Hyperglycemia and Acute Ischemic Stroke

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Stroke is the second leading cause of mortality worldwide [1]. It is the most common cause of permanent disability in adults as well as an important contributor to depression and other neuropsychiatric disorders – all at significant cost to health and community services [2]. In 1998, approximately 770,000 cases of clinically manifested stroke were registered in the United States and more than 10 million patients were estimated to have first-ever silent magnetic resonance imaging-confirmed infarcts or hemorrhages. These findings demonstrate that the incidence of stroke is substantially higher than suggested by estimates based solely on clinically overt events [3]; in other words, the true burden of stroke and its consequences is underestimated.

Timely recognition and treatment are imperative to reduce stroke-related morbidity and mortality, and the management of risk factors for stroke is especially important for stroke prevention. Diabetes mellitus is one well-recognized risk factor for a wide spectrum of vascular diseases, including stroke [4–6]. The role and the management of hyperglycemia in the acute phase of ischemic stroke, however, have not been investigated in depth. We present a review of the current knowledge of hyperglycemia in relation to acute ischemic stroke.

Experimental data and mechanisms

There is a large body of data on stroke and hyperglycemia in animal models. The detrimental effect of global cerebral ischemia that causes a selective destruction of vulnerable neurons could be intensified by glucose pretreatment in monkeys [7]. The data in more recent studies on reproducible animal stroke models suggest that brain infarction and acute elevation in glucose stores result in aggravation of anaerobic glycolysis and brain tissue acidosis [8,9]. The real role of direct toxicity on the ischemic brain is difficult to estimate. Studies on hyperglycemic subjects showed aggravated ischemic brain lesions due to raised blood glucose concentrations [10] and its consequences, such as intra- and extracellular acidosis and post-ischemic alkalosis.

The physiologic range of pH is one of the important conditions for normal neuronal metabolism. During the ischemic process, the brain tissues undergo acidification [11] as a result of anaerobic glycolysis and an associated hydrolysis of adenosine triphosphates [12]. The presumption that acidosis is probably responsible for the aggravation of ischemic brain damage may be supported by the notion that brain infarcts are not observed in hypoglycemic conditions in which acidosis is absent [13].

The mechanisms by which acidosis enhances brain damage in ischemic conditions are not clear, but two possible variants have been proposed. The first stems from the well-established acidosis *in vitro* that acts by enhancing iron-catalyzed free radical reactions; this may occur *in vivo* [14]. The second is that the enhanced DNA fragmentation demonstrated in animal models is thought to be caused by acidosis-related free radical formation; this raises the possibility that acidosis-related cell injury might be mediated by DNA damage [15]. The relative deficit of insulin is another important feature of stroke in hyperglycemic conditions; insulin insufficiency means that the peripheral uptake of glucose is decreased so that the amount of glucose available to diffuse into the brain is increased. Finally, it is important to consider the increased amount of circulating free fatty acids that may impair endothelium-dependent vasodilation, a condition associated with heightened risk of stroke [16].

Clinical data

Hyperglycemia is a frequent finding in acute stroke patients regardless of their previous blood glucose levels [17]. Moreover, serious illness is often accompanied by hyperglycemia, considered to be part of the adaptive metabolic response to stress and independent of whether or not the patient has a history of diabetes mellitus. Whether hyperglycemia adversely affects stroke outcome or primarily reflects stroke severity remains an unresolved issue.

Williams et al. [17] conducted a clinical trial in 656 patients between 1993 and 1998 to ascertain the prevalence, severity and consequences of hyperglycemia on hospital admission among acute ischemic stroke patients. They found that hyperglycemia at admission to hospital was present in 40% of patients with acute

stroke and concluded that hyperglycemia was associated with increased short- and long-term mortality as well as with increased inpatient costs.

From the stroke patient's point of view, there is a wide spectrum of clinically important manifestations of hyperglycemia. The incidence and degree of reactive hyperglycemia are related to the type, location and severity of the acute stroke. Thus, a more severe hyperglycemic response is more prevalent in patients with hemorrhagic stroke and brain-stem infarction compared with patients with cerebral infarction. There are more comatose subjects among hyperglycemic patients, and their hospital mortality is significantly higher [18]. The possible mechanisms of a hyperglycemic reaction following acute stroke could be underlying latent diabetes, hypothalamic dysfunction, increased secretion of growth hormone, irritation of the glucose regulatory centers, and non-specific reaction to acute stress and tissue injury with the associated autonomic, hormonal and metabolic alterations [18].

In a study on 138 stroke patients treated with intravenous recombinant tissue plasminogen activator, admission hyperglycemia was associated with a higher risk of hemorrhagic conversion of the infarct [19]. It would thus be reasonable to consider that hyperglycemia is responsible for blood-brain barrier disruption and that it promotes hemorrhagic transformation of an ischemic stroke. Patients who develop reactive hyperglycemia after stroke are likely to have undiagnosed borderline diabetes, i.e., dysglycemia. Their blood glucose levels are higher than normal, but still below the threshold for diabetes. These patients probably have more extended underlying atherosclerotic vascular pathology and are at higher risk of vascular disease than normoglycemic patients [20].

All the effects of hyperglycemia mentioned above are apparently important in the ischemic penumbra, the region of brain tissue surrounding the core of infarct with injured but still viable neurons. In a rabbit model of stroke, insulin treatment of hypoglycemic subjects that developed less cellular acidosis in the ischemic penumbra resulted in their having a smaller infarct volume compared with hyperglycemic rabbits. Thus, hyperglycemia may lead to the recruitment of potentially salvageable neurons into the infarction [21]. These hypotheses were supported by the results of a study on 63 acute stroke patients who were prospectively evaluated with serial diffusion-perfusion weighted MRI and acute blood glucose measurements. The hyperglycemia in patients with perfusion-diffusion mismatch (most probably in the regions of the penumbra) was associated with greater acute-subacute lactate production, which, in turn, was independently associated with reduced salvage of mismatch tissue. In the non-mismatch patients, blood glucose did not correlate with outcome measures, nor was there any acute-subacute increase in lactate in this group. The authors concluded that acute hyperglycemia increases brain lactate production and facilitates conversion of hypoperfused at-risk tissue into the infarction, an event that may adversely affect stroke outcome [22].

Another report [23] investigated the management of hyperglycemia with insulin in critically ill patients (i.e., myocardial infarction and surgical intensive care). A better long-term outcome was shown in patients who suffered from myocardial infarction and who underwent meticulous blood glucose control. In addition, 1,548 surgical intensive care patients had been randomly allocated to either the conventional approach (insulin infusion started only when blood glucose levels exceeded 12 mmol/L) or intensive insulin therapy (insulin infused to maintain blood glucose at a level of 4.5–6.1 mmol/L, or 80–110 mg/dl). Intensive insulin therapy reduced intensive care mortality by more than 40% [23].

The safety of controlling insulin blood glucose levels was initially proved in a small pilot study on 53 acute stroke patients, although no significant difference in the outcomes of two groups was noted [24]. In the last published update of this study, The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK), Gray and colleagues [25] aimed to describe the immediate recovery of post-stroke hyperglycemia in treated and control patients, thus providing evidence for the use of glucose/potassium/insulin infusions as a means of maintaining euglycemia. In the preliminary results, glucose/potassium/insulin infusions were revealed as being a safe and effective tool for correcting post-stroke hyperglycemia, but the clinical benefits of routine management of hyperglycemia remain to be determined.

Published by the American College of Endocrinology Consensus Development Conference on Inpatient Diabetes and Metabolic Control, the following upper limits for glycemic targets were intended to provide clinicians with guidelines for promoting improved outcomes:

- Intensive care unit
  110 mg/dl (6.1 mmol/L)

- Non-critical care units
  110 mg/dl (6.1 mmol/L) – preprandial
  180 mg/dl (10 mmol/L) – maximal glucose

Values above 180 mg/dl (10 mmol/L) are an indication to monitor glucose levels more frequently to determine the direction of any glucose trend and the need for more intensive intervention. Achieving these targets may require consultation with an endocrinologist or diabetes specialist. The use of standardized treatment protocols developed by multidisciplinary teams is recommended. The American College of Endocrinology and American Association of Clinical Endocrinologists strongly support the need for early detection of hyperglycemia in the hospital and an aggressive management approach to improve outcomes.

In its new recommendations (2003/2004), the European Stroke Initiative (EUSI) suggests immediate insulin titration if an acute stroke patient's blood glucose level reaches 200 mg/dl or 10 mmol/L and higher. Unless the blood glucose level is known, no carbohydrate concentration should be given to a stroke patient.

Conclusion

There is no doubt that hyperglycemia has a deleterious impact on ischemic stroke. Although the currently available evidence supports the implementation of intensive insulin therapy in cardiologic and surgical intensive care, a comparable benefit for stroke patients awaits further investigation. Randomized controlled trials of

aggressive glycemic control in acute stroke are needed to better understand the underlying mechanisms of hyperglycemia among these patients. We expect that insulin treatment of suitable stroke patients is likely to become standard practice in their management.

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640K ought to be enough for anybody

Bill Gates, 1981

Capsule

Size control in growth

Developmental size control is very poorly understood, especially in vertebrates. Why do different body parts attain particular relative and absolute sizes, and then stop growing? In the case of limbs, continued growth and patterning of the embryonic bud depends upon the maintenance of a positive feedback loop between Sonic hedgehog and fibroblast growth factors. Scherz et al. describe the timing mechanism that terminates this feedback loop and hence determines the length of the digits and the number of phalanges they contain. Over time, an expansion occurs in the number of cells in the posterior limb bud that cannot support the intermediate steps of the feedback loop downstream of Sonic hedgehog. When the size of this non-responsive zone grows broader than the range of Sonic hedgehog diffusion, the loop is broken.

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