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Assessment of Glycemic State and Intracerebral Hemorrhage: Review Article

Ahmed Essam Mohamed Harby*, Sawsan Abdel aziz Yousef, Wafaa Samir Mohamed, Emad Latif Agban
Department of Neurology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Ahmed Essam Mohamed Harby, **Mobile:** (+20) 01143614994, **E-Mail:** ahmedharby402@gmail.com

ABSTRACT

Background: Intracerebral hemorrhage (ICH) remains the second leading cause of stroke accompanied with great mortality rate and severe neurological deficits. For ICH patients, available treatment options are still limited, therefore early recognition and improving results requires careful management of potential sources of harm.

Objective: Review of literature about glycemic state and intracerebral hemorrhage.

Methods: We searched PubMed, Google Scholar, and Science Direct for relevant articles on glycemic state and intracerebral hemorrhage. However, only the most recent or thorough studies were taken into account between October 2000 and April 2023. The authors also evaluated the value of resources culled from other works in the same genre. Documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to be qualified as scientific research.

Conclusion: Patients with diabetes mellitus (DM) appear to develop a self-protective mechanism in response to chronic hyperglycemia by preferentially down-regulating glucose transporters (GLUT-3 as well as GLUT-1), which allows glucose to enter cells independently of insulin and thus reduces the acute fluctuation of glucose concentration and endothelial cell apoptosis. Hyperglycemia due to stress is a temporary condition characterized by higher-than-normal blood sugar levels. Myocardial infarction, ischemic stroke, and intracerebral haemorrhage are all serious illnesses in which this phenomenon is frequently observed.

Keywords: Glycemic state, Intracerebral hemorrhage.

INTRODUCTION

After ischemic stroke, intracerebral haemorrhage (ICH) is the most prevalent cause of severe disability and death due to stroke. Half of all deaths from ICH happen within the first 2 days, and the first week, with a 30-day mortality rate of 35-52% [(1)].

Bleeding into the parenchyma of the brain is the primary cause of intracerebral haemorrhage (ICH). Pathologies that lead to ICH can be broken down into the following categories: arterial (small and big artery disease), venous, vascular malformation, hemostatic, and other [(2)].

ICH (intracranial haemorrhage) occurs due to two major sporadic cerebral small vessel diseases: hypertensive arteriopathy, which triggers ICH in the small perforating artery area of the deep grey nucleus, brainstem, and white matter. Also, vasculitis microangiopathy that includes lobar regions; and cerebral amyloid angiopathy (CAA), which leads to lobar ICH because of rupture of tiny arteries in the superficial cortical and leptomeningeal layers of the brain. Rarely, it can even affect very deep nuclei. Although hypertensive arteriopathy can produce both deep and lobar ICH, research classifies ICH as "non-lobar (deep and infra-tentorial)" or "lobar" based on the suspected prevalent underlying causative small artery disease [(3)].

The second most common type of stroke, intracerebral haemorrhage has a high fatality rate and causes significant neurological impairments. As there are currently few treatment options for ICH patients, it is crucial that risk factors for negative outcomes be identified and managed as soon as possible [(4)].

Primary Injury:

ICH's first pathological harm is mechanical compression from a hematoma, which raises intracranial pressure and raises the chance of brain herniation. Poor prognosis and high mortality rates are linked to secondary injuries such cerebral edema and brain hernia in ICH cases [(5)].

Hyperventilation, steroid administration, mannitol, and glycerol are some of the treatments for cerebral edema, however they do not reduce intracranial pressure or prevent further brain injury [(6)].

Secondary Brain Injury:

Inflammation

More and more research points to inflammatory processes being involved in ICH-induced brain damage. It is believed that activation and polarization of microglia and macrophages play important pathophysiological functions as well [(7)].

To keep neurons, the extracellular matrix, and the blood-brain barrier (BBB) stable under normal circumstances, microglia/macrophages perform environmental monitoring. Pathological alterations such as BBB injury, edema, cell death, and so on result from cerebral bleeding because of the excessive microglia/macrophages that release a huge number of inflammatory factors and generate inflammatory waterfall reaction [(8)].

Microglia and macrophage activation results in two distinct cell types: classically activated microglia/macrophages (M1 phenotype) and alternatively activated microglia/macrophages (M2 phenotype) (M2 phenotype) [(9)].

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Chronic hyperglycemia is the primary symptom of diabetes mellitus, which is caused by a deficiency in insulin production, insulin action, or both, as well as alterations in carbohydrate, lipid, and protein metabolism [10].

Non-traumatic there are two types of intracranial bleeding: main and secondary. Hemorrhagic conversion of an ischemic stroke, drug misuse, and vascular abnormalities are all considered secondary causes of ICH. Primary ICH accounts for 85% of all ICH and is associated with persistent hypertension or amyloid angiopathy [11].

The effects of what we eat on our bodies are substantial. The need for energy to do even mundane physical tasks is obvious, and this need persists even while in rest. Substrates such as carbohydrates, fats, and proteins are metabolized by our tissue to produce usable energy. Tissues rely on glucose as their primary energy source, despite the fact that the energy yield from 1 g of fat is more than twice that of 1 g of carbohydrate or protein. Glucose is the sole fuel for the brain and red blood cells, and both depend on a steady supply being delivered by the bloodstream [12].

Blood glucose levels are maintained by maintaining a balance between the rates of glucose generation by the liver and the rates of its removal by peripheral tissues, both of which are influenced by insulin (mainly skeletal muscle). When blood glucose levels are low, the body's adipose tissue supplies non-esterified fatty acids (NEFA) to the body's skeletal muscle, liver, and kidneys for use as an alternative energy source. Maintaining metabolic homeostasis requires these processes to be finely tuned in response to fluctuations in insulin secretion. Substrate switching between tissues to meet metabolic demands, such as the postabsorptive to postprandial transition, is highly regulated by the central nervous system (CNS) [13].

Diabetic patients are more likely to experience ICH with numerous topographies than nondiabetic patients, and diabetics with hemorrhagic stroke tend to have larger hematomas. The higher risk for multiple topographical bleeding has been linked to the recognized impairment of the microvasculature caused by diabetes. Patients with diabetes may be more likely to experience multiple, concurrent intracerebral haemorrhages due to the unique angiopathy brought on by diabetes in tiny arteries [14].

It's common knowledge that diabetes mellitus raises the odds of having either a clot-causing or a bleed-causing stroke. Furthermore, hyperglycemia following ICH is linked to hematoma growth, a poor functional result, and an increased risk of dying [15]. Inpatient hyperglycemia is indicative of either underlying diabetes mellitus or stress-induced hyperglycemia (SIH) [16].

Hyperglycemia due to stress is a temporary condition characterized by higher-than-normal blood sugar levels. Myocardial infarction, ischemic stroke, and intracerebral haemorrhage are all serious illnesses in which this phenomenon is frequently observed [17].

Stress hyperglycemia is caused by a complex interaction between the hypothalamic-pituitary-adrenal (HPA) axis, the sympathoadrenal system, and proinflammatory cytokines (TNF-alpha, IL-1, and IL-6) [18].

Increased gluconeogenesis, glycogenolysis, and insulin resistance are hallmarks of the neuroendocrine response to stress. However, stress-induced hyperglycemia seems to result mostly from elevated glucose production in the liver rather than decreased glucose extraction in the tissues [18].

Peripheral insulin resistance is also triggered by inflammatory mediators as cytokines TNF-alpha, IL-1, IL-6, and C-reactive protein [18]. Additionally, adipokines' release was disrupted (decreased adiponectin as well as increased zinc-alpha2 glycoprotein) from adipose tissue, which is a key role in the genesis of insulin resistance during acute illness [18].

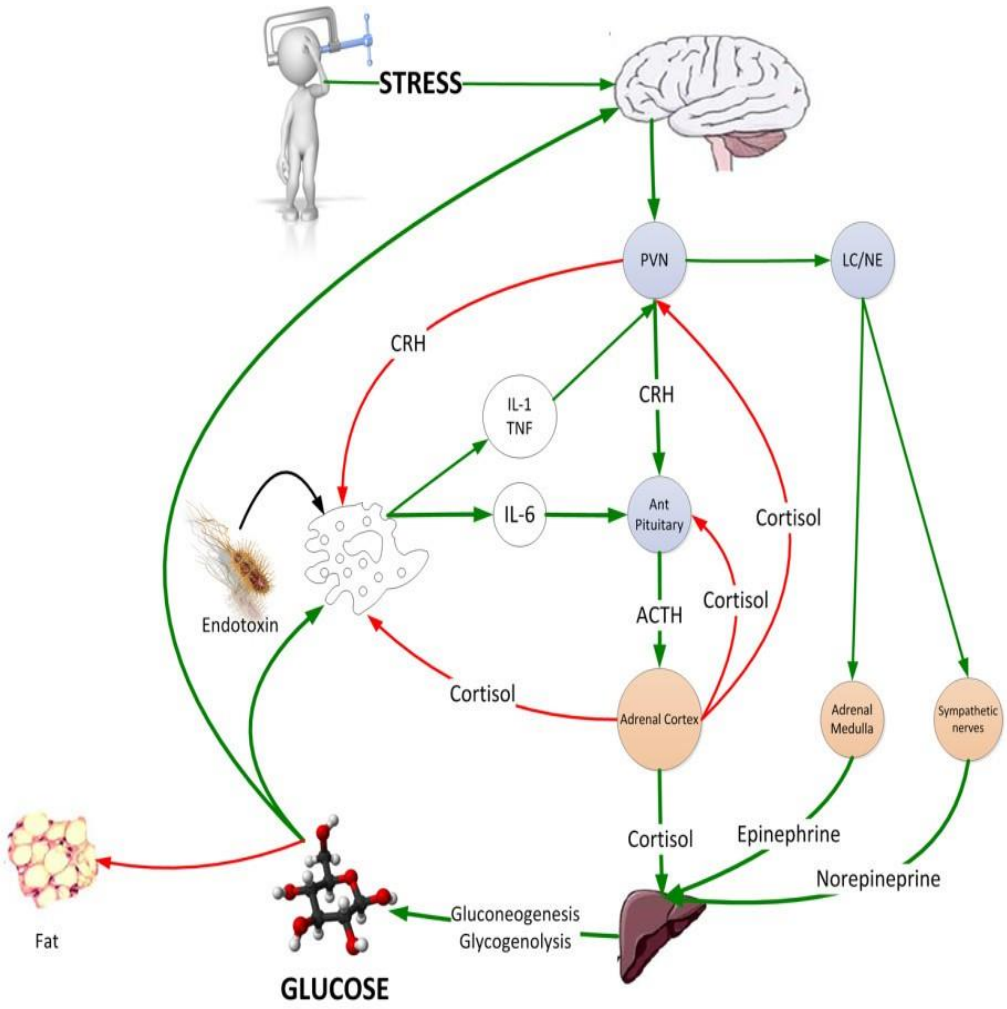

Figure (1): The hormonal and neurochemical reactions to stress [18]. [Adrenocorticotropic (ACTH) hormone; Corticotropin-Releasing Hormone (CRH); Locus Ceruleus/Noradrenergic (LC/NE) system; Nucleus paraventricular (PVN)].

In patients with ICH, SIH may more accurately indicate high blood glucose due to ICH than conventional measures of hyperglycemia caused by diabetes. However, the stress hyperglycemia ratio (SHR) allows us to reliably differentiate between SIH and hyperglycemia caused by diabetes. [19].

Nathan *et al.* [20] developed the formula "Estimated average glucose=(1.59HbA1c)-2.59" to convert HbA1c to estimated average glucose. Then, to describe relative hyperglycemia, namely SIH, SHR is devised, where SHR = entrance blood glucose / estimated average glucose [17].

When adjusted for chronic glycemic state, SHR has been proposed as an index that more faithfully captures the full scope of SIH. SHR has been shown to be a valuable predictor of mortality and recurrence of acute myocardial infarction following percutaneous coronary intervention [16].

Additionally, secondary neurological deterioration within 48 hours, mortality within 30 days, and poor mRS scores at 3 months were also found to be independently linked with SHR in ICH patients [19].

Stress hyperglycemia has been linked to poorer functional outcomes following ICH, even in patients without diabetes mellitus, according to previous research. This may be explained by the fact that cells in diabetics have adapted to high blood glucose levels over time, making them less sensitive to the effects of hyperglycemia [16,21].

Patients with diabetes mellitus (DM) appear to develop a self-protective mechanism in response to chronic hyperglycemia by preferentially down-regulating glucose transporters (GLUT-1 and GLUT-3), which allows glucose to enter cells independently of insulin and thus reduces the acute fluctuation of glucose concentration and endothelial cell apoptosis. Patients with DM have a better prognosis for hyperglycemia following ICH, and this phenomenon may explain why [16].

The methods via which SIH contributes to ICH are intricate. There is evidence to show that hyperglycemia after ICH is linked to a higher neutrophil-to-lymphocyte ratio, which in turn may promote further brain damage through inflammatory responses [22].

Second, through increasing lactate buildup and intracellular acidosis, stress hyperglycemia may cause direct toxic injury to brain tissue. Free radical production and lipid peroxidation may be exacerbated by intracellular acidosis, which may hasten the recovery time from nerve damage [23].

Finally, cytotoxic edema and neuronal apoptosis may ensue from stress hyperglycemia due to an increase in free calcium in the cytoplasm, which in turn causes calcium influx into mitochondria and disrupts the process of ATP synthesis [15].

Stress hyperglycemia-induced downregulation of brain aquaporin-4 expression is associated with increased blood-brain-barrier breakdown and subsequent severe vasogenic brain edoema, both of which contribute to poorer functional outcomes following ICH [24].

When ICH occurs, stress hyperglycemia contributes to poor outcomes by increasing hematoma size through plasma kallikrein [15]. Additionally, it was discovered that a greater FBG level was connected to a higher risk for hospital death [4]. In patients with aneurysmal subarachnoid haemorrhage, FBG outperformed random blood glucose (RBG) in predicting poor clinical outcome. This could be because RBG is limited in its ability to capture significant intraindividual variation, which could lead it to inaccurately reflect an individual's long-term status [25].

There is no denying the reality that blood glucose levels change regularly over time due to the many factors that affect them. In addition, there may be individual differences in the time it takes for ICH to develop before blood glucose levels are measured. Therefore, it is challenging to standardize blood glucose levels, and comparisons may only be made over a rather narrow time window. HbA1c, on the other hand, is a biomarker of long-term (about 3 months) glycemic status that is widely used for monitoring diabetic vascular damage, such as atherosclerosis and microangiopathic changes, and has been shown to be independently associated with poor outcome in patients who have suffered an ischemic stroke [26].

Vascular damage and adverse effects on sICH were hypothesized to be associated with long-term hyperglycemia exposure rather than its shorter counterpart [27].

Patients with sICH have been demonstrated in certain trials to have a bad prognosis if their HbA1c levels are high. These findings corroborate previous research showing that patients diagnosed with diabetes using the HbA1c criterion have a poor long-term outcome following an acute brain hemorrhage [28].

HbA1c appears to be a better predictor of bad outcomes in patients with SICH, according to small cohort studies. In addition, after thrombolysis, HbA1c is a better predictor of the symptomatic hemorrhagic change of acute ischemic stroke [29].

These results corroborate those of a large cohort study that discovered a J-type association between HbA1c and the danger of sICH. HbA1c levels below 6.5% were associated with the lowest risk [30].

Patients with sICH did not differ from the general population in terms of hematoma volume, neurological impairment, or clinical prognosis, according to another study [25].

The guidelines stress the significance of maintaining tight management of blood glucose levels following ICH. Mixed ischemic and hemorrhagic stroke patients benefited from a series of therapies (controlling hyperglycemia, fever, and swallowing difficulty) in a cluster randomised study. However, there is still some confusion over the best way to treat hyperglycemia and what glucose level can be considered therapeutic [19].

CONCLUSION

Patients with diabetes mellitus (DM) appear to develop a self-protective mechanism in response to chronic hyperglycemia by preferentially down-regulating glucose transporters (GLUT-3 as well as GLUT-1), which allows glucose to enter cells independently of insulin and thus reduces the acute fluctuation of glucose concentration and endothelial cell apoptosis. Hyperglycemia due to stress is a temporary condition characterized by higher-than-normal blood sugar levels. Myocardial infarction, ischemic stroke, and intracerebral haemorrhage are all serious illnesses in which this phenomenon is frequently observed.

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