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 acidosis. 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 develop-
ment of infarction and an increased infarction size after
vasospasm. Further investigation is needed to explain this
association. An increased BMI and a history of hyperten-
sion are factors that cannot be modified once SAH has
occurred. Nevertheless, their presence, based on the find-
ings of the present study, should alert the treating physician
to an increased risk of worse outcome after vasospasm.

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grade patients with spontaneous subarachnoid hemorrhage. Clin
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Response: Stress-induced hyperglycemia has been shown to predict both death and poor functional recovery in
survivors after ischemic stroke.1 In patients who experience spontaneous intracerebral hemorrhage, stress-induced hy-
perglycemia may also predict death.2

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 out-
come or may be only an epiphenomenon of the stress re-
response to SAH.3,4 Two of these studies showed that an ele-
vated plasma level of glucose, independent of the severity
of bleeding, predicted poor outcome.1,4 In one study,1 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 sub-
arachnoid blood, reach significance as a predictor. In multi-

variate models from these previous studies,1,3,10 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,5 an important part of the metabolic
syndrome in addition to hypertension, obesity, and dys-
lipidemia. Besides the severity of bleeding, we performed
simultaneous additional adjustments for BMI and history of
hypertension, and we found that the significance of an in-
creased 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 treat-
ment on overall outcome after SAH is tested. On the oth-
er hand, the time window needed to obtain normoglycemia
and favorable overall outcome in response to insulin treat-
ment after aneurysm rupture may be quite short, perhaps
only a few hours.

Blood pressure (BP) in the general population is raised
dependently by age, BMI, pulse rate, amount of regular
alcohol use, and sodium intake.1,11 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 an-
euryism rupture and an increased risk of permanent cerebral
ischemic lesions.4,5 In a cohort study of patients with unrup-
tured 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.7 An-
euryism 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,8 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 pa-

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