine the exact increases and decreases in insulin infusion rates over time. Such protocols have not been compared in head-to-head trials. They appear to have similar glucose-lowering efficiency and low risk of clinically significant hypoglycemia (<40 mg/dL). Computerized protocols are likely superior to paper-based protocols because they eliminate human error in calculating the infusion rate adjustments, they facilitate accurate data storage, and they have built-in reminders to recheck glucose levels.

Rapid and safe hyperglycemia correction requires glucose monitoring every 1 to 2 h. Capillary, venous, or arterial glucose measurements differ somewhat in a consistent fashion over a large range of levels, but all are considered appropriate and reliable for monitoring. Transdermal and subcutaneous glucose sensing devices are also available, but they reflect the blood glucose with 15 to 30 min delay and thus should be supplemented with blood measurements when the blood glucose levels are dropping rapidly. Computerized programs for storing and tracking the glucose levels over time are ideal because they can show the results in a useful output rapidly.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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Papers of particular interest, published recently, have been highlighted as:

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