# Hyperglycemia as a Prognostic Factor In Acute Ischemic Stroke Patients

Thesis

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in General Intensive Care


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بسم الله الرحمن الرحيم

# قالوا

## سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

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**Mahmoud Abdallah Mohamed**

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# List of Abbreviations

| Abbr. | Full-term |
|---|---|
| **ACTH** | : Adrenocorticotrophic hormone (ACTH |
| **ADA** | : American Diabetes Association |
| **ASPECTS** | : Alberta Stroke Program Early CT score |
| **ATP** | : Adenosine Triphosphate |
| **BG** | : Blood Glucose |
| **BMI** | : Body mass index |
| **BP** | : Blood pressure |
| **CT** | : Computed tomography |
| **CTA** | : Computed tomography angiography |
| **DBP** | : Diastolic blood pressure |
| **DM** | : Diabetes mellitus |
| **DSA** | : Digital subtraction angiography |
| **DWI** | : Diffusion weighted imaging |
| **EEG** | : Electroencephalography |
| **FFAs** | : Free fatty acids |
| **HbA1c** | : Hemoglobin A1c |
| **HPA** | : Hypothalamic-pituitary-adrenal |
| **IA** | : Intra-arterial |
| **ICA** | : Internal carotid artery |
| **ICP** | : Intracranial pressure |
| **ICU** | : Intensive care unit |
| **IL-1** | : Interleukin-1 |
| **IV** | : Intra-venous |
| **MAP** | : Mean arterial blood pressure |

**MCA** : Middle cerebral artery

**MRI** : Magnetic resonance imaging

**NASCET** : North American Symptomatic Carotid Endarterectomy Trial

**NIHSS** : National Institute of Health Stroke Scale

**NINDS** : National Institute of Neurological Disorders and Stroke

**OGTT** : Oral glucose tolerance test

**OR** : Odds ratio

**POC** : Point of care

**PPAR1** : Peroxisome proliferator-activated receptors-l

**Rt-PA** : Recombinant tissue-plasminogen activator

**SBP** : Systolic blood pressure

**SQ** : Subcutaneous

**TCD** : Transcranial Doppler

**TIA** : Transient ischemic attack

**TIAs** : Transient ischemic attacks

**TNF-a** : Necrosis factor-a

**TNF-a** : Tumor necrosis factor

**TOAST** : Trial of ORG 10172 in Acute Stroke Treatment

**TOAST** : Trial of Org in Acute Stroke Treatment

**TPN** : Total parenteral nutrition

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# Abstract

**Background:** Hyperglycemia is encountered in 20% to 40% of acute stroke patients, with or without a pre-morbid diagnosis of diabetes mellitus. Hyperglycemia is a risk factor for infarct expansion and poor outcome through the first 72 hours of hospitalization in both diabetics and non-diabetics. **Aim of the Work:** to study the glycemic status after acute ischemic stroke and assess its role in influencing stroke out-come as regards the duration of hospital stay, motor deficit outcome and mortality. **Patients and Methods:** This retrospective study was conducted in Elzaiton specialized hospital and Ain Shams University from June 2016 to June 2017 on 80 patients after approval of local medical ethical committee. Patients with acute ischemic stroke without other major comorbidities within 24 hours of onset of symptoms were evaluated. **Results:** The study revealed that hospital stay mean was 12.04±9.61 (in control group) and 21.36±12.49 (in uncontrolled group), with p-value < 0.022 S. A highly statistically significant difference between controlled and uncontrolled according to increase motor power at ICU admission in controlled a highly statistically significant difference between controlled and uncontrolled according to increase motor power discharge in controlled group. A highly statistically significant difference was found between both groups as regards outcome (mortality). **Conclusion:** Hyperglycemia is common among acute stroke patients and is associate with less favorable outcome as regards mortality, hospital stay and functional outcome and euglycemic control is recommended in these patients.

**Key words:** Hyperglycemia, Acute Ischemic Stroke

# Introduction

Whereas diabetes mellitus is clearly a risk factor for the occurrence of stroke and for its poor prognosis, hyperglycemia without pre-existing diabetes mellitus is also linked to increased mortality and morbidity in stroke patients ***(Heuschmann et al., 2004).***

It was found that 24% of adults with diabetes and hyperglycemia are being hospitalized at least once in the year ***(Umpierrez et al., 2002).***

The influence of diabetes mellitus as an independent predictor of the incidence of ischemic stroke is well recognized and relates to a variety of causes ***(Jorgensen et al., 2004).*** Similarly, several studies have indicated that patients with diabetes are more likely to die or to have substantial neurological disability after acute stroke than nondiabetic subjects ***(Candelise et al., 2005).***

However, between 20% and 40% of patients admitted with ischemic stroke are hyperglycemic, often without a pre-existing diagnosis of diabetes ***(Kiers et al., 2000).***

Another study suggests that the relative risk of death in hyperglycemic nondiabetic stroke patients is increased by 3.3% ***(Capes et al., 2001).*** Another analysis has confirmed the importance of acute hyperglycemia as a predictor of outcome after stroke ***(Bruno et al., 1999).***

# Aim of the Work

To study the glycemic status after acute ishemic stroke and assess its role in influencing stroke out-come as regards the duration of hospital stay, motor deficit outcome and mortality.

# Stress Hyperglycemia

Hyperglycemia is a commonly encountered issue in critically ill patients in the intensive care setting even in the absence of pre-existing DM, and is associated with increased morbidity and mortality regardless of the reason for admission. Furthermore, both the admission as well as the mean glucose level during the hospital stay is strongly associated with patient outcomes ***(Egi et al., 2008).***

One study described hyperglycemia during hemorrhagic shock; and it is now well known that acute illness or injury may result in hyperglycemia, insulin resistance and glucose intolerance, collectively termed stress hyperglycemia ***(Badawi et al., 2012).***

Stress hyperglycemia is very common among critically ill patients. The frequency of hyperglycemia depends on the type of patients being studied. ***(Langouche and Van den Berghe, 2006)***

Prevalence of hyperglycemia range from 32% to 38% in community hospitals 41% of critically ill patients with acute coronary syndromes, 44% of patients with heart failure and 80% of patients after cardiac surgery ***(Ling et al., 2012).*** The occurrence of hyperglycemia is even more evident in critically ill patients where 31% of the population will have at least one blood glucose reading (200 mg/dl) and nearly 100% will have a blood glucose (110 mg/dl) during intensive care unit ***(Kansagara et al., 2011).***

These patients may have previously undiagnosed diabetes, receiving a diagnosis for the first time and others might manifest "stress hyperglycemia" during an acute illness that resolves by the time of discharge; ***Table1 (McCowen et al., 2001).***

**Table (1):** Risk factors for development of stress hyperglcemia in critical illness

| Factor | Major Mechanism |
|---|---|
| Preexisting diabetes mellitus | Insulin deficiency (relative or absolute) |
| fusion of catecholamine pressors | Insulin resistance |
| Glucocorticoid therapy | Insulin resistance |
| Obesity | Insulin resistance |
| Increasing Acute Physiology and Chronic Health Evaluation (APACHE) score | Higher counterregulatory hormone levels* Insulin deficiency |
| Older age Excessive dextrose administration | Glucose removal rates overwhelmed in the face of |
| Pancreatitis (acute and chronic) | ongoing hepatic glucose production Insulin deficiency |
| Sepsis | Insulin resistance |
| Hypothermia | Insulin deficiency |
| Hypoxemia | Insulin deficiency |
| Uremia | Insulin resistance |
| Cirrhosis | Insulin resistance |

***(McCowen et al., 2001)***

## PATHOGENESIS

The mechanisms underlying the development of hyperglycemia in critical illness include a release of counter-regulatory stress hormones (corticosteroids and catecholamines) and proinflammatory mediators and the administration of exogenous corticosteroids, vasopressors, and parenteral solutions containing dextrose. Gluconeogenesis, with glucagon as the

prime mediator (but also cortisol and epinephrine), seems to be the most important contributor to stress hyperglycemia ***(Dungan et al., 2009).*** Critical illness also deranges the immune system and the inflammatory response. This response becomes nonspecific, causing oxidative stress, mitochondrial dysfunction, cell death, and tissue injury and ultimately leading to organ failure ***(Mizock, 2001).***

**Pathophysiology of Stress Induced Hyperglycemia**

Hospital related hyperglycemia results from activation of insulin counter regulatory hormones caused by stress. Glycemic control is further impaired by administration of drugs which increase insulin resistance such as catecholamines and steroids. Severe hyperglycemia is a catabolic state associated with adverse electrolyte and volume shifts ***(Wexler and Cagliero, 2007).*** Mechanisms include high tissue and circulatory concentration of inflammatory cytokines and a reduction of glucose uptake capacity in peripheral tissues ***(Marik PE, Raghavan M., 2004).*** There is increased hepatic glucose production, depressed glycogenesis, and glucose intolerance.

Increased production of counter regulatory hormones i.e. glucagon, catecholamines, cortisol and growth hormone and tumour necrosis factor (TNF-a) increases insulin resistance thereby decreasing insulin action ***(Umpierrez et al., 2002).***

These cumulative metabolic alterations result in hyper-glycemia, glucosuria, ketonuria, osmotic diuresis and loss of

water and electrolytes resulting in dehydration, hemodynamic instability and poor tissue perfusion. Osmotic diuresis can predispose to symptomatic hyponatremia. Loss of lean body mass, negative nitrogen balance causes impaired healing and decreased resistance to infection ***(Pakhetra et al., 2011).***

**Physiological effects of stress:**

There are many types of stress associated with hospitalization and illness. There are psycological, emotional and physical stressors. ***Mechanick, (2006)*** reported in a review of the mechanisms of stress hyperglycemia that, "A 'stressor' is an event that constitutes a threat to homeostasis. 'Stress, on the other hand, is the response to a stressor and consists of a physiologic component and a behavioural component".

Stressors can be further categorized as either cognitive such as fear, depression, bereavment ***(Mechanick, 2006)*** or non-cognitive (physical such as injury, surgery, infection, pain) ***(Saladin, 2007).***

The stress response is the body's uniform reaction to all types of stress; stress hyperglycemia is one of the physiological components of stress response caused by cognitive and non-cognitive stressors associated with hospitalization and illness ***(Saladin, 2007).***

Stress and critical illness have numerous effects on physiology. The stress response changes endocrine secretions and causes many metabolic changes.