Post Stroke Hyperglycemia as a Marker of Stroke Severity and Prognosis: A Cohort Study

Thesis
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By

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Abstract

Background : Stroke is the third most leading cause of death worldwide after coronary heart disease and cancer especially ischemic infarcts. Hyperglycaemia is common in patients with acute stroke, occurring in up to 60% of patients overall and approximately 12–53% of acute stroke patients without a prior diagnosis of diabetes, **Aim of the Work:** The aim of this work is study of the glycemic status after acute stroke and assess the role of glycemic status in influencing stroke outcome. **Patients and Methods:** This was a prospective cohort study conducted in the Critical Care Department of Ain-Shams University Hospitals and Damanhour Medical National Institute for six months from January 2018 to June 2018. **Conclusion:** From our study we can conclude that diabetes mellitus as a risk factor in cases of stroke leads to increase complications and worsens the outcome in cases of stroke whether hemorrhagic or ischemic. **Recommendations:** From our study we recommended strict control of diabetes mellitus when present in cases of stroke to avoid bad outcome and to prevent complications in these cases.

Keywords: AP-1: Activator protein-1, CNS : Central nervous system, MMPs : Matrix metalloproteinases, MSOD :Mitochondrial superoxide dismutase, PAI-1: Plasminogen activator inhibitor-1, PSH: Post stroke hyperglycaemia, ROS : Reactive oxygen species

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List of Abbreviations

AP-1	:	Activator protein-1
AS	:	Acute stroke
BBB	:	Blood–brain barrier
CBC	:	Complete blood picture
CDC	:	Center for Disease Control
CNS	:	Central nervous system
CT	:	Computed tomography
DM	:	Diabetes mellitus
DNA	:	Deoxyribonucleic acid
Egr-1	:	Early Growth Response-1
FDA	:	Food and Drug Administration
GKI	:	Glucose-potassium-insulin
GLIAS	:	Glycemia in Acute Stroke study
HDL	:	High density lipoprotein
HG	:	Hyperglycemia
ICU	:	Intensive Care Unit
I-kB	:	Inhibitor kappa B
IU	:	Insulin units
LDL	:	Low density lipoproteins
IL	:	Interleukin
ICH	:	Intra-cerebral hemorrhage
IS	:	Ischemic stroke
MMPs	:	Matrix metalloproteinases
mRNA	:	Messenger Ribonucleic acid
MSOD	:	Mitochondrial superoxide dismutase
MCP-1	:	Monocyte chemoattractant protein
NIHSS	:	National Institute Of Health Stroke Scale
NO	:	Nitric oxide

List of Abbreviations (Cont.)

NF-kB	:	Nuclear Factor kB
NMDA	:	N-methyl-D- aspartate
PAI-1	:	Plasminogen activator inhibitor-1
PSH	:	Post stroke hyperglycaemia
RCT	:	Randomised controlled trials
ROS	:	Reactive oxygen species
WHO	:	The World Health Organization
TF	:	Tissue Factor
TNF	:	Tumor Necrosis Factor
VISTA	:	Virtual International Stroke Trials Archive

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Introduction

Stroke is the third most leading cause of death worldwide after coronary heart disease and cancer especially ischemic infarcts. Hyperglycemia is common in patients with acute stroke, occurring in up to 60% of patients overall and approximately 12–53% of acute stroke patients without a prior diagnosis of diabetes ***(Guyomard et al., 2009)***. The incidence of post-stroke hyperglycemia was approximately 45% in studies with frequent glucose measurements and a cut-off of 126 mg/dl to define hyperglycemia ***(Allport et al., 2006)***.

Several mechanisms underlying hyperglycemia after ischemic stroke have been proposed. Specifically, ischemic stroke–related cytokines have been shown to activate the hypothalamus–pituitary–adrenal axis, leading to increased serum glucocorticoid levels and activation of the sympathetic autonomic nervous system, leading to catecholamine release, resulting in excessive glucose production and insulin resistance ***(Chan et al., 2005)***.

Studies of stroke patients associated with hyperglycemia suggested that ‘stress hyperglycemia’ (raised blood glucose levels without a previous diagnosis of diabetes) was associated with a poorer outcome ***(Khairollah et al., 2007)***.

Hyperglycemia in acute stroke patients has been associated with longer in-hospital stay, increased cost and mortality, that's why management of patients with hyperglycemia-associated acute stroke is of utmost importance ***(Bruno and Levine, 2002).***

Aim of the Work

The aim of this work is study of the glycemic status after acute stroke and assess the role of glycemic status in influencing stroke outcome.

Chapter (1)

Acute stroke

Background:

Stroke is a ubiquitous killer of almost unmatched proportions. The World Health Organization (WHO) estimates that around 17.5 million people succumb annually to cardiovascular diseases, making this the world's most deadly category of disease. Of cardiovascular diseases, stroke, which is responsible for 6.7 million of those deaths, is second only to coronary heart disease ***(WHO, 2016)***. The majority of these deaths take place in low-income and middle-income countries; however, even in the United States, stroke claims enough lives to rank as the fifth leading cause of death ***(CDC, 2016)***.

Stroke kills about 140, 000 Americans each year that's 1 out of every 20 deaths. Someone in the United States has a stroke every 40 seconds. Every year, more than 795, 000 people in the United States have a stroke. About 610, 000 of these are first or new strokes. About 185, 00 strokes nearly 1 of 4 are in people who have had a previous stroke. ***(Benjamin et al., 2017).***

This translates to one stroke death every 4 minutes. Even so, mortality alone hardly accounts for the total suffering caused by stroke. Stroke is the leading cause of disability in the US ***(Krishnamohan, 2017)*** because of the

severity and frequency of impairment left in its wake; in fact, only 10% of stroke patients ever recover completely ***(Crocco and Goldstein, 2014).*** For many survivors, approximately 4.5 million in the United States, the life that remains after stroke barely resembles the one that preceded it ***(Chandra et al., 2017)***.

According to the National Institutes of Neurological Disorders and Stroke, five kinds of disability can result after initial stabilization: paralysis or other motor difficulties, sensory disturbances, cognitive impairment, and emotional disturbances. Patients can also experience urinary incontinence and sexual impairment. They can be victims of a number of chronic pain disorders ***(Chandra et al., 2017)***.

Types of Stroke:

Ischemic Stroke (IS):

Ischemic stroke (IS) is a major type of stroke, defined broadly as a neurological deficit that is caused by impaired blood flow to a focal area of the brain. It is responsible, at about 87% for the majority of all strokes ***(Crocco and Goldstein, 2014)***. Within this large proportion, however, many different subtypes are concealed. IS can be classified relatively according to the clot that precipitates it ***(Chandra et al., 2017)***.

A population-based study by Petty et al. (1999), for example, recognizes five separate causative categories: large-vessel cervical or intracranial atherosclerosis with >50% stenosis (16%), cardioembolic (29%), lacunar (16%),

uncertain cause (36%), and other (3%). In addition, ischemic strokes can be subdivided according to the infarct position; due to its centrality to the discussion of clinical presentation,Since some areas of the cerebrovascular tree are more essential to survival than others, mortality varies substantially across these subtypes. Overall, in-hospital mortality for IS has been reported to be 5-10% ***(Crocco and Goldstein, 2014; Chandra et al., 2017)***.

The risk factors of stroke are also highly heterogeneous. But, they may be generally clumped into two camps: modifiable and non-modifiable ***(Chandra et al., 2017)***. Major non-modifiable factors include age, gender, ethnicity, and genetic predisposition. Age is considered most important; the mean age of onset for ischemic stroke is 70.5 years ***(Ledyard, 2013)***. Genetic factors, by contrast, are currently considered to be relatively minor ***(Rockman and Maldonado, 2013)***.

Of the modifiable risk factors, the most important are hypertension, dyslipidemia, diabetes mellitus (DM), and smoking ***(Krishnamohan, 2017)***. Others include obesity, heavy alcohol consumption, and renal insufficiency. The importance of prevention by risk factor modification cannot be understated ***(Rockman and Maldonado, 2014)***.

Pathophysiology:

The primary mechanism by which stroke causes injury is the focal deprivation of blood flow to the cerebral parenchyma. While a variety of phenomena can result in such ischemia, large-arterial atherosclerosis is the most

prevalent. In atherosclerosis, accumulations of fatty material in the arterial subintima induce platelet clumps. These clumps then attract thrombin, fibrin, and erythrocyte debris that can ultimately coagulate to a size that poses stenotic risk to the cerebral vasculature ***(Chandra et al., 2017)***.

The resulting thrombus deprives cells of the cerebral parenchyma of the oxygen they need to function, causing pathology. Plaque development and succeeding stenosis are not necessarily *in situ*, However, Plaques can also travel to the cerebral circulation from another location, in which case they are called emboli. The heart, by way of atrial fibrillation, is the most common source of these, but they can come from other diseased parts of the arterial system, as well ***(Goldstein et al., 2014)***.

There are many other pathogenic routes to cerebral ischemia. In addition to the large-vessel infarcts which involve the carotid, vertebral, and basilar arteries, as well as major branches of the circle of Willis, small-vessel (or lacunar) infarcts are also a major etiology. Commonly by lipohyalinosis or micro-atheroma, but also occasionally by the same mechanism by which larger arteries are blocked, the blockage of these small, penetrating arteries running at right angles to the major branches produces the focal deficits characteristic of stroke. Some less frequently observed causes include acute arterial dissection secondary to fibromuscular dysplasia, hematologic disorders such as sickle cell anemia, and recreational use of cocaine or amphetamines ***(Ledyard, 2013; Chandra et al., 2017)***.