Editorial

Plasma glucose levels and outcome after aneurysmal subarachnoid hemorrhage

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Serum glucose levels are commonly elevated in patients with acute cerebrovascular events, even in the absence of preexisting diabetes and insulin intolerance.

Hyperglycemia following brain injury has been recognized since 1858 when Claude Bernard observed the development of glycosuria in the experimental setting after he punctured the floor of the fourth ventricle. More recently numerous studies have been performed to elucidate the relationship between elevated plasma glucose levels and outcomes in patients with acute cerebrovascular insults including aneurysmal subarachnoid hemorrhage (SAH). Plasma glucose is directly and indirectly regulated (among other hormones) by circulating catecholamines and corticosteroids. Therefore, elevated glucose levels after ischemic or hemorrhagic stroke reflect the stress response to the neurological insult and constitute a biological circulating marker of neurological damage associated with worse outcome.

Experimental and clinical studies have unequivocally demonstrated that elevated glucose levels exert a detrimental effect after cerebral ischemia. In ischemic tissues there is a shift toward anaerobic metabolism. During ischemia, especially incomplete ischemia such as the one that occurs after SAH-induced vasospasm, hyperglycemia provides an abundant substrate for anaerobic glycolysis. This leads to excessive lactate accumulation and greater acidoisis. Acidosis when associated with energy failure may lead to cell death. Because of these experimental and clinical observations, active lowering of elevated blood glucose after cerebral infarction is recommended in most published guidelines, even for nondiabetic patients.

In this issue, Juvela and colleagues report their findings in 175 patients with aneurysmal SAH who were admitted to the hospital within 48 hours. The authors measured the plasma level of glucose at admission and corresponding fasting values the morning after aneurysm occlusion. They also meticulously recorded the patients’ medical histories, healthy habits, and body mass indices (BMIs). A multivariate analysis was conducted to identify those factors associated with outcomes at 3 months and the appearance of cerebral infarction. In this study, increased plasma glucose levels at admission were found to predict poor outcomes independent of patient age; clinical condition; or the amount of subarachnoid, intraventricular, or intracerebral blood. This finding confirms previous observations but again fails to define a clear mechanistic link between glucose levels and outcome. In other words, is hyperglycemia causally related to poor outcome or is an elevated plasma level of glucose just another predictor of greater neurological damage? Based on the aforementioned studies, one would expect hyperglycemia to be associated with a worse outcome in patients with vasospasm after infarction, and this study could have established a causal link between the two. The investigation by Juvela and colleagues failed to reveal such an association, however, because reactive hyperglycemia was actively corrected after admission by administering insulin.

In a multivariate analysis, an increased BMI and a history of preexisting hypertension were associated with the development of brain infarction. Increased body mass (obesity) and hypertension along with insulin resistance, dyslipidemia, and a systemic inflammatory state are part of the “metabolic syndrome” associated with an increased risk of cardiovascular diseases. The reasons for a causal relationship between increased BMI plus a history of hypertension and cerebral infarction after vasospasm are purely speculative. As suggested by Juvela, et al., a history of hypertension might increase the risk of infarction after vasospasm by shifting the autoregulation curve to the right. Additionally, an underlying associated vasculopathy with subsequent impairment of the microcirculation might increase the susceptibility of tissues at risk in ischemic areas. Therefore, vasculopathy could be responsible for the association between hypertension and worse outcome.

In summary, the report by Juvela and colleagues confirms that an elevated plasma level of glucose at admission after aneurysmal SAH is a predictor of poor outcome. The question of whether hyperglycemia is associated with increased risk of infarction in patients with delayed cerebral ischemia from SAH-induced vasospasm is not answered by this study. Nevertheless, existing experimental findings and clinical evidence of cerebral ischemia make it prudent to recommend active correction of reactive hyperglycemia to prevent its potential deleterious effects in incomplete ischemia from vasospasm. An increased BMI and a history of
hypertension before SAH were associated with the development of infarction and an increased infarction size after vasospasm. Further investigation is needed to explain this association. An increased BMI and a history of hypertension are factors that cannot be modified once SAH has occurred. Nevertheless, their presence, based on the findings of the present study, should alert the treating physician to an increased risk of worse outcome after vasospasm.

References

RESPONSE: Stress-induced hyperglycemia has been shown to predict both death and poor functional recovery in survivors after ischemic stroke. In patients who experience spontaneous intracerebral hemorrhage, stress-induced hyperglycemia may also predict death.

After SAH, a patient’s plasma glucose values at admission correlate with the severity of bleeding, particularly with the patient’s clinical condition; these values can thus be used to predict or mediate the occurrence of poor outcome or may be only an epiphenomenon of the stress response to SAH. Two of these studies showed that an elevated plasma level of glucose, independent of the severity of bleeding, predicted poor outcome. In one study, the plasma glucose level, due to its high correlation with the clinical condition of the patient, did not, after simultaneous adjustment for the clinical condition and amount of subarachnoid blood, reach significance as a predictor. In multivariate models from these previous studies, the authors took into account only the variables of severity of bleeding and patient age as confounding factors when they tested the association between hyperglycemia and impaired outcome.

In addition to the severity of stroke, the extent of stress-induced hyperglycemia may be affected by dysglycemia or insulin resistance, an important part of the metabolic syndrome in addition to hypertension, obesity, and dyslipidemia. Besides the severity of bleeding, we performed simultaneous additional adjustments for BMI and history of hypertension, and we found that the significance of an increased admission glucose level as a predictor for poor or impaired outcome decreased only slightly. This finding indicates that metabolic syndrome or insulin resistance with a possible underlying vasculopathy could only be used to a slight extent to explain why admission glucose levels predict outcome. Even a significant association between hyperglycemia and poor outcome after SAH in humans, after adjusting for several possible confounding factors, as we did, does not necessarily mean a causal relationship. A causal relationship could be demonstrated in a controlled clinical trial in which the effect of ultra-early insulin treatment on overall outcome after SAH is tested. On the other hand, the time window needed to obtain normoglycemia and favorable overall outcome in response to insulin treatment after aneurysm rupture may be quite short, perhaps only a few hours.

Blood pressure (BP) in the general population is raised independently by age, BMI, pulse rate, amount of regular alcohol use, and sodium intake. Elevated BP values and a history of hypertension before SAH, and possibly patient age, elevated BMI, and heavy alcohol consumption may lead to an increased rate of death or poor outcome after aneurysm rupture and an increased risk of permanent cerebral ischemic lesions. In a cohort study of patients with unruptured aneurysms, which also included patients with SAH who died before hospital admission soon after the primary hemorrhage or ultra-early repeated bleeding, systolic BP values and a history of long-term hypertension before SAH were significant independent predictors of fatal SAH. Aneurysm size and patient age also seemed to be important risk factors but had a less predictive effect on the severity of bleeding than BP values.

In the International Cooperative Study on the Timing of Aneurysm Surgery, pre-SAH medical conditions (mostly history of hypertension) and high systolic BP values after aneurysm rupture predicted, independent of several other prognostic factors, death and poor outcome both in all patients with SAH who were admitted to participating centers and, among that group, those patients who were treated surgically. Recently, an elevated BMI was found to predict the appearance of permanent ischemic lesions on follow-up computerized tomography scans; this was independent of the severity of the bleeding, patient age, sex, history of hypertension, occurrence of delayed cerebral ischemia, and duration of temporary occlusion of the proximal artery during surgery. Part of this increased risk from BMI may be due to the proxy effect of factors associated with BMI, for example, BP values. Patients with elevated BMIs may also recover less well from aneurysm surgery. In the present study, the risk of infarction was raised by a high BMI or hypertension, which are components of the metabolic syndrome. Metabolic syndrome (insulin resistance, obesity,
hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, and, possibly, increased inflammatory or coagulation activity) elevates the risk for ischemic cardio- and cerebrovascular events. Recently, elevated plasma D-dimer values, a marker of increased coagulation activity, significantly correlated with poor outcome after SAH.5 Sustained elevated blood coagulation activity after SAH seems to predict, independent of the severity of the SAH, patient age, and hyperglycemia, the possibility of a poor outcome (S Juvela, et al., unpublished data).

Patient age, sex, and genetic characteristics are risk factors that cannot be modified. Health habits, BMI, BP values, and hypertension are modifiable risk factors; for example, hypertension is a well-known risk factor for spontaneous intracerebral hemorrhage and, to a lesser extent, for SAH. By taking into account modifiable risk factors, one can partly avoid the development of a serious disease or influence, to some degree, its outcome if this kind of disease appears. Hypertension increases the risk of an SAH and impairs patient outcome after aneurysm rupture.7 Outcome after SAH is mainly determined by the severity of the initial bleeding, but is also affected by patient age as well as by disease-(delayed ischemia, repeated bleeding, hydrocephalus, and so forth) and treatment- (temporary or permanent proximal artery clipping) associated factors. Although the metabolic syndrome does not seem to increase the severity of bleeding, it may impair outcome by increasing the risk for post-SAH cerebral ischemia, which is not unexpected given that patients with the metabolic syndrome are known to be prone to ischemic cardio- and cerebrovascular diseases. After SAH, the risk of cerebral ischemia is high for 2 weeks. Furthermore, patients with the metabolic syndrome may need a more careful follow-up period after aneurysm rupture than others to avoid ischemic complications.

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References


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