Research Article

Association between Metabolic syndrome and atherothrombotic stroke: A clinical study in Minia University Hospital, Neurology department

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Abstract
Background: Stroke is the most common reason for disability and the third cause of mortality in the world per year. The Metabolic syndrome (MetS) is known as an independent risk factor of coronary artery disease and stroke. This study was planned to assess the relationship between MetS and risk of ischemic stroke, whether stroke patients with MetS differ from other ischemic stroke patients in demographic variables, stroke presentation, stroke severity, neuroimaging and prognosis. **Study Design:** Hospital-based, prospective observational study. The study population constituted of patients with first-ever atherothrombotic ischemic stroke who were admitted to Neurology department during the period of 6 months. Patients were subjected to clinical examination, screening for MetS components, brain imaging, transthoracic echocardiography and carotid duplex. **Results:** MetS was of higher frequency in ischemic stroke patients compared to other previous studies, more in females and older age. MetS with DM patients had the worst clinical presentation and the worst in-hospital outcome. High HDL-C was the predictor for worse clinical presentation. **Conclusion:** The higher the number of MetS components, the higher the risk of ischemic stroke.
Keywords: Atherothrombotic ischemic stroke & Metabolic syndrome.

Introduction
Stroke is defined as an "acute neurologic dysfunction of vascular origin with symptoms and signs corresponding to the involvement of focal areas in the brain" [1]. Stroke is the most common reason of the disability that affects more than 700 000 individuals and the third cause of death in the world per year [2]. Ischemic stroke is the commonest type of stroke & constitutes 80% of all strokes. Approximately 45% of ischemic strokes are caused by small or large artery thrombus, 20% are embolic in origin, and others have an unknown cause [3]. Atherothrombotic Ischemic stroke risk factors include arterial hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, alcohol consumption, oldness, male gender,….etc [4]. Patients with Metabolic syndrome (MetS) are at 2 to 4 fold increased risk of stroke[5&6]. According to the NCEP ATP III definition, MetS is present if three or more of the following five criteria are met: waist circum-ference (WC) > 40 inches (males) or 35 inches (females), BP > 130/85 mmHg, fasting triglyceride (TG) level > 150 mg/dl, fasting high-density lipoprotein cholesterol (HDL-C) level < 40 mg/dl (males) or 50 mg/dl (females) and fasting blood sugar > 100 mg/dl [7]. Each of the components of the MetS is associated with higher stroke risk to various degrees. Analysis of individual factors causes considerable modification of observed risk because of the inter-relationship of these factors. Therefore, studying the MetS as a whole may provide a better estimation of the true risk for ischemic stroke [2]. This study was aimed to assess the relationship between MetS and risk of ischemic stroke, whether stroke patients with MetS differ from other ischemic stroke patients in demographic variables, stroke presentation, stroke severity, neuroimaging and prognosis.

Material & Method
The study was conducted in the Department of Neurology, Minia University Hospital.
The study population constituted of patients with first-ever atherothrombotic ischemic stroke who were admitted to Neurology department during the period of 6 months (between 1/1 /2016 and 1/7 /2016).

Criteria included

Patients ≥ 40 years old with a diagnosis of the first ever symptomatic atherothrombotic ischemic stroke (according to the diagnostic criteria of TOAST by neurological specialists)[8].

Patients were excluded if there was a Source of embolus as AF, moderate to severe valvular heart disease or intracarotid/cardiac thrombus. Strokes with an undetermined etiology despite an extensive evaluation. Or past history of previous stroke, severe cardiorenal or nutriational disorder.

The study population included 113 patients.

. Patients were subjected to clinical examination, screening for MetS components, brain imaging, transthoracic echocardiography and carotid duplex.

Patients were classified into 4 groups: Isolated MetS, MetS with DM, DM alone and Neither MetS nor diabetic. According to 1999 WHO Consultation recommendations for the diagnosis of DM, patients with previously diagnosed or with FBS >125 mg/dl were considered as having DM.

Data analysis was done with Statistical Package for Social Sciences (SPSS IBM) version 22.0. The differences between the groups were examined by an independent t-test, one way ANOVA test and the Chi- square test. Multiple linear logistic regression analysis was calculated for the outcome variable (having multiple brain ischemic lesions in brain imaging, GCS & NIHSS) of the explanatory variables (MetS and its components).

Results

One hundred and thirteen patients diagnosed with first ever athero-thrombotic ischemic stroke were included in this study; 60 males (53%) and 53 females (47%). Eighty six patients (76%) had MetS criteria (including both Isolated MetS and MetS with DM); 37 males (43%) & 49 females (57%).

Table (1): Socio-demographic data of studied groups:

Variable	Isolated MetS (n= 36)	MetS with DM (n=50)	DM without MetS (n=10)	Neither MetS nor DM (n=17)	Total (n=113)	P
Age (mean, SD)	62.14±11.28	67.64±11.34	64.9±7.3	59.29±9.67	64.39±11.14	**.023***
Sex (N, %)						
Male	18 (50%)	19 (38%)	8 (80%)	15 (88%)	60 (53%)	**.001***
Female	18 (50%)	31 (62%)	2 (20%)	2 (12%)	53 (47%)	

Isolated Met S Metabolic Syndrome without DM, *Met S with DM* Metabolic syndrome with DM. ***** significant result.

Patients having MetS with DM were older (67.64 ± 11.34 years old) ,while patients without MetS nor DM were the youngest (59.29 ± 9.67 years old). The frequency of MetS with DM was significantly higher in female patients (62%), while 80% of patients suffering from DM without MetS were males (P= .001).

Table (2): Characteristics of MetS components and lipid profile of studied groups

Variable	Isolated MetS (n=36)	MetS with DM (n=50)	DM without MetS (n=10)	Neither MetS nor DM (n=17)	Total (n=)	P
SBP	137.58±18.68	136.34±20.43	124.9±9.3	125.53±15.1	134.1±18.87	**.048***
DBP	84.94±9	82±12.65	77.3±9.7	82.24±8.1	82.55±10.8	.235
FBS	112.64±9	204.96±88.56	178.7±72	107.1±10.58	158.5±77.2	**.0001***
WC	98.5±12.4	102.16±14.3	79.1±9.93	86.47±11.75	96.59±14.9	**.0001***
TGS	113.97±53	132.5±78.2	99.3±26.56	111.47±35.37	120.5±62.6	.295
HDL-C	32.89±10.97	35.5±12.77	41.5±14.1	39.94±13.89	35.87±12.67	.123
LDL-C	125.7±39.3	132.18±44.71	133.8±36.37	130.4±38.28	130±41	.895
TC	185.2±54.2	200.34±62.9	197.1±51.6	195.88±52.6	194.55±57.47	.689
HTN (N of patients)	26(72%)	37(74%)	2(20%)	6(35%)	71(62.8%)	**.001***
Central obesity (N of patients)	27(75%)	44(88%)	1(10%)	4(23.5%)	76(67%)	**.0001***
High TGS (N of patients)	7(19.4%)	15(30%)	_	1(5.8%)	23(20.3%)	**.054***
Low HDL-C (N of patients)	32(88.9%)	41(82%)	4(40%)	7(41.2%)	84(74.3%)	**.0001***

SBP Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HTN* Hypertension, *FBS* Fasting Blood Sugar, *WC* waist circumference, *TGS* Triglycerides, *HDL-C* High Density Lipoprotein Cholesterol, *LDL-C Low Density Lipoprotein Cholesterol, TC Total Cholesterol*, *Isolated Met S* Metabolic Syndrome without DM, *Met S with DM* Metabolic syndrome with DM. ***** significant result.

The frequency of HTN, central obesity and hyper-triglyceridemia was significantly higher in patients having MetS with DM (P= .001, .0001 & .054), while low HDL frequency was significantly higher in Isolated MetS patients ($P \leq .0001$).

Table (3) Clinical assessment at presentation

Variable	Isolated MetS (n=36)	MetS with DM (n=50)	DM without MetS (n= 10)	Neither MetS nor DM (n=17)	Total (n=113)	P
GCS	10.97± 2.7	10.38±3.4	10.9±2.47	11.35±2.87	10.76±3	.658
NIHSS	16.67±5.99	17.9±5.5	17.8±.88	15.76±5.57	17.18±5.55	.502

GCS Glasgow Coma Scale Score, *NIHSS* National Institute of Health Stroke Scale Score, *Isolated Met S* Metabolic Syndrome without DM, *Met S with DM* Metabolic syndrome with DM

It was observed that patients having MetS with DM had the lowest GCS score and the highest NIHSS score (10.38±3.4 & 17.9±5.5) while patients without Met S nor DM had the highest GCS score and the lowest NIHSS score (11.35±2.87 & 15.76±5.57), however this difference did not reach the conventional level of statistical significance.

Table (4) Brain imaging in studied groups:

	Isolated MetS (n=36)	MetS with DM (n=50)	DM without MetS (n=10)	Neither MetS nor DM (n=17)	P
Single lesion	26 (72%)	38 (76%)	8 (80%)	11 (65%)	
Multiple lesions	10 (28%)	12 (24%)	2 (20%)	6 (35%)	.782

Isolated Met S Metabolic Syndrome without DM, *Met S with DM* Metabolic syndrome with DM.

Table (4) shows that most of patients with Isolated MetS (72%) and 76% of patients having MetS with DM had single infarction in brain imaging.

Table (5): Clinical Outcome in studied groups

	Isolated MetS (n=36)	MetS with DM (n=50)	DM without MetS (n=10)	Neither MetS nor DM (n=17)	P
Died	10 (27.8%)	24 (48%)	3 (30%)	4 (23.5%)	.**029***
Stable	11 (30.5%)	11 (22%)	1 (10%)	1 (5.9%)	
Improved	12 (33.3%)	12 (24%)	6 (60%)	12 (70.6%)	

Isolated Met S Metabolic Syndrome without DM, *Met S with DM* Metabolic syndrome with DM. ***** significant result.

Table (5) shows that patients having Met S with DM had significantly higher percentage of death (48%) than other groups. While, higher percentage of improvement was in patients without Met S nor DM (70.6%).

In all studied patients, multiple linear regression analysis predicting GCS revealed that HDL level was the most significant predictor for GCS followed by TC and LDL (Table 6). In Isolated MetS group, HDL-C level was the most predictor for GCS followed by WC but was statistically insignificant. While, in MetS with DM group, LDL level was the most significant predictor for GCS followed by TC and with tendency to significance HDL-C.

In all studied patients, HDL level was significantly predicting NIHSS score at clinical presentation (Table 7). But in Isolated MetS group, FBS level was the most predicting NIHSS score at clinical presentation but statistically insignificant. While, in MetS with DM group, TC level was the most predicting NIHSS score at clinical presentation with tendency to significance followed by LDL-C.

Table (6): Multiple linear regression analysis predicting GCS in all studied patients (n=113)

Variable	Unstandardized Coefficients	Part correlation	Partial correlation	Sig
HDL	-.116-	-.277	-.282	**.004***
TC	.056	.232	.239	**.014***
LDL	-.053-	-.203	-.211	**.031***
WC	-.037-	-.172	-.180	.067
TGS	-.011-	-.159	-.167	.089
SBP	-.022-	-.092	-.097	.323
DBP	.037	.087	.092	.351
Age	-.022-	-.076	-.080	.417
FBS	.001	.024	.026	.796

GCS Glasgow Coma Scale Score, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *FBS* Fasting Blood Sugar, *WC* waist circumference, *TGS* Triglycerides, *HDL-C* High Density Lipoprotein Cholesterol, *LDL-C Low Density Lipoprotein Cholesterol, TC* Total Cholesterol. ***** significant result**.**

Table (7): Multiple linear regression analysis predicting NIHSS in all studied patients (n=113)

Variable	Unstandardized Coefficients	Part correlation	Partial correlation	Sig
HDL	.164	.212	.217	**.026***
SBP	.056	.129	.134	.173
TC	-.055-	-.125	-.130	.185
LDL	.054	.112	.117	.236
Age	.051	.098	.102	.301
TGS	.009	.073	.077	.438
WC	.024	.060	.063	.524
DBP	-.036-	-.046	-.048	.628
FBS	.001	.014	.015	.880

NIHSS National Institute of Health Stroke Scale Score, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *FBS* Fasting Blood Sugar, *WC* waist circumference, *TGS* Triglycerides, *HDL-C* High Density Lipoprotein Cholesterol, *LDL-C* Low Density Lipoprotein Cholesterol, *TC* Total Cholesterol. ***** significant result**.**

Discussion

The frequency of MetS in this study (76%) was higher than other previous studies [9-12]**.** Patients having MetS with DM were the oldest age (67.64 ± 11.34 years old) (P=.023). This was consistent with Mathew**,** who found that prevalence of most individual factors of the MetS increases with age[10]. Sixty-two percent of patients having MetS with DM were females. This is in agreement with Liu et al.**,** who showed that 70.3% of MetS patients with acute ischemic stroke were females[11]. Many studies showed that MetS increases the risk of ischemic stroke in females but not in males[13-15].

The higher frequency of MetS among ischemic stroke female patients in this study can be explained by:

First, there is a true sex difference in prevalence which was approved by aforementioned studies.

Second, perhaps the sex difference with respect to ischemic stroke and MetS resulted from sex differences in diagnostic criteria for MetS. We used waist circumference cut off for male ≥ 94cm, female ≥80cm.

Third, TC levels in female patients with Isolated MetS and MetS with DM were higher than in males of both corresponding groups. It is well known that lipid abnormalities are associated with atherosclerosis. MetS might encourage lipid abnormalities in females more than in males. Among the patients of MetS with DM group, 88% had central obesity, 82% had low HDL-C and 74% were hypertensive**.**

Similarly, Koren-Morag et al. found that the higher the number of MetS components, the higher the risk of ischemic stroke [14].

Seventy-six percent of MetS with DM patients and 72% of patients with Isolated MetS had a single brain lesion. This is against Kotani et al., who found that MetS had a significant positive association with multiple lesions of intracranial athero-thrombotic stroke in females, but not males[16]. This could be attributed to that 69% of the studied patients had infarction affecting more than one lobe (large single infarction)**.** It was found that High HDL-C was the predictor for worse clinical presentation (lower GCS & higher NIHSS)**.** This can be attributed to that HDL cholesterol levels may not expect functionality and anti-inflammatory properties of HDL[17]**.** HDL undergoes prominent structural and functional modifications in the acute phase and inflammation restricting the anti-inflammatory role of HDL but also with the conception of proinflammatory HDL[18,19].This is supported by Zeljkovic et al.**,** who reported that acute ischemic stroke patients had increased amount of small-sized HDL particles[20].

Conclusion

In this study, MetS was of higher frequency in ischemic stroke patients compared to other previous studies, more in females and older age. The higher the number of MetS components, the higher the risk of ischemic stroke. High HDL-C was the predictor for worse clinical presentation. TC and LDL-C were also

involved as main predictors for clinical presentation in MetS with DM group. Thus, diagnosing and adequately managing MetS is an important step in preventing cerebrovascular disease. So, there is need to target the population with one or more components of MetS as they are at high risk of developing stroke in the future. DM, dyslipidemia and obesity are the main MetS components affecting atherthrombotic ischemic stroke presentation in our study.

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