Introduction

Stroke is defined as either symptoms lasting more than 24 hours or imaging of an acute clinically relevant brain lesion in patient with rapidly vanishing symptoms, patients with symptoms lasting less than 24 hours but with infarction imaged by MRI have been reclassified as having stroke instead of transient ischemic attack***(Chong and sacco;2005)***.

The association of hyperglycemia and brain injury had already been described by Claude Bernard in 1849, for a longtime hyperglycemia was understood only as an epiphenomenon due to the stress of an acute injury, its impact on the neurological recovery was ignored for a long time and the increase in blood glucose level was understood as an adaptive response to provide glucose for an exclusive glucose consuming tissue ***(Hamilton et al; 1995).***

Causes of hyperglycemia in critical ill patients include diabetes mellitus stimulation of stress hormones (epinephrine, cortisol), glucocorticoid therapy, continuous enteral nutrition and decreased activity ***(Malhortra et al; 2006).***

Stress hyperglycemia is defined as a transient plasma glucose level above 200 mg/dL and it is thought to be caused by the increased levels of cortisol, glucagon, and epinephrine, these hormones increase gluconeogenesis and decrease peripheral

uptake of glucose to ensure substrate availability***(Umpierrez et al; 2002).***

A meta-analysis suggests that the relative risk of death in hyperglycemic non-diabetic stroke patients is increased by 3.3 (95% confidence interval, 2.3 to 4.6), recent analyses confirm the importance of acute hyperglycemia as a predictor of outcome after stroke ***(Capes et al;2001)***

Hyperglycemia also produces a hyper-coagulable state partly through the increased expression of tissue factor which is both pro coagulant and pro inflammatory also it activate factor VII of the coagulation cascade ultimately resulting in the generation of thrombin a protease capable of converting fibrinogen to fibrin and activating platelets ***(Aljada et al;2004).***

Hyperglycemia appears to be independently associated with poor outcome and reduced reperfusion. Additionally normoglycemic patient should not be given excessive glucose containing IV fluids this may lead to hyperglycemia and may exacerbate ischemic cerebral injury through blood sugar control tightly with insulin therapy, fluid, thrombolytic and heparin or heparin derivative, with the goal of establishing normoglycemia (90-140 mg/dl) close monitoring of blood sugar level should continue throught out hospitalization to avoid hypoglycemia ***(Adams et al;2007).***

Acute stroke

The WHO has defined stroke as a clinical syndrome characterized by rapidly developing symptoms and/or signs of focal, and at times global (for patients in coma), loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. The definition excludes transient ischemic attack (TIA), which is defined as, rapidly developed clinical signs of focal or global disturbance of cerebral function lasting less than 24 hours, with no apparent non-vascular cause ***(Hatano et al;2009).***

With more widespread use of modern imaging techniques for the brain, up to one third of patients with symptoms lasting ≤ 24 hours have been found to have an infarction, this has led to a new tissue-based definition of TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction ***(Easton et al;2009).***

Approximately 85% of all first-ever strokes are ischemic; 10% are caused by primary intracerebral hemorrhage and approximately 5% are from subarachnoid hemorrhage ***(Rothwell et a;2004).***

Within ischemic stroke, 25% are caused by large artery disease, 25% by small vessel disease, 20% by cardiac embolism, and 5% by other rarer causes, and the remaining 25% are of undetermined etiology (***Pendlebury et al;2009).***

Aim of the Study

The aim of the present work is to discuss pathophysiology of acute cerebral stroke, pathophysiology, management of hyperglycemia in acute cerebral stroke and effect of hyperglycemia on stroke outcome.

Pathophysiology of Hyperglycemia

➢ Overview of Postprandial Glucose Metabolism

In healthy individuals without DM, the regulation of blood glucose concentration is maintained through hormonal,neural, and hepatic autoregulatory mechanisms Under normal circumstances, a postprandial increase in blood glucose concentration stimulates the release of insulin from the pancreas, specifically the b-cells. Insulin mediates peripheral glucose disposal and suppresses glucogenesis in the liver, this process maintains blood glucose homeostasis ***(Robinson and van Soeren, 2010).***

After uptake into the skeletal muscle, glucose either is directed to glucagon formation (pathway for carbohydrate storage) or glycolysis (used in the Kreb's cycle, resulting in energy production),excess glucose also can be stored in the liver or converted to fatty acids for storage in adipose tissue ***(Montori and Bistrian, 2009).***

➢ *Altered Glucose Metabolism in Critical Illness*

Critical illness induces a number of adaptive changes inhuman physiology; the most prominent are changes in the neuroendocrine function, An increase in counter regulatory hormones, such as glucagons, epinephrine,norepinephrine, and growth hormone, results in increased hepatic glucose production

and decreased peripheral glucose uptake, subsequently inducing a hyperglycemic state ***(Montori and Bistrian, 2009).***

In addition, critical illness exacerbates the circulation of abnormal levels of cytokines particularly tumor necrosis factor, alpha, and interleukin further elevating serum glucose Patients with DM exhibit a greater response to counter regulatory hormones, and may not increase insulin secretion as a compensatory response to needed levels, resulting in even higher glucose levels ***(McCowen, 2008).***

- ***Pathophysiology of Hyperglycemia in Diabetes Mellitus***

Classic type 1 diabetes is thought to result from an auto-immunologic destruction of the insulin-producing islet beta cells. Accordingly, these patients have absolute insulin deficiency and invariably require insulin treatment. The onset of type 1 diabetes is not limited to young age. Specifically, 5–30% of adult patients initially diagnosed with type 2 diabetes actually have type 1 diabetes, as suggested by the finding of circulating glutamic acid decarboxylase antibodies directed toward the patients' islets of Langerhans ***(Turner et al;2006).***

Furthermore, patients with type 1 diabetes can also express autoantibodies to islet cell cytoplasm or autoantibodies to insulin ***(Atkinson et al;2005).***

Concomitant autoimmune endocrinopathies such as thyroid dysfunction or especially adrenal insufficiency (Addison's crisis) have to be considered in type 1 diabetics, particularly in the unstable ICU patients with unexplained altered mental status, hypotension, or weakness ***(Boord et al;2002).***

Type 2 diabetes has a completely different, multifactorial pathophysiology, it is typically accompanied by the metabolic syndrome, this includes not only glucose intolerance but also insulin resistance, central obesity, dyslipidemia, and hypertension, all well-documented risk factors for cerebrovascular disease (**Eckel *et al;2005).***

However, not only lifestyle factors but also genetic elements are involved in the pathogenesis of type 2 diabetes, which is evident considering the 2.4-fold increased risk in individuals with a positive family history (**Stumvoll *et al;2005).***

Given the high prevalence of environmental and genetic risk factors, it is not surprising that type 2 diabetes is now being increasingly diagnosed in obese young and adolescent people, particularly in western nations ***(Turner et al;2006).***

In contrast to type 1 diabetes, the main problem in patients with type 2 diabetes is not absolute insulin deficiency but, rather, insulin resistance with ensuing relative insufficiency of insulin production. Insulin resistance is said to be present when the

biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of endogenous glucose preproduction in the liver ***(Dinneen et al;2000).***

Type 2 diabetes can be treated with a calorie-restricted diet, oral hypoglycemic agents, or insulin. It is usually a progressive disease, and even if it can be controlled by oral hypoglycemic agents initially, may ultimately require insulin treatment ***(Boord et al;2002).***

- ***Prevalence of Transient Hyperglycemia in Previously Non diabetic ICU Patients***

There are discrepancies in the definition of stress hyperglycemia in critical illness, mainly with respect to the cut-off value by which one defines hyperglycemia, in-homogeneity of study populations, and varied timing of blood sampling; therefore, the prevalence of stress induced hyperglycemia is difficult to assess. With more studies demonstrating benefits of tight glucose control in peri-operative and critically ill patients emerging every year, the previously accepted threshold of 200 mg/dL plasma glucose has been lowered by most investigators to 110–150 mg/dL **(*Finney et al;2003).***

In a large series of mixed surgical ICU patients, ***Van den Berghe*** and colleagues reported 75% of all patients, including diabetics, had blood glucose levels exceeding 110 mg/dL at

admission, and 12% of all patients were actually ≥ 200 mg/dL, while ***Latham*** and colleagues found that 21% of cardiothoracic surgery patients developed postoperative blood glucose levels of ≥ 200 mg/dL and reported a direct correlation between the degree of hyperglycemia and the rate of infections ***(Latham et al;2001).***

Wide variations are observed in non-diabetic patients with acute myocardial infarction, with stress hyperglycemia reported in 3% to 71% of patients (**Capes *et al;2006).***

➢ *Pathophysiology of Hyperglycemia in Critical Illness*

- ***Cellular Glucose Transport***

Despite large timely fluctuations in supply and demand, plasma glucose levels are normally controlled within a narrow range between 80 and 125 mg/dL in a fasting state. Interestingly, 80% of systemic glucose utilization occurs by non–insulin mediated glucose uptake under basal conditions, mainly by the central nervous system ***(Bruno et al;2002).***

Muscle glucose uptake accounts for only about 20% in a resting state, half of which occurs as insulin mediated. Another 30 to 40% of total glucose uptake is stored in the liver in the form of glycogen ***(Matthias et al;2006).***

Glucose transport into cells occurs as facilitated diffusion using one of five different glucose transporter (GLUT) channel

proteins. GLUT 1–mediated insulin independent transport occurs in most tissues and accounts for basal glucose uptake, whereas the membrane presence of GLUT 4 is specifically and reversibly up-regulated by insulin, On a cellular level, insulin binds to the insulin receptor, causing auto-phosphorylation and tyrosine-kinase–mediated phosphorylation of insulin receptor substrate second messenger molecules 1 and 2, Insulin receptor substrate 1 then activates the phosphatidylinositol 3-kinase system, which is a required step for the translocation of preformed and intracellularly stored GLUT 4 transporter molecules to the cell membrane ***(Matthias et al;2006).***

During moderate hyperglycemia, cells usually respond with an internalization of GLUT transport molecules to protect themselves from glucose overloading ***(Klip et al;1999).***

Interestingly, although, total body glucose uptake is typically increased in critical illness, which has mainly been attributed to non–insulin-mediated glucose uptake in tissues such as the central nervous system or blood cells (**McCowen *et al;2008).***

Several factors typically observed in critical illness, including proinflammatory cytokines, endothelin-1, transforming growth factor-β, or tissue hypoxia, were shown to upregulate GLUT 1 and GLUT 3 isoforms in various tissues, thereby leading to concentration- dependent

cellular glucose uptake and compromising the protective response against hyperglycemia (**Vanhorebeek *et al;2005).***

- ***Metabolic Stress Response***

The degree of the systemic response to stress correlates with the intensity of the challenge, critically ill patients commonly enter a hypermetabolic state, with distinct alterations of their carbohydrate metabolism as part of the physiologic stress response, the classic endocrine reaction to a stressful challenge consists of the activation of the sympatho-adrenal and the hypothalamo-pituitary-adrenal axis, leading to increased plasma levels of catecholamines and glucocorticoids, both of which help induce hyperglycemia in critical illness ***(Matthias et al;2006).***

Other hormones, such as corticotrophin, growth hormone and glucagon, are also found to be elevated in response to physiologic stress ***(Rolih et al;2000).***

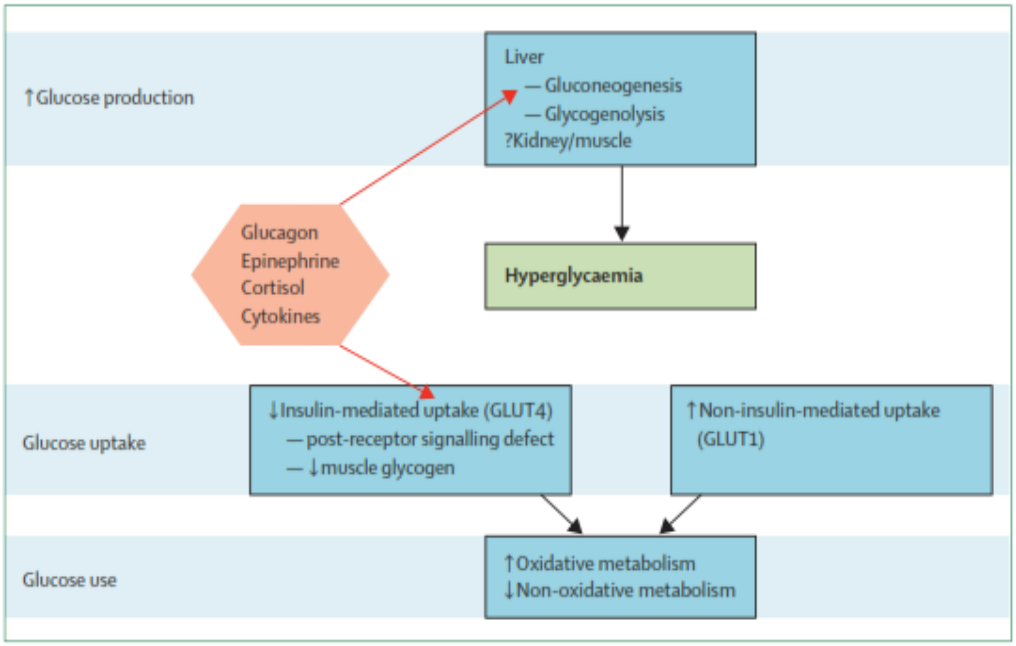
These counter-regulatory hormones inhibit hepatic glycogenesis and peripheral glycolysis while promoting gluconeogenesis, hepatic and muscle glycogenolysis, and peripheral lipolysis ***(McCowen et al;2008).***

Glucagon, which mainly promotes hepatic glycogenolysis and gluconeogenesis, was shown to be a major factor for the development of hyperglycemia in burn patients ***(Dhindsa et al;2004).***

Peripheral glycolysis and the breakdown of glycogen, lipids, and later, muscle protein provides the substrates for hepatic gluconeogenesis in the form of pyruvate, glycerol, and alanine ***(Mizock et al;2005).***

- ***Peripheral and Hepatic Insulin Resistance***

Proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6were both shown to have the potential to induce a state of peripheral and hepatic insulin resistance (**Ma *et al;2006).***

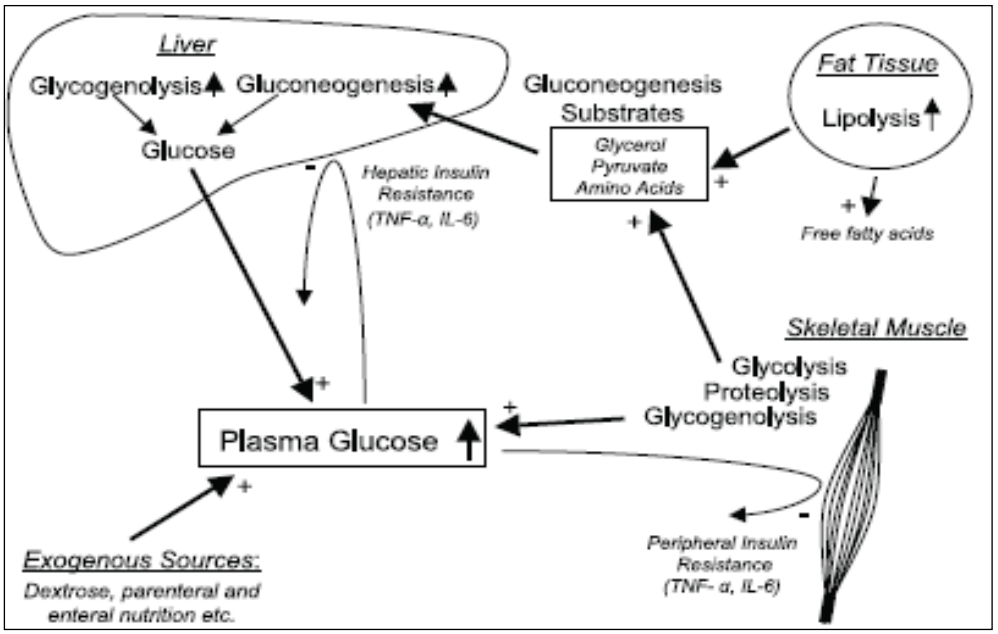


Figure(1): Glucose metabolism in stress hyperglycemia ***(Matthias et al;2006).***

- ***Other Factors Promoting Stress Hyperglycemia***

Increased gluconeogenesis fueled by proteolytic, lipolytic, and glucolytic metabolites combined with hepatic insulin resistance are considered the main causes of stress-induced hyperglycemia, but more obvious factors such as exogenous dextrose, enteral or total parenteral nutrition, and simple bed rest can further aggravate this picture Dextrose administered at a rate of > 4 mg/kg/min to patients with total parenteral nutrition was shown to increase the rate of hyperglycemia in non-diabetic patients by 50%(**Rosmarin *et al;1996).***

Bed rest alone, even in the absence of obvious disease, leads to impaired skeletal muscle glucose uptake combined with increased fasting plasma insulin concentrations, both hallmarks of peripheral insulin resistance (**Desai *et al;2000).***



Figure(2): Simplified over view of glucose metabolism during stress. ***(Matthias et al;2006).***

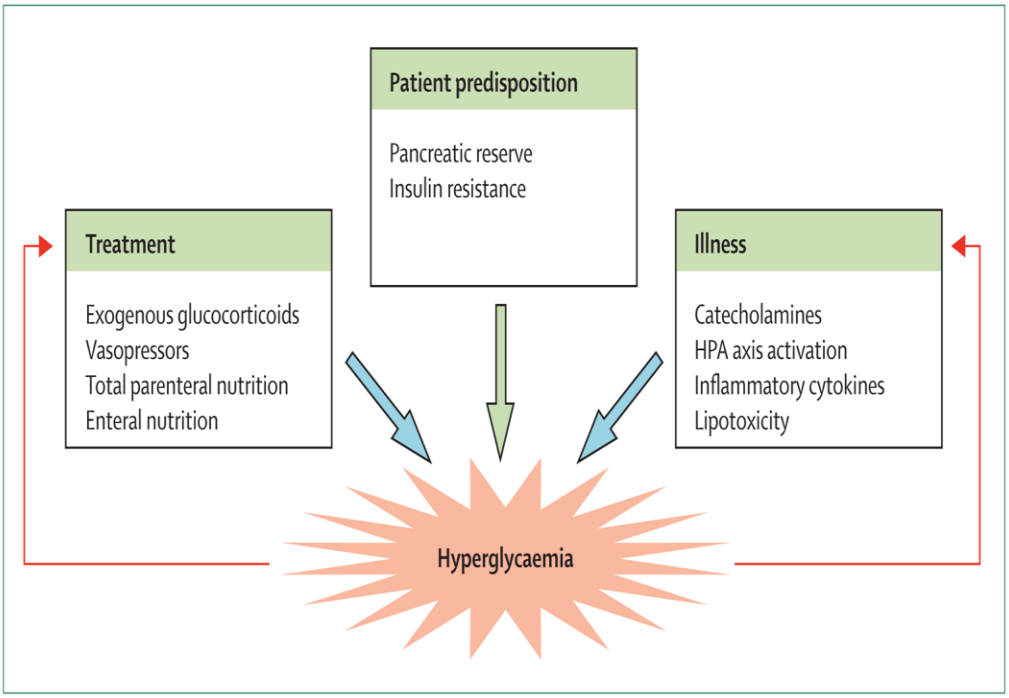
- ***Pathophysiology of Hyperglycemia in Acute Stroke***

Hyperglycemia after acute stroke may be attributable to several underlying mechanisms. These include: a non-specific reaction to acute stress; autonomic, hormonal, and metabolic alterations as a result of tissue injury; uncovering of underlying latent diabetes by the acute stroke; activation of the hypothalamo-hypophyseal-adrenal axis attributable to a direct effect of brain ischemia on the pituitary; and irritation of the glucose regulatory centers in the brain by a stroke ***(Matthias et al;2006).***

By far, the most popular belief is that stroke related hyperglycemia is a stress response with activation of the

hypothalamo-hypophyseal-adrenal axis, which leads to an increase in cortisol and catecholamines. According to this simple explanation, the poor stroke outcome in patients with hyperglycemia may be because more severe stroke induces higher levels of catecholamines and corticosteroids and represents an epiphenomenon associated with a poor outcome rather than having any causal relationship ***(Murros et al;2009).***

Hyperglycemia in acute stroke is probably the result of multiple factors, including cytokine-induced resistance to insulin action **(Garg *et al;2011).***



Figure(3): Multifactorial causes of stroke related hyperglycemia (***Dungan et al;2009).***