
Stress Hyperglycemia in Acute Stroke Patients

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Abstract

Objective: To detect stress hyperglycemia in non diabetic patients with a acute stroke and to find its relation to age, sex, smoking, severity of stroke and CT finding.

Patients & Methods: From April to September 2004, 104 patients admitted to Al-Yarmouk Teaching Hospital, with acute stroke diagnosed clinically and by brain CT scan were tested for the presence of hyperglycemia if it is present; estimation of HbA_{1c} was done, to exclude those with prior DM.

Results: Four patients showed hyperglycemia and normal HbA_{1c} (i.e. < 5.2 %) which means stress hyperglycemia but no relation was found between stress hyperglycemia and age, sex, smoking, consciousness status and CT findings.

Conclusion: Stress hyperglycemia is not very rare, so it should be looked for. Further studies are needed to elucidate any relation with sex, severity and MRI or CT findings and to find out its optimal therapy.

Key words: Stress, Hyperglycemia, Acute Stroke

Introduction

During daily clinical practice, we commonly encounter hyperglycemia, in acutely ill patients. Thirty percent of patients admitted to an urban general hospital have fasting glucose more than 7 mmol/l (126 mg/dl) or two readings of random glucose levels more than 11.1 mmol/l (200mg / dl) ^[1]. The rate can be higher (40-50%) , if patients with acute stroke are taken, or hyperglycemic limit is taken at a lower level ^[2,3]. Thirty percent of admitted patients with hyperglycemia (10% of total admitted patients) have no past history of diabetes mellitus .

This hyperglycemia can be attributed to either prior undiagnosed diabetes mellitus with increasing hyperglycemia due to stressful illness or to hyperglycemia arising in non diabetic patients because of the effect of stress (stroke , myocardial infarction, septicemia, injuries, .. etc.) On counter-regulatory hormones secretion (glucagons, cortisol growth hormone and epinephrine) and cytokines ^[1].

In diabetic patients the effect of counter-regulatory hormones, will be even more prominent due to impaired secretion of insulin and insulin resistance ^[1].

Other causes of hyperglycemia should be ruled out, as excessive calories from enteral and parenteral nutrition as well as dextrose containing fluids given to acutely ill patients. Diabetogenic drugs should be asked for as corticosteroid, sympathomimetic drugs and immunosuppressant such as tacrolimus and cyclosporine ^[1].

Stroke is a common disease, it is the most frequent cause of permanent disability and it is the third leading cause of death among Americans, as more than 500 000 Americans sustain cerebrovascular accidents yearly ^[4].

It is well known, that diabetes increases the risk of ischemic stroke by 2-4 folds and it adversely affects the prognosis ^[5, 6, 7, 8], but its association with hemorrhagic stroke is controversial ^[9]. The prevalence of previously diagnosed diabetes, in acute stroke is 8-20 % but 16-24 % may have undiagnosed diabetes too ^[5], there is another significant proportion of patients who develop stress hyperglycemia that vanish with time. In this group of patients , the level of hyperglycemia is not a predictor marker for developing future diabetes , which may be predicted more by estimating the level of admission S. Fructosamine, as shown by Wahid et al in 2002 ^[10].

In patients without history of diabetes mellitus, blood glucose increases after the onset of acute stroke and this increase are related to the severity of stroke ^[11].

Patients with ischemic stroke and stress hyperglycemia are at increased risk of in-hospital mortality and poor functional outcome ^[2,3,8,11,12,13,14,15]. Acute post stroke hyperglycemia has been associated with larger infarction size, increased edema and decreased cerebral blood flow regardless to the presence of prior diabetes ^[3, 14]. Most human studies did not mention a relation between hyperglycemia and intracerebral hemorrhage, but Bruno et al in 2002 ^[16] showed that higher admission glucose level, in acute ischemic stroke predisposes for symptomatic intracerebral hemorrhage even without thrombolytic treatment.

Surprisingly one study performed by Nagi, et al in 1999 ^[17] which reached the conclusion that acute hyperglycemia has both positive and negative effects depending on the collateral cerebral blood flow, if this is insufficient, then it worsen the

neuronal damage, while it may protect neuronal tissue if there is only moderate degree of impaired cerebral blood flow, by improving substrate supply, while subsequent studies did not show that favorable effect of acute hyperglycemia.

However, there is an increasing evidence that maintaining euglycemia and treatment with insulin or with glucose-insulin-potassium (GIK) even in non diabetic hyperglycemic patients is helpful in limiting organ damage after stroke, even though, it may be accompanied by insulin resistance^[18].

Patients & Methods

Subsequent patients sustaining acute stroke and admitted to the medical wards of Al-Yarmouk Teaching Hospital, during the period from April to September 2004, were included in the study. Only patients with positive Brain Computerized Tomography Scan consistent with acute stroke were included. They were 104 patients, 50 being males and 54 female. Their ages were ranging from 27-84 years (mean = 62 years).

On admission and the days after, we took a full history from the patient or his family regarding age, interval from initiation of stroke till admission, history of polyuria, weight loss or proved diabetes, hypertension, the drugs used, as well as history of steroid intake or other diabetogenic drugs or dextrose containing fluids. We then assessed the level of consciousness and the reports of CT scan.

Random blood glucose was estimated in the emergency department, at the patient arrival, and then daily fasting plasma glucose testing was performed by using enzymatic and colorimetric method GOD /POD.

Patients who receive corticosteroid or dextrose water infusion were excluded from the study. If fasting plasma glucose was equal to or more than 7 mmol/L or random plasma glucose was equal to or more than 11.1 mmol/L and the patient had no history of prior diabetes, we did HbA1c for him to estimate the previous glycemic level during the last 2-3 months. HbA1c is determined by variant hemoglobin AK program using ion exchange high

performance liquid chromatography (HPLC), which has been certified by National Glycohemoglobin Standardization Program^[19].

If HbA1c was more than 6%, this might reliably diagnose diabetes and if it was less than 5.2 %, this might reliably exclude it^[20], we regard the later as having stress hyperglycemia. So patient were categorized into those with previous DM and those without. The last group was further classified into those with euglycemia and others with hyperglycemia; the latter was also classified into those with undiagnosed diabetes and patients with stress hyperglycemia.

Statistical analysis was performed using Chi-square test for the differences between the percentages in different groups and Independent t-test for the differences between the means of different groups. P value of 0.05 or less was considered as the level of significance.

Results:

Of the 104 patient tested, 38 subjects (37%) were having hyperglycemia as shown in fig. (1). Twenty one patient (55% of those with hyperglycemia, i.e. 21 % of the total CVA patients) gave history of prior diabetes, 5 of them (24% of diabetics) were taking insulin. Of the 17 patients with hyperglycemia, but without prior history of diabetes, those who show HbA1c figures higher than 6% were 11 comprising 11% of total stroke patients, i.e. 30 % of hyperglycemic CVA patients as shown in table (1).

Patients with hyperglycemia but normal HbA1c, i.e. lower than 5.2% were 4 (mean HbA1c 5%) comprising 4% of total stroke patients (table 1) Two patients remained unclassified, their HbA1c were 5.5 % and 5.9 %. Tables 2, 3, 4 and 5 together with the figures 2, 3 and 4 show the age group, sex, smoking habit and level of consciousness in these groups. Only one patient with stress hyperglycemia was smoker (25%), but 26 of the other groups, whether diabetic or not were so (25% of total) and 8 patients (8%) were ex-smokers.

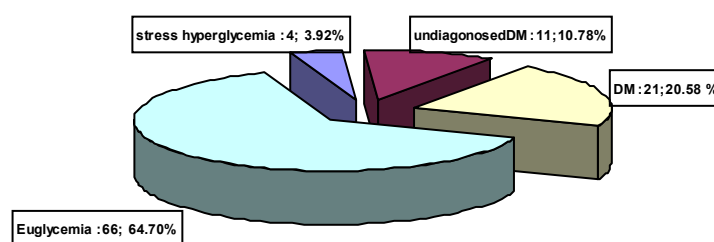


Fig. (1): Pie Chart of the euglycemic and the different hyperglycemic groups in the study (the *total number is 102 as two patients were not included in the chart, unclassified group*)

Table I: The HbA1c of the undiagnosed DM and stress Hyperglycemia

Group	N	Minimum	Maximum	Mean	Standard Deviation
UNDIAGNOSED DM	11	6.5	9.1	7.318	0.9379
STRESS HYPERGLYCEMIA	4	4.8	5.1	4.975	0.1258
Total	15	4.8	9.1	6.693	1.3350

*P<0.008(highly significant difference)

Table 2: The age groups of different euglycemic and hyperglycemic groups.

AGE (YEARS)	DM		EUGLYCEMIA		STRESS HYPERGLYCEMIA		UNDIAGNOSED DM	
	No	%	No	%	No	%	No	%
<40	-	-	2	2	-	-	-	-
40-49	4	19.0	4	6.1	-	-	1	9.1
50-59	4	19.0	16	24.2	1	25.0	2	18.2
60-69	10	47.6	26	39.4	1	25.0	5	45.5
70-79	3	14.3	15	22.7	2	50.0	2	18.2
≥80	-	-	3	4.5	-	-	1	9.1
Total	21	20.6	66	64.7	4	3.9	11	10.8
Mean ± SD	59.4±8.55		62.3±10.32		66.8±12.29		64.0±8.53	

*P>0.05 (No significant difference)

Table 3: The sex distribution in different groups

Group	Female		Male	
	No	%	No	%
DM	11	52.4	10	47.6
EUGLYCEMIA	33	50.0	33	50.0
STRESS HYPERGLYCEMIA	3	75.0	1	25.0
UNDIAGNOSED DM	5	45.5	6	54.5
TOTAL	52	51	50	49.0

* $P>0.05$ (No significant difference)

Table 4: The smoking habits in different groups

Group	Smoker		Ex-smoker		Non smoker	
	No	%	No	%	No	%
DM	3	14.3	4	19.0	14	66.7
EUGLYCEMIA	19	28.8	3	4.5	44	66.7
STRESS hyperglycemia	1	25.0	-	-	3	75.0
UNDIAGNOSED DM	4	36.4	1	9.1	6	54.5
TOTAL	27	26.5	8	7.8	67	65.7

* $P>0.05$ (No significant difference)

Surprisingly the level of blood glucose at emergency department for those with stress hyperglycemia was ranging from 7.7 to 12 mmol/L (mean = 10.7 mmol/L). Fasting plasma glucose of this group was ranging from 7.7 to 12 mmol/L (mean = 9.2) as shown in table (6) and .No one of the four patients gave history of weight loss, polyuria or family history of diabetes. All patients with stress hyperglycemia sustained cerebral infarction, but one of them developed hemorrhagic infarction, while 9 of the remainder

patients whether diabetics or not, sustained cerebral hemorrhage or hemorrhagic infarction table (7). (9% of the total stroke patients). No one of the stress hyperglycemic patients got lacunar infarction, while 9 (9% of the total stroke patients) got it, 6 were non diabetic (6%) and 3 diabetics (3% of the total), only 3 cases with lacunar infarction gave history of hypertension. There were two cases that sustained insular infarction (2% of the total) but no one of them sustained hyperglycemia. Table (8).

Table 5: The consciousness status

Group	Conscious		Stupor		Coma	
	No	%	No	%	No	%
DM	14	66.7	3	14.3	4	19.0
EUGLYCEMIA	51	77.3	9	13.6	6	9.1
STRESS HYPERGLYCEMIA	3	75.0	-	-	1	25.0
UNDIAGNOSED DM	6	54.5	3	27.3	2	18.2
TOTAL	74	72.5	15	14.7	13	12.7

*P>0.05 (No significant difference)

Table 6: The Glucose level in different groups

Group	Emergency* blood glucose	Fasting Plasma glucose on 2 nd day of admission **	Fasting Plasma glucose on 3 rd day of admission ***
DM	17.02±16.73	12.46±4.01	11.26±3.72
EUGLYCEMIA	9.29±1.26	5.79±0.60	-
STRESS HYPERGLYCEMIA	10.70±2.97	9.35±0.86	9.13±1.97
UNDIAGNOSED DM	10.39±4.46	10.5±3.49	10.54±1.76
TOTAL	9.12±8.78	8.09±3.70	10.64±3.20
P value	<0.001*	<0.001*	>0.05

*P<0.001 (highly significant difference).

**P<0.001 (highly significant difference).

***P>0.05 (non significant difference)

Table 7: Stroke types.

Group	Hemorrhagic stroke				Cerebral infarction				Total
	Cerebral haem.		hemorrhagic inf.		Non lacunar		Lacunar		
DM	2	9.5%	1	4.7%	17	80.9%	1	4.7%	21
UNDIAGNOSED DM	1	9.9%	0	45.4%	8	72.7%	2	18.1%	11
STRESS HYPERGLYCEMIA	0	0%	1	25%	3	75%	0	0%	4
EUGLYCEMIA	4	6.6%	1	1.5%	55	83.3%	6	9%	66
Total	7	6.8%	3	2.9%	83	81.3%	9	8.8%	102

*P>0.05 (No significant difference)

Table 8: Insular infarction in the different groups.

Group	YES		NO	
	No	%	No	%
DM	-	-	21	100
EUGLYCEMIA	2	3.0	64	97.0
STRESS HYPERGLYCEMIA	-	-	4	100
UNDIAGNOSED DM	-	-	11	100
TOTAL	2	-	100	-

*P>0.05 (No significant difference)

Discussion

According to this study 37% of all stroke patients admitted to hospital were having hyperglycemia which approximates what is found in other studies (6-50%) [2,3,5,7,27]. The slightly lower rate of stress hyperglycemia our study may be related to the higher level above which we regarded patients as hyperglycemic, while in William et al [2] study, for instance, they regarded admitting random plasma glucose equal to or above 130 mg/100 cc (7.2 mmol/l) as hyperglycemia.

This study showed that stress hyperglycemia occurred in 4% of the admitted patients with acute stroke. In a retrospective study done by Bravata et al in 2003, that reviewed the records of acute ischemic stroke patients admitted to 10 hospitals from may 1996 to December 1998 showed that 90 acute stroke patients presented with hyperglycemia without prior history of diabetes, the prevalence vary from 31% down to 6% depending on the maximum glucose cut off used to define hyperglycemia as 140 mg /100 cc (7.8 mmol/L) or 200 mg /100 cc (11.1 mmol/L), respectively, only one of them had been evaluated for the presence of DM by measuring HbA1c [21].

In this study we found 75 % of the patients with stress hyperglycemia were females (although not statistically significant), this is, somewhat, similar to what was found in William et al study which showed preponderance of women among admitted hyperglycemic patients with acute stroke. Also we found that our patients remained hyperglycemic throughout their stay in hospital similar to what was found in William et al study.

No relation between age or smoking habits and stress hyperglycemia was found in this study

Szczudlik, A. et al study [14] in 2001, on 262 patient with ischemic stroke showed that those

with stress hyperglycemia had higher stroke severity than those with diabetes or with euglycemia. They had larger ischemic lesions on computer Tomography (CT) than diabetics. They had also higher 30 day mortality than euglycemics, one year mortality was similar in both transient hyperglycemic and diabetics that were higher than that in the normoglycemics. Other experimental studies showed that hyperglycemia exacerbates ischemic lesions and is associated with an increase in edema and size of infarction and it decreases cerebral blood flow [3].

Another study done by Christensen and Boysen [11] in Denmark in 2002 on 445 stroke patients with no history of diabetes showed that blood glucose increases after the onset of acute stroke and the increase is related to severity of stroke. In this study we did not find more severe cases in patients with stress hyperglycemia (depending on level of consciousness), but one case was deeply comatose and CT showed hemorrhagic infarction with mass effect and pressure on lateral ventricles (statistically insignificant).

Another study by Dora [15] in 2004 in Turkey showed that hyperglycemia in the early period of cerebral infarction is associated with increased edema and has adverse effect on short term prognosis. Actually because of the small number of cases and that we did not follow up these patients, we can not state the relationship between stress hyperglycemia and short term prognosis.

A study by Kagansky, N. et al [22] showed also that admission hyperglycemia in patients with stroke, whether diabetics or not is associated with worse clinical outcome, this association is more consistent in the non lacunar

type of stroke. In this study all of the stroke patients with stress hyperglycemia were sustaining non lacunar infarction

Two cases only in our study got insular infarction, according to CT report, no one of them developed stress hyperglycemia, while in Allport L.E. et al study [23], it was shown that insular cortical ischemia may be associated with the production of post stroke hyperglycemia by inducing possible, sympatho-adrenal dysfunction owing to the belief that brain insular region is a site of autonomic connectivity. In this study we depended on brain CT scan to find out if insular involvement is present, while in Allport's study they used T₂ weighted MRI.

In this study the unrecognized DM presenting with stroke was 11%, which was rather less than what was found in other studies as Gray et al [5] study which showed incidence of 16-24 %.

Conclusion

- 1-Stress hyperglycemia is not a rare phenomenon and as it might be associated with increased mortality and poor outcome in stroke patients, it is prudent to look for and treat.
- 2-As diabetes is common and many cases being undiagnosed together with the high association between it and stroke, the latter offer a good opportunity to test the presence of undiagnosed diabetes.
- 3-The small number of patients with stress hyperglycemia in our study was due to the higher level of plasma glucose that was regarded as hyperglycemia. Further studies are needed, taking lower plasma glucose (FPG at or above 6.1 mmol/l and/or 2-hpg at or above 7.2 mmol/l) as the lower limit of hyperglycemia to give more information about sex, severity of stroke, CT findings, prognosis and the optimal management of these patients

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