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Prognostic Value of Dysglycemia in Cerebral Hemorrhage in Patients with Metabolic Syndrome

KEYWORDS: Metabolic syndrome, intracerebral hemorrhage, Dysglycemia, Hypertension, Obesity.

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ABSTRACT *Background: Metabolic syndrome is increasing worldwide, and is increasing in women than men, and is increasing in parallel with increasing age and obesity. Dysglycemia is one of IDF 2006 criteria for definition of metabolic syndrome. Aim of the work is to evaluate the role of dysglycemia in cases of cerebral hemorrhage in patients with metabolic syndrome. Patients and methods: 240 patients presented with hemorrhagic stroke were divided into two groups according to IDF criteria (2006), full investigations, including laboratory investigations, ECG, chest x-ray and brain CT. Results and Conclusion: Among 240 patients with cerebral hemorrhage 77 patients have metabolic syndrome (32%), 22 patients had obesity, hypertension and dyslipidemia, 31 patients had obesity, hypertension and diabetes and 24 patients had all metabolic syndrome components. As regard dysglycemia, the presence of metabolic syndrome increases relative risk of dysglycemia by 2.5 fold in Met.s patients than non Met.s patients also, dysglycemia increases relative risk of mortality of cerebral hemorrhage with Met.s by 1.04 fold than with normal glucose tolerance.*

Introduction

Intracerebral Hemorrhage(ICH)

ICH is a devastating disease with high rates of mortality and morbidity (Elliot and Smith, 2010). The overall incidence is 12 to 15 ones per 100,000 population per year (Gebel and Broderisk, 2000).

After initial Hemorrhage, hematoma expansion and peri -hematoma edema result in secondary brain damage and worsened outcome (Elliot and Smith, 2010). .

Factors associated with poor outcome include large hematoma volume (> 30ml), posterior fossa location, older age and admission mean arterial blood pressure> 130 mmHg (Hemphill et al.,2001) .

Primary ICH has a number of different causes including hypertension, amyloid angiopathy and arteriovenous malformation (David L Cohen., 2000)

Multiple factors have been identified as risk factors including hypertension (Chobanian AV et al., 2003), cigarette smoking which is associated with double risk for ischemic stroke (Rodriguez., et al 2003). Dyslipidemias including hyper-total cholesterol, low HDL and elevated triglycerides, all are associated with increased risk for stroke (Amarenco P et al., 2006). Also, diabetic patients have both an increased susceptibility to atherosclerosis and an increased prevalence of pro-atherogenic risk factors, notably hypertension and abnormal blood lipids (Kissela et al., 2005). A glycohemoglobin goal of 7.0% has been recommended by the American Diabetes Association to prevent long-term micro angiopathic complications in patients with type 2 diabetes (Skyler et al., 2009). The decrease in glycohemoglobin was associated with the positive effects of intensive treatment on the overall risk of CVD. The number of strokes, however, was too few to evaluate the impact of improved Glycemia during the trial, and as with type 2 diabetes, there remains no evidence that tight glycemic control reduces stroke risk (Nathan et al., 2005) .

Metabolic syndrome (Met.S)

International diabetes federation (IDF) described a syndrome as a recognizable complex of symptoms and physical or biochemical findings for which a direct cause is not understood. The components coexist more frequently than would be expected by chance alone (Alberti et al., 2006). This definition focused on the presence of insulin resistance, identified by hyperinsulinemia, impaired glucose tolerance (IGT), or the diagnosis of T2D, which had to be present, dyslipidemia (reduced HDL-C and increased trigycerides), hypertension and micro albuminuria. International Diabetes Federation (IDF, 2006) include the following criteria; central obesity defined as waist circumference >94 cm for male and >80 cm for female for arabe population, and two of the following: 1-Triglycerides>150 mg/dl. 2-HDL-C:<40 mg/dl for men ,<50 mg/dl for women. 3-Bp >130/85 mm Hg. 4-FPG >100 mg/dl (IDF, 2006). The prevalence of Meta S is increasing throughout the world, prevalence increase dramatically in women over the time but did not change in men (Harzallah et al., 2006). Also, Met S is more prevalent with each decade of life, increasing in parallel with age-related increases in obesity (Mokdad et al., 2001). While presence of Met S in youth may be important predictor of future risk for diabetes and CVD (Zimmet et al., 2007).

Abdominal obesity and insulin resistance appear to be at the core of pathophysiology of the Met S and its individual components (Marc Cornier et al.,2008). Worldwide increase in the prevalence of obesity in the recent decades is rising and likely a cause of rising incidence of insulin resistance and Met S (Eckel et al., 2005). The combination of obesity, physical inactivity, and consumption of an atherogenic diet is believed to lead to insulin resistance (Grundy SM 2005) . Individuals are generally defined as insulin sensitive or insulin resistant by their response to an oral or IV glucose or insulin stimulus (Pacini G 2006), insulin resistant individuals demonstrate impaired glucose metabolism or tolerance by an abnormal response to glucose challenge, elevated fasting glucose levels and/or overt hyperglycemia (Bravata et al., 2004).

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The liver plays a major role in substrate metabolism, increase in FFA flux have been shown to impair hepatic insulin action, this includes increases in hepatic glucose output. Synthesis of proinflammatory cytokines, and major change in lipoprotein metabolism (Bergman et al., 2007). In the liver of insulin-resistant patients, FFA flux is high, triglyceride synthesis and storage are increased and excess TGS is secreted as VLDL (Lewis and Steiner 1996).

The relationship between insulin resistance and hypertension has been established (Bonora et al., 2007) each component of metabolic syndrome contributed to the increased risk of hemorrhagic stroke except for low HDL level and hyperglycemia, significant excess risk of stroke was found associated with diabetes but not with borderline glucose dysfunction (Iso H et al., 2004). Among all risk factors high blood pressure and hyperglycemia were most prevalent in community (Wang et al., 2004), the association between metabolic syndrome and stroke cannot be explained only by isolated hyperglycemia without the presence of other accompanying risk factors (Liu et al., 2007).

Aim of the work:
The aim of this study is to evaluate role of dysglycemia in cases of cerebral Hemorrhage in patients with metabolic syndrome.

Patients and methods:
This study included 240 patients presented with hemorrhagic stroke, the patients were divided into two groups according to absence or presence of metabolic syndrome according to IDF criteria (2006), Group I included 77 hemorrhagic stroke patients with Met S criteria. Group II included 163 hemorrhagic stroke patients without Met S with inclusion criteria; cerebral stroke patients diagnosed clinically and confirmed by brain CT. Exclusion criteria; space occupying lesion in brain, infectious brain disease, and evidence of recent ischemic stroke. All patients were subjected to thorough clinical examination including full history, full general examination with special attention to blood pressure and thorough neurological examination. Also, patients done anthropometric measures including waist circumference, Hip circumference and waist hip ratio.

Also, routine investigations including laboratory investigations, ECG, chest x ray and neuroimaging and also, severity assessment using GCS score and APACHE II score.

Statistical analysis:
All data were analyzed using SPSS software version 17, including Chi-square test, and student t-test, A p value < 0.05 was considered statistically significant relative risk of component of metabolic syndrome on mortality of patients was obtained using logistic regression analysis (relative risk).

Results:
Among 240 patients with cerebral hemorrhage, 77 patients have metabolic syndrome (33%), 22 patients had obesity, hypertension and dyslipidemia, 31 patients had obesity, hypertension and diabetes, and, 24 patients had all metabolic syndrome components table (1). Also, a comparison of the mean value ± SD of various variable in hemorrhagic stroke patients with and without metabolic syndrome. It shows significant increase in age, SBP, MAP, FBS, LDL, uric acid, CRP, triglyceride, WC, smoking, APACHE score and mortality rate in metabolic syndrome group compared to non Met S group. Meanwhile, there is significant decrease in the mean value ± SD of GCS & HDL in metabolic syndrome group table (2). There is significant increase in mortality (P < 0.001) with increasing hypertension in patients of cerebral hemorrhage with metabolic syndrome table (2), also, metabolic syndrome increase relative risk of hypertension by 23 fold in Met S patients (table 5). Also, metabolic syndrome increase relative risk of dyslipidemia by 2 fold (table 6).

As regard dysglycemia, table (7) shows that presence of metabolic syndrome increase relative risk of dysglycemia by 2.5 fold in Met S patients than non Met S patients, in addition, dysglycemia increase relative risk of mortality of patients with cerebral hemorrhage with Met S by 1.04 fold than those with normal glucose tolerance (table 8). Increasing number of metabolic syndrome components increase significantly the mortality rate (P < 0.001) (tables 3,4) and there is increased relative risk of metabolic syndrome Perce on mortality of patients with cerebral hemorrhage by 2.34 fold than non metabolic syndrome patients.

Table (1): Prevalence of met.S among hemorrhagic stroke patients as a whole (n = 240).

Number of component	Type of comp	No of patients	% from total
(3) comp	OBES + HTN + DYSL	22	9%
(3) comp	OBES + HTN + DM	31	13%
all comp	All Comp	24	10%
Total	----	77	(77 ÷ 240) = (32%)

HTN (Hypertension), DM (Diabetes mellitus), DYS (Dyslipidemia), OBES (Obesity), Met.S (Metabolic syndrome)

Table (2): Comparison of the mean ± SD of various variables in hemorrhagic stroke patients with and without metabolic syndrome.

Variable	MET SYND +ve N = 77 (32%)	MET SYND –ve N = 163 (68%)	t	P
Age (years)	65.52 ± 5.77	57.95 ± 5.73	111.345	< 0.001
Sex Male Female	 38 (48%) 39 (52%)	 102 (63%) 61(37%)	c2 = 56.933	0.03
SBP (mmHg)	177.24 ± 18.12	155.88 ± 31.95	95.835	0.024
DBP (mmHg)	93.59 ± 6.83	85.17 ± 12.51	134.21	< 0.001
MAP (mmHg)	121.42 ± 8.91	106.24 ± 9.52	91.856	< 0.001
GCS	6.16 ± 2.16	8.08 ± 2.79	27.88	< 0.001
FBS (Mg/dl)	145.09 ± 40.58	133.96 ± 37.44	35.028	< 0.001
LDL-C (Mg/dl)	117.52 ± 12.49	111.27 ± 14.87	92.195	0.051
HDL-C (Mg/dl)	41.67 ± 8.22	44.32 ± 7.44	49.648	< 0.001
UA (Mg/dl)	8.510 ± 1.835	7.970 ± 1.67	45.434	0.023
CRP (Mg/dl)	31.76 ± 19.99	12.50 ± 15.31	15.568	< 0.001
TG (Mg/dl)	170.48 ± 33.42	157.76 ± 40.5	49.980	0.002
APACHE score	23.90 ± 6.17	19.35 ± 5.42	37.936	< 0.001
WC (cm)	92.44 ± 4.14	81.28 ± 11.16	218.542	< 0.001
Smoking N(%)	75 (78%)	110 (53%)	c2 = 132.355	< 0.001
Mortality N(%)	56 (58.33%)	58 (28.43%)	c2 = 24.744	< 0.001

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Table (3): Effect of number of components of metabolic syndrome on mortality of patients with cerebral hemorrhage.

Met.S	NO of Comp	NO of cases	NO of Deaths	No of Survived	MORT Rate	c2	P
Yes	3	53	23	30	44%	103.51	<0.001
Yes	4-5	24	16	8	66.6%		
Total	---	77	39	38	51%	---	---

Table (4): Comparison between number of component as regarding mortality rate of patients with cerebral hemorrhage.

Three components	All components	c2	P
44%	66.6%	91.53	<0.001

Table (5): Relative risk of metabolic syndrome on hypertension in hemorrhagic stroke patients.

Group	Metabolic syndrome		Total
	+ve	-ve	
HTN	76	108	184
NON HTN	1	55	56
Total	77	163	240

RR = 76/184 ÷ 1/56 = 23 fold

Table (6): Relative risk of metabolic syndrome on dyslipidemia in hemorrhagic stroke patients.

Group	Metabolic syndrome		Total
	+ve	-ve	
DYSL	47	58	105
NON DYSL	30	105	135
Total	77	163	240

RR = 47/105 ÷ 30/135 = 2 fold

Table (7): Relative risk of metabolic syndrome on dysglycemia in hemorrhagic stroke patients.

Group	Metabolic syndrome		Total
	+ve	-ve	
DM	55	64	119
NON DM	22	99	121
Total	77	163	240

RR = 55/119 ÷ 22/121 = 2.5 fold

Table (8): Relative risk of dysglycemia on mortality of patients with hemorrhagic stroke with metabolic patients.

Group	Metabolic syndrome		Total
	+ve	-ve	
DESEASED	29	15	44
SURVIVED	21	12	33
Total	50	27	77

RR = 29/44 ÷ 21/33 = 1.04 fold

Table (9): Relative risk of metabolic syndrome Perce on mortality of patients with cerebral hemorrhage.

Group	Metabolic syndrome		Total
	+ve	-ve	
DESEASED	45	45	90
SURVIVED	32	118	150
Total	77	163	240

RR = 45/90 ÷ 32/150= 2.34 fold

Discussion

Metabolic syndrome is becoming a health risk not only prevalent among US and European populations, but also in many countries. Over the past decade a series of research findings have produced preliminary clues on the relationship of metabolic syndrome and stroke (Hu et al., 2004).

Of different proposed criteria for the definition of Met S, we decided to use the IDF definition 2006 of metabolic syndrome, the main differences of IDF criteria and others are (1) it was developed more recently in 2006 and (2) the definition for elevated fasting glucose was reduced from ³ 110 mg/dl to ³ 100 mg/dl. Therefore, lowering the glucose threshold could help the classification of Met S toward stroke risk. In this study we looked for the prevalence of metabolic syndrome in subjects with cerebral hemorrhage and evaluate the role of dysglycemia in mortality and risk value in cerebral hemorrhage in metabolic syndrome patients.

In this study 240 patients with hemorrhagic stroke were included, according to presence or absence of Met S we found 77 patients had Met S and 163 had no Met S and according to component distribution we found 24 patients had five components of Met S and 31 patients had three components of Met S including DM, this 55 patients had DM in metabolic syndrome group patients. As regard the effect of Met S on mortality of patients with hemorrhagic stroke, we found that mortality rate significantly increased in patients with metabolic syndrome in comparison to non metabolic (58.33% vs 28.43%, $P < 0.001$, $n = 240$). This result was in agreement with several prospective studies that shown the metabolic syndrome was associated with increased morbidity and mortality not only for patients with cardiovascular disease but also for patients with stroke events (Najarian et al., 2006). As well relative risk index as regard mortality between two groups of study, there is 2.34 fold increased risk of mortality in metabolic syndrome group.

And this is consistent with many previous studies revealing that metabolic syndrome was associated with increased mortality and morbidity of cerebral stroke (Mc Neill et al., 2005).

Moreover, more analysis of data to reveal synergetic effect of Met S components on mortality rate of patients with hemorrhagic stroke, we found that if number of components of Met S increase, the mortality rate also increase ($P < 0.001$).

Each component of metabolic syndrome contributed to the increased risk of hemorrhagic stroke among these components of Met S was hypertension and by comparing mean ± SD of MAP between the two groups of study, we found that patients with Met S had statistically significant increase in MAP in comparison to non Met S (121 ± 8.93 vs 106 ± 9.5 respectively) and by investigating the relatives risk of Met S on hypertension we found that patients with Met S had increased risk of cerebral hemorrhage by 23 fold more than non metabolic syndrome patients and by estimating the risk of increased hypotension (MAP ³ 120) on mortality of patients with Met S, we found that it increased mortality of those patients by 1.947 fold than those normotensive and this in agreement with multicenter study, that found that increased SBP > 140 to 150 mmHg after ICH doubled the risk of death (Zhang et al., 2008).

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As regard, dyslipidemia in the form of low HDL and high TGs, we compared the mean ± SD of the two groups and we found that patients with metabolic syndrome have statistically significant low level of serum HDL-C and high TG in comparison to non metabolic subjects. As regard these results with cerebral hemorrhage we found that TG ³ 170 mg/dl increased the mortality of patients with cerebral hemorrhage 3 folds more than those with TG > 170. Also we found that level of HDL < 41 mg/dl increased mortality of patients with cerebral hemorrhage 1.4 fold more than those with level ³ 41 mg/dl.

As regarding hyperglycemia as being prevalent in our community, we evaluated it as a component of Met S and its relation to cerebral hemorrhage, we found that there was increase in mean ± SD of level of fasting blood glucose level in metabolic syndrome patients than non Mets (145.09 ± 40.2 vs 113.93 ± 37.43 respectively with a high P value < 0.001).

Also, by evaluating the risk of metabolic syndrome on incidence of glucose intolerance in patients with cerebral hemorrhage, we found that patients with metabolic syndrome had an increased risk of glucose intolerance by 2.5 fold more than non metabolic patients, also among the group of metabolic syndrome, patients with hyperglycemia carries 1.04 fold increased risk of mortality with cerebral hemorrhage, although this risk of mortality is low but these findings are very valuable in preventing metabolic syndrome risk of cerebral hemorrhage, as it emphasis that the cut off point of FBS from ³ 110 to ³ 100 mg/dl that used by IDF definition, and consequently good controlling of hyperglycemia lead to decreased risk of stroke and decreasing complications and this is in agreement with Gami et al., (2007) who stated that a small change in the fasting blood glucose threshold have an important impact on the associated cardiovascular risk. So, we agree with Wang et al., (2004) in that among all risk factors of metabolic syndrome high blood pressure and hyperglycemia were most prevalent in community.

From above study we have many factors affecting the outcome of patients with cerebral hemorrhage. Metabolic syndrome Perce carries a high risk and can be used as a predictor of mortality.

Dysglycemia as a component of metabolic syndrome after adjustment for other risk factors increased risk of cerebral stroke by 2.5 fold than non metabolic syndrome. Also increased risk of mortality among group of met S patients by 1.04 who have cerebral hemorrhage so we recommend: inclusion of metabolic syndrome in guidelines for management of cerebral stroke patients and for early detection and tight control of hyperglycemia as a small change in fasting blood glucose threshold have an important impact on associated cerebral stroke risk.

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