Correlating CT findings of stroke with hyperglycemia in acute ischemic stroke patients

Ameer Shaker* MD, (FIBMS, FICNS)*, Laith Ahmed Khalaf MD (DMRD, FJMC)*,MohammedTuamaJebur MD, FICNS*

ABSTRACT

Background: Studies show that diabetic patients have a higher incidence of ischemic stroke than non-diabetic patients. In the Framingham study the incidence of thrombotic stroke was 25 times higher in diabetic men and 36 times higher in diabetic women than in those without diabetes

Objectives: aim of this study to analyze topography in diabetic patients.

Type of study: Cross sectional study.

Methods: 48 patients with acute stroke were classified into 4 groups: euglycemic, stress hyperglycemia, newly diagnosed diabetics, and known diabetics.

Results:no significant differences were found in the type, site or size of stoke between the 4 groups, higher levels of blood sugars and hemoglobin $HbA1_c$were significantly higher with chronic white matter ischemia in stroke patients.

Conclusions: hyperglycemia, diabetics and chronic glycemic disturbance may play role in the pathophysiology of white matter ischemia.

Key words: diabetic, hyperglycemia, white matter ischemia, stroke

Al-Kindy College Medical Journal 2017: Vol.13 No.2
Page: 78-82

- Department of neurology, Baghdad teaching hospital
* *Received 30th Nov 2016, accepted in final 25th July 2017*
Corresponding to : Ameer Shaker *email:* ali.ne75@yahoo.com, ameerne38@gmail.com

Epidemiological studies show that diabetic patients have a higher incidence of ischemic stroke than non-diabetic patients[1,2]. In the Framingham study the incidence of thrombotic stroke was 25 times higher in diabetic men and 36 times higher in diabetic women than in those without diabetes[3]. Previous studies have found a range of prevalence of undiagnosed diabetes in acute stroke populations from 6%[4] to 42%[5]. The type and topography of diabetes-related cerebral infarction may differ from brain infarcts in non-diabetics. Diabetes mellitus (DM) is a major health and economic problem; it is a chronic epidemic disease occurring across the world with multiple complications. The size of the diabetic population worldwide, according to the International Diabetes Federation (IDF), is expected to consist of 380 million peoples by 2025.The main types of DM are type 2 DM, formerly called non-insulin-dependent DM (NIDDM), is observed in 90% of the diabetic population and is characterized by insulin resistance in peripheral tissues and an insulin secretory defect of the beta cell. This form of DM develops gradually and is occult at earlier stages so that the onset of diabetes usually precedes the clinical manifestations and diagnosis for many years. The remaining 10% includes mainly patients with type 1 DM and also some other less frequent types such as gestational diabetes, drug-induced diabetes and MODY (maturity-onset diabetes in youth). The cerebrovascular mortality in the diabetic population is high due to the coexistence of coronary heart disease and cerebrovascular disease. In the MRFIT cohort, diabetic patients had a threefold increased likelihood of developing a stroke. Particularly among subjects younger than 55 years, the risk of stroke is increased more than tenfold in diabetic patients. Diabetes also increases stroke-related mortality, while the risk of dementia following a stroke is increased by threefold. [6]

Methods : A 40 patients with acute ischemic stroke, all had CT scan. These patients were admitted to Baghdad teaching hospital from 1st of January 2014 to 1st of February 2015.Written consentient were taken from the patients participate in this study. Ischemic Stroke is an imprecise term used to describe the sudden onset of a persistent neurological deficit(lasting more than 24 hour) caused by partial or complete blockage.Thirteen of the 40 patients (32 %) had a history of previous stroke. Fasting plasma glucose, glycosylated hemoglobin (HbA1c), packed cell volume, urea,creatinine,cholesterol,triglycerides and HDL were all measured.HbA1c concentration, free of labile A1C, was measured by The Bio-Rad D-10 Hemoglobin A1c system that utilizes principles of ion-exchange high-performance liquid chromatography (HPLC).

Patients were divided into four groups: euglycemicpatients with no history of DM (fasting plasma glucose < 7 mmol/l or <126 mg/dl), including euglycemicpatients with normal HbA1c concentration (< 6.5%) ; patients with stress hyperglycemia (no history of diabetes, glucose > 7.8 mmol/l or >140 mg/dl, HbA1c < 6.5%); newly diagnosed patients with DM (no history of diabetes, glucose > 7 mmol/l or >126 mg/dl, HbA1c > 6.5%); and known patients with DM. Diagnosis of D.M was done using WHO criteria for fasting glucose. CT was performed in all of the 48 patients with a Philips Brilliance 64-slice CT scanner using 120 kV and 300 mAs and stroke windows level 40 HU/windows width 40 HU and no contrast was used. No multiplanar reconstruction was used. Stroke type, site, and size data were taken from all of 40 patients who had CT scans. Six diagnostic stroke types were used: cortical infarct; lacunar infarct; striatocapsular infarct; brainstem or cerebellar infarct;and extensive infarction.All infarcts and

lesions were reported, including the presence or absence of chronic ischemic white matter changes, also called leukoaraiosis. Ischemic infarcts were classified into three groups according to size: not visible or small (no lesion or one with a maximum diameter of 5 mm visible in not more than two adjacent slices); medium (intermediate between small and large); and large (involving at least one complete vascular territory).

Results: Patients were divided into four groups'16 patientsnormoglycemicwith no history of DM, 20 patients with DM, 3 patients with stress hyperglycemia, and 1 patient with newly diagnosed DM.

Table (1): patients characteristics subdivided according to DM

Variables	Normoglycemic	Stress hyperglycemia	New onset DM	DM
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age	64.56 ± 15.13	66 ± 12.29	50	68 ± 10.29
PCV	43.26 ± 6.59	46.67 ± 7.55	24	42.06 ± 9.77
Cr	0.94 ± 0.54	0.75 ± 0.15	0.95	0.96 ± 0.58
Urea	62.81 ± 69.29	31.67 ± 16.0.7	70	54.2 ± 25.19
Cholesterol	204.89 ± 28.62	177.7 ± 59.1	233	218.89 ± 27.38
Triglyceride	139.26 ± 19.14	103.97 ± 39.58	163	150.73 ± 37.13
HDL	40.89 ± 12.4	39.27 ± 3.45	33	44.55 ± 10.64
FBS	113.21 ± 0.52	163.53 ± 30.77	276	230.71 ± 82.31
HbA1C	5.39 ± 0.52	6.03 ± 0.55	8.4	7.11 ± 0.36
	No (percent)	No (percent)	No (percent)	No (percent)
Gender (female)	9 (56.3%)	1 (33.3%)	0	12 (60%)
Gender (male)	7 (43.8%)	2 (66.7%)	1(100%)	8 (40%)
Hypertensive	12 (75%)	3 (100%)	0	17 (85%)
Smoker	3 (18.8%)	1 (33.3%)	0	9 (45%)

Table (2): type of stroke in all patients using CT scan

	Normoglycemic (16)	Stress hyperglycemia + DM (24)	OR	P value
Lacunar	3	5	1.14	0.601
Striatocapsular	2	2	0.636	0.529
Brainstem / cerebellar	3	4	0.837	0.592
Cortical	4	8	1.5	0.42
Extensive infraction	4	5	0.789	0..525
Leukoaraiosis	2	10	5	0.049

Table (3): size of the infract in patients

	Normoglycemic (16)	Hyperglycemia + DM (24)	OR	P value
Large	11	10	0.325	0.087
Medium	1	3	2.143	0.471
Small	4	11	2.538	0.159

Table (4): HbA1c for patients with stroke divided according to leukoaraiosis

	No leukoaraiosis	Leukoaraiosis	P value
HbA1c	6.17 ± 1.07	6.85 ± 0.52	0.01

Discussion : These results revealed that 50%of the patients presenting with stroke to emergency unit have known DM;this rate is higher than the prevalence reported in comparable age group in the general population of Busselton (Western Australia) with a prevalence of 3.4% of known diabetics [7]. Kiers *et al* had shown a high prevalence of both known diabetes (17.0%) and newly diagnosed diabetes (11.4%) in patients presenting with stroke to an acute hospital stroke unit[8]. Previous reports of the prevalence of diabetes in acute stroke have provided widely varying results, which may reflect different methods of measurement of HbA1c[4,5]. Riddle and Hart[5] measured HbA1c in patients with recent stroke or transient ischemic attacks and found that 42% of such patients had abnormal concentrations. In a study by Oppenheimer *et al*[4] the concentration of HbA1c free of labile A1c was determined with an isoelectric focusing technique;they found only a 6% prevalence of undiagnosed diabetes in patients with acute stroke. The two criteria for the diagnosis of diabetes; an elevated fasting plasma glucose > 7 mmole(126 mg/dl) and HbA1c > 6.5%. Various mechanisms have been implicated to explain the higher incidence of stroke in

diabetic and hyperglycemic patients. These include an alteration of post-ischemic cerebral blood flow related to impaired cerebral autoregulation[9], a hyperosmolar effect of blood glucose[10], and interference with collateral blood flow in the peri-ischemic zone due to proliferative angiopathy of small cerebral blood vessels[11]. Pulsinelli*et al*suggested that excessive accumulation of lactic acid resulting from anaerobic glycolysis by an ischemic brain is the most likely explanation of the enhanced brain damage in hyperglycemic animals[10].

Thirty seven percent of our patients have small or invisible lesions (infarction) because mainly performed early CT scans in our study, so in acute cerebral infarction, CT scans are often normal, and measurement of lesion size by CT scan should ideally be performed at 7-10 days[12]. Patients in our study with large infarcts on clinical criteria might therefore have shown no abnormality or only a small lesion on an early CT scan.

We found no statistically significant differences in the type, site or size of strokebetween the 2 groups, although our numbers were small. Kiers *et al*[8] had shown that there was marginally greater proportion of patients with a diagnosis of cortical infarction in newly diagnosed diabetics when compared with the euglycemic, non-diabetic patients. Otherwise, no difference were found in the types of stroke between the four groups and no difference were found in the proportion of stroke types between euglycemic and combined hyperglycemic groups; Kiers *et al*[8] found also that there is no significant difference was found between the four groups with regard to sites of symptomatic and asymptomatic lesions on CT scan. In particular, there was no difference in the incidence of asymptomatic lacunas or leukoaraiosis. Kiers *et al*[8] found also that compared with euglycemic, non-diabetic patients there was a marginally greater number of large lesions in patients with stress hyperglycemia. In the newly diagnosed diabetics there were a larger number of patients with either a small lesion or normal CT scan [8].

Twelve patients had leukoariosis in our study, 10 of whom (83%) were hyperglycemic compared with (17%), 2 patients were euglycemicand this difference is statistically significant. and when we compare HbA1c mean in patients with leukoariosis and patients without leukoariosis, we find statistical significant,some studies assessing the relationship between WMD and DM, metabolic syndrome, dyslipidemia, higher levels of fasting glucose, and increased insulin resistance yielded controversial results[13].In these studies, however, HbA1c was not analyzed. A similar study by Heo*et al*[13] showed rather unexpected negative association between HbA1c and severe WMD in diabetic patients.

They did not take into consideration DM in their multivariate analysis, and their statistical methods differed from other studies. In the study of Murray et al [14] high HbA1c was associated with deep white matter hyperintensities. But this study had a relatively small sample size that was comprised primarily of elderly participants. Manschot*et al*[15] showed that brain atrophy and white matter changes in patients with DM might be responsible for cognitive decline and observed a modest association between HbA1c and white matter hyperintensities in a small cohort of patients with DM. A Magnetic resonance imaging (MRI) has been used in a number of studies to examine cerebral structure in patients with type 1 and type 2 diabetes and has pretty consistently found thebrains of such subjects to have leukoariosis, which are hyperintense white matter lesions[16,17] . One study found that 69% of middle-aged adults with long-standing type 1 diabetes had abnormal MRI scans, compared with 12% of healthy, aged-matched volunteers, with an increased number of larger, high-signal lesions in the cerebrum, cerebellum, and brain stem being the primary abnormality identified[16]. However, this was not confirmed by a more recent published study in which relatively young patients (25–40 years old) with type Idiabetes for more than 15 years did not have a significant difference in white matter hyperintensities compared with healthy controls. In addition, white matter hyperintensities did not correlate with depressive history, retinopathy, severe hypoglycemia, glycemia control, and most neurocognitive tests (with the exception of delayed memory)[18] . This is in agreement with previous studies[19,20]. The reason for the discrepancy may have been that subjects in the former study had more severe microvascular complications and those differences in cardiovascular risk factors between subjects with diabetes and controls were not controlled for. In patients with type 2 diabetes, these white matter hyperintensities have been noted to correlate with reduced performance on tests of attention, executive function, information processing speed, and memory[17,21]. The nature of these white matter lesions is uncertain, but investigators have hypothesized that they could represent demyelination, increased water content, angionecrosis, cystic infarcts, or gliosis (i.e. brain tissue scarring)[22] . Rozanski*et al*[23] found that in patients with first acute ischemic stroke (AIS), white matter ischemia was significantly associated with age, HTN and higher levels of HbA1c, but not elevated levels of TG, LDL, or total cholesterol. They say that this is the first study that they know of that shows a correlation between elevated HbA1c and WMD burden. Median levels of HbA1c were 5.7 to 5.9% in patients with any sign of WMD, vs. 5.3% in patients without hyperintensities. Interestingly, DM alone did not correlate as strongly, which they felt may be explained by the fact that patients diagnosed with DM may be under better control, thus have lower HbA1c's. In their study, DM was associated with WMD severity only in univariate analysis, but not in multiple regression analysis. Higher levels of HbA1c seemed to be stronger associated with WMD compared with the diagnosed DM variable.This may be explained by the fact that patients with glycemic disturbances, such as prediabetic or impaired glucose regulation, may have HbA1c levels >5.7% but not yet diagnosed with DM according to guidelines. Conversely, patients with DM may have tightly controlled glucose levels and, therefore, HbA1c levels below 5.7%. For the majority of patients, higher levels of HbA1c are associated with DM as expected. Therefore, poor glycemic control, with even slight disturbances reflected by HbA1c, may also be a risk factor for WMD. Median levels of HbA1c in groups of patients with any sign of WMD were 5.7% to5.9% versus 5.3% in patients without hyperintensities, and hence within the 5.7% to 6.5% range recommended by the

American Diabetes Association to diagnose prediabetic or high risk for DM.HbA1c is used to approximate serum glucose levels over the past 3 months. It is an end product of nonenzymaticglycation and thus a surrogate marker of glycemia. HbA1c presumably does not play a role in the development of microvascular changes in the brain.Whereas, hyperglycemia has been shown to lead to microinfarctions and white matter lesions indirectly;these processes could be explained by capillary thickening followed by narrowing of vessel lumen and subsequent chronic ischemia as found in the brains of patients with DM and WMD.Endothelial dysfunction in hyperglycemic states may also contribute to small vessel injury.The differences in levels of HbA1c were highly significant in their study but rather low, so that further investigations in larger cohorts are needed to explore the subgroup of patients with levels in the prediabetic range and confirm their findings before it could be used as a potential marker for increased WMD risk. White matter ischemia has gained interest in the potential role it may play in cognitive decline and as a risk factor in stroke, and by all accounts appears related to ongoing microvascular damage.All this underscores the critical importance of risk factor monitoring and management, hopefully long before a first stroke[23]. On the other hand, from 3 patients who had stress hyperglycemia,2 of them or 66.7% had large infarct size because size and severity of cerebral injury may be relevant in the causation of stress hyperglycemia and large strokes may lead to hyperglycemia[24-27]. Kiers et al had found a marginally greater number of large lesions in patients with stress hyperglycemia compared with the euglycemic, non-diabetic patients[8].Both fasting glucose and HbA1c should be estimated in clinical studies to enable differentiation between patients with stress hyperglycemia and those with unrecognized diabetes. Hyperglycemia detected during acute illness is associated with adverse outcomes. Among patients without known diabetes admitted to hospital with myocardial infarction (MI), stroke, pneumonia, and exacerbation of chronic obstructive pulmonary disease (COPD), higher glucose levels are associated with in-hospital and longer-term mortality, intensive care unit admission, prolonged length of stay, and discharge to long-term nursing care. Hyperglycemia during acute illness may be caused by drugs such as systemic corticosteroids, thiazides, phenytoin, phenothiazines, protease-inhibitors, and beta-agonists or as a result of "stress hyperglycemia" where counter-regulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone promote hepatic gluconeogenesis. Hyperglycemia detected during acute illness may also be the first clinical evidence of underlying or incipient type 2 diabetes[28].

References

1. Garcia MJ, McNamara PM, Gordon T, Kannell WB. Morbidity and mortality in diabetics in the Framingham population. Diabetes 1974; 23:105-11.
2. Toyama K, Nerishi S, Kawamoto S, Kato H, Miyake S, Nagataki S. Risk factors of cerebro-cardiovascular dis- orders in mild diabetes. Tohoku J7 Exp Med 1983;141(suppl);535-40.
3. Kannell WB, McGee DL. Diabetes and cardiovascular disease. The Framingham Study. JAMA 1979;241: 2035-8.
4. Oppenheimer SM, Hoffbrand BI, Oswald GA, Yudkin JS. Diabetes mellitus and early mortality from stroke. BMJ 1985;291:1014.
5. Riddle Mc, Hart J. Hyperglycemia, recognised and unrecognised, as a risk factor for stroke and transient ischemic attacks. Stroke 1982;13:356-9
6. Raptis AE, MarkakisKP,Mazioti MC ,RaptisSA,Dimitriadis GD. What the radiologist needs to know about the diabetic patient. Insights Imaging.2011 FEB 2; 2:193-203
7. Glatthaar C, Welborn TA, Stenhouse NS, Garcia-Webb P. Diabetes and impaired glucose tolerance. A prevalence estimate based on the Busselton 1981 Survey. Med 3Aust 1985;143:436-40.
8. Kiers L,Davis S M, Larkins R, Hopper J, Tress B, Rossiter S C, Carlin J, Ratnaike S. Stroke topography and outcome in relation to hyperglycaemia and diabetes. J NeurolNeurosurg Psychiatry.1992;55: 263-27
9. Bentsen N, Larsen BO, Lassen NA. Chronically impaired autoregulation of cerebral blood flow in long-term diabetics. Stroke 1975;6:497-502.
10. PulsinelliWA,Waldman S, Rawlinson D, Plum F. Moderate hyperglycaemia augments ischemic brain damage: a neuropathologic study in the rat. Neurology 1982; 32:1239-46.
11. Alex M, Bacon EK, Goldenberg S, Blumenthal HT. An autopsy study of cerebrovascular accident in diabetes mellitus. Circulation 1962;25:663-73.
12. Brott T, Marler JR, Olinger CP, et al. Measurements of acute cerebral infarction: lesion size by computed tomography. Stroke 1989;20:871-7.
13. Heo SH, Lee SH, Kim BJ, Kang BS, Yoon BW. Does glycated hemoglobin have clinical significance in ischemic stroke patients? ClinNeurolNeurosurg. 2010;112:98-102.
14. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ. Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. Radiology. 2005;237:251-257.
15. Manschot SM, Brands AM, van der Grond J, Kessels RP, Algra A, Kappelle LJ, et al; Utrecht Diabetic Encephalopathy Study Group. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes. 2006;55:1106-1113.
16. Dejgaard A, Gade A, Larsson H, Balle V, Parving A, Parving HH 1991 Evidence for

diabetic encephalopathy. Diabet Med 8:162-167 [PubMed]

17. Akisaki T, Sakurai T, Takata T, Umegaki H, Araki A, Mizuno S, Tanaka S, Ohashi Y, Iguchi A, Yokono K, Ito H 2006 Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). Diabetes Metab Res Rev 22:376–384 [PubMed]
18. Weinger K, Jacobson AM, Musen G, Lyoo IK, Ryan CM, Jimerson DC, Renshaw PF 2008 The effects of type 1 diabetes on cerebral white matter. Diabetologia 51:417–425 [PubMed]
19. Brands AM, Kessels RP, Hoogma RP, Henselmans JM, van der BeekBoter JW, Kappelle LJ, de Haan EH, Biessels GJ 2006 Cognitive performance, psychological well-being, and brain magnetic resonance imaging in older patients with type 1 diabetes. Diabetes 55:1800–1806 [PubMed]
20. Yousem DM, Tasman WS, Grossman RI 1991 Proliferative retinopathy: absence of white matter lesions at MR imaging. Radiology 179:229–230 [PubMed]
21. Manschot SM, Brands AM, van der Grond J, Kessels RP, Algra A, Kappelle LJ, Biessels GJ 2006 Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 55:1106–1113 [PubMed]
22. Biessels GJ, Kappelle AC, Bravenboer B, Erkelens DW, Gispen WH 1994 Cerebral function in diabetes mellitus. Diabetologia 37:643–650 [PubMed]
23. RozanskiM,RichterTB,GrittnerU,EndresM,FiebachJB,Jungehulsing GJ. Elevated Levels of Hemoglobin A1c Are Associated With Cerebral White Matter Disease in Patients With Stroke. Stroke.2014 FEB 25 ;45:1007-1011.
24. Woo J, Lam CWK, Kay R, Wong AHY, Teoh R, Nicholls MG. The influence of hyperglycaemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. Arch Neurol 1990;47: 1174-7.
25. Melamed E. Reactive hyperglycemia in patients with acute stroke. . NeurolSci 1976;29:267-75.
26. Cox NH, Lorains JW. The prognostic value of blood glucose and glycosylated haemoglobin estimation in patients with stroke. Postgrad Med J 1986;62:7-10.
27. Samanta A, Blandford RL, Burden AC, Castleden CM. Glucose tolerance following strokes in the elderly. Age Ageing 1986;15:1 11-13.
28. McAllister David A. ,Hughes Katherine A.,LoneNazir, Mills Nicholas L., SattarNaveed, McKnight John,Wild Sarah H. Stress Hyperglycaemia in Hospitalised Patients and Their 3-Year Risk of Diabetes: A Scottish Retrospective Cohort Study**.** journal.pmed. 2014 August 19. DOI: 10.1371