

The effect of oxidant-antioxidant balance on the one-year prognosis of patients with acute ischemic stroke: a case-control study

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Abstract

Background

Stroke is a major cause of mortality and morbidity. Also, free radicals and oxidative stress are deleterious factor in the stroke progression. We aimed to evaluate the association between oxidative stress markers and odds of having risk factor for stroke or developing stroke.

Methods

The present case control study conducted on 556 participants in Imam-Reza hospital, Tabriz, Iran. Subjects were divided into three group, including individuals with acute ischemic stroke, at risk of stroke, and healthy controls. All enrolled participants except for controls underwent neurological examinations and brain magnetic resonance imaging (MRI). Stroke-related disability and stroke severity were evaluated by modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS), respectively. Serum malondialdehyde (MDA) level and total antioxidant capacity (TAC) were measured within 48 hours of stroke. One-way ANOVA and Chi-square tests for comparing characteristics between groups, multivariable logistic regression for odds of stroke based on MDA and TAC quartiles, and Spearman's correlation were used.

Results

Serum MDA was significantly higher in stroke group than controls in addition to systolic and diastolic blood pressure, cholesterol, and triglyceride. Higher levels of MDA increased odds of stroke development ($P < 0.001$), however TAC and MDA were not associated with having risk factors for stroke ($P = 1.00$ and 0.27 , respectively). Also, TAC level was negatively associated with baseline ($\rho = -0.28$; $P = 0.04$) and follow-up ($\rho = -0.31$; $P = 0.03$) NIHSS scores. Moreover, MDA was correlated with mRS score at follow-up ($\rho = -0.26$; $P = 0.04$).

Conclusions

The balance between antioxidants and oxidants markers might reveal a new approach in this context. Despite recent efforts to identify the source of oxidative stress as well as cessation of the production of oxygen radicals in stroke, further studies are warranted.

Background

According to the findings Global Burden of Disease (GBD) study, the disability-adjusted life-years (DALYs) attributable to stroke was 116.4 million (95% uncertainty interval (UI): 111.4, 121.4) in 2016 globally, which hemorrhagic stroke had a higher proportion than ischemic one (1). It was estimated that

80.1 million prevalent cases of stroke in 2016 worldwide (1). Over 1990–2016, the age-standardized incidence and mortality rate of stroke declined by 36.2% and 8.1%, respectively, however, it is stroke is the second cause of leading death in the world after cardiovascular diseases (2–4). The incidence of stroke initiated to continuously increase from the age of 30 and it is higher in men, whereas it is not prominent (1).

Oxidative stress is defined as an imbalance between pro- and anti-oxidants which has implicated in the pathogenesis of several chronic diseases such as stroke (5). It plays an important role in the central nervous system and can directly cause tissues damage through several mechanisms (6). The brain uses glucose almost exclusively as its source of energy, and due to low capacity of energy storage in the brain, it requires a steady flow of blood and glucose (7). The low blood flow decreases the amount of oxygen and glucose, which follows a cascade of events that leads to production of reactive oxygen species (ROSs) and free oxygen radicals (7, 8). ROSs are necessary for various functions such as a vascular tunic, oxygen pressure monitoring, and erythropoietin production in low concentrations. In contrast, excessive amounts of oxidants may irreversibly oxidize macromolecules and cause severe cell injury (9). Antioxidant defense system is a special mechanism of dealing with damages induced by free radicals in the body. Healthy persons have a balance between the production of free radicals and antioxidant defense system, but a disruption in this balance, induces the oxidative stress that contribute to progression of stroke (10, 11).

The oxidative stress can be measured using the oxidized products of macromolecules such as nucleic acids, lipids, proteins, and deoxyribonucleic acid (DNA). Lipid peroxides are unstable lipid radicals, which are derived from the oxidation of polyunsaturated fatty acids and can be converted to a different composition such as malondialdehyde (MDA) (12). MDA can cause irreversible disruption of the enzymes, receptors and membrane transfer mechanisms (13). In addition, it has been shown a direct correlation between increases in MDA and poor functional recovery in acute ischemic stroke (14). Total antioxidant capacity (TAC) measurement is a useful tool for the evaluation of the antioxidant capacity to prevent and protect against oxidative damage to membranes and other cellular components (15).

In the present study, the importance of oxidative stress role in the pathogenesis of acute ischemic stroke is taken into account. To our best of knowledge, no study has examined the long-term effects of oxidative stress on the clinical outcomes of stroke patients. The aim of this study was to investigate changing in markers of oxidative stress and antioxidant capacity to find if there is any correlation between those and risk of stroke. Also, the correlation between severity and disability of stroke and biochemical markers were assessed.

Methods

Subjects and Design

The present case control study was conducted in Imam-Reza hospital in Tabriz, Iran from March 2017 to June 2019. Subsequently, 216 patients with stroke, 152 patients at risk of stroke, and 188 healthy

controls matched for age and sex were included. Patients with stroke needed to have a definite diagnosis of stroke by a physician using magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI). Inclusion criteria for group of at risk population was to have at least one of the underlying diseases, including hypertension, type 2 diabetes, and hyperlipidemia. Exclusion criteria were history of hemorrhagic infarction, nervous system diseases, chronic diseases such as chronic kidney, liver, and biliary tract diseases, infectious and autoimmune diseases, antioxidant intake over the past three months, and smoking.

Written informed consent was obtained from all of the participants at the beginning of the study. The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences (Ethics number: TBZMED 94/3-4/3).

Clinical assessments

An expert neurologist underwent neurological examinations for all enrolled cases, and further evaluation by brain MRI with DWI in order to confirm an acute stroke. Ischemic stroke was defined as focal neurologic deficits due to vascular causes lasting more than 24 hours and could not be explained by other causes (16). Stroke-related disability and stroke severity were evaluated by modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS), respectively (17, 18).

Biochemical assessments

Blood samples were collected from participants within 48 hours following the stroke. Serum MDA level was measured using the thiobarbituric acid reactive substance (TBARS) assay (Radioimmunoassay Kit). TAC was measured by the values extracted from ferric-reducing antioxidant power (FRAP) assay that was adjusted based on Iranian foods. The ability of dietary antioxidants for reducing ferric to ferrous ion is calculated by FRAP and are expressed by mmol per 100 g of foods (19).

Statistical Analysis

The included participants were classified into quartiles based on their TAC and MDA. One-way analysis of variance (ANOVA) and Chi-square test were used to compare general and demographic characteristics between the three groups for continuous and categorical variables, respectively. Multivariable logistic regression in two different models, without adjustment and with adjustment for age, sex, and body mass index (BMI), were used in order to evaluate the relationship between TAC and MDA and odds of stroke or having risk factors for stroke. Correlation between all the variables were assessed with the Spearman correlation coefficient. P values less than 0.05 were considered as statistical significance. The Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA) was used for performing statistical analysis.

Results

Baseline characteristics

A total of 556 participants were included in this study (216 in stroke group; 152 in group at risk of stroke; and 188 individuals in control group). Overall, the mean age of participants was 72.32 years and 41.01% were females. Moreover, we found a higher mean serum concentration of TAC in the patients at risk of stroke compared to healthy and stroke patients (3909.29 $\mu\text{mol/L}$ in at risk group vs. 3905.98 $\mu\text{mol/L}$ in controls and 3909.29 $\mu\text{mol/L}$ in stroke group). Nevertheless, the mean serum MDA level was lower in the at risk of stroke group than the control group (1.75 vs. 1.85 $\mu\text{mol/L}$) (Table 1). The baseline characteristics of participants in each group are presented in Table 1.

Table 1
Baseline characteristics of participants.

Variables	Healthy control group (n = 188)	Stroke group (n = 216)	Stroke risk group (n = 152)
Female gender ^{&}	96 (51.1%)	68 (31.5%)	64 (42.1%)
Age [§] (year)	73.32 (9.43)	71.76 (9.88)	71.89 (10.22)
BMI [§] (kg/m ²)	26.55 (4.93)	26.92 (5.85)	27.03 (6.33)
Length of Hospitalization [§] (day)	ND	11.06 (20.16)	ND
NIHSS-baseline	ND	8.28 (8.90)	ND
NIHSS-follow-up	ND	5.11 (4.86)	ND
MRS- discharge	ND	2.63 (0.78)	ND
MRS- follow-up	ND	1.78 (1.08)	ND
DBP [§] (mmHg)	73.62 (9.13)	81.17 (11.92)	87.89 (14.55)
SBP [§] (mmHg)	123.09 (14.95)	148.08 (28.02)	150.79 (25.93)
Total cholesterol [§] (mg/dl)	167.17 (42.97)	200.06 (62.03)	176.68 (41.58)
Triglyceride [§] (mg/dl)	119.26 (20.19)	175.20 (91.61)	148.50 (59.29)
LDL [§] (mg/dl)	97.81 (26.15)	118.80 (62.58)	111.03 (37.81)
HDL [§] (mg/dl)	42.18 (9.31)	46.10 (12.66)	43.36 (13.09)
Serum TAC [§] (μmol/L)	3905.98 (879.89)	3687.35 (801.56)	3909.29 (983.87)
Serum MDA [§] (μmol/L)	1.85 (0.36)	2.08 (0.24)	1.75 (0.41)

[&] Gender is presented as number (percent); there was no significant differences between gender of three group based on Chi-square test (p-value = 0.13).

[§] These data are presented as mean (standard deviation).

Abbreviations: BMI: Body Mass Index; DBP: Diastolic Blood Pressure; NIHSS: National Institutes of Health Stroke Scale; MRS: Modified Rankin Scale; SBP: Systolic Blood Pressure; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TAC: Total Antioxidant Capacity; MDA: Malondialdehyde; ND: Not Determined.

A significant difference was shown among patients with stroke and control group in term of baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP), which were significantly higher in both stroke group and at risk of stroke group than healthy controls. In addition, we found significantly increased levels of triglyceride (TG) and total cholesterol in the stroke group than healthy ones (P < 0.001) (Table 2).

Table 2
Comparison of baseline characteristics between Healthy control, Stroke and diabetes groups.

Variables	Group 1	Group 2	Mean difference	P-value*
Age	Healthy control	Stroke group	1.55	0.72
		Stoke risk group	1.42	0.80
BMI	Healthy control	Stroke group	-0.36	0.94
		Stoke risk group	-0.47	0.92
DBP	Healthy control	Stroke group	-7.55	0.00
		Stoke risk group	-14.27	0.00
SBP	Healthy control	Stroke group	-18.71	0.00
		Stoke risk group	-27.70	0.00
Total cholesterol	Healthy control	Stroke group	-32.88	0.00
		Stoke risk group	-9.51	0.69
Triglyceride	Healthy control	Stroke group	-55.94	0.00
		Stoke risk group	-29.24	0.13
LDL	Healthy control	Stroke group	-20.99	0.13
		Stoke risk group	-13.22	0.48
HDL	Healthy control	Stroke group	-3.91	0.34
		Stoke risk group	-1.17	0.91
Serum TAC	Healthy control	Stroke group	218.62	0.46
		Stoke risk group	-3.31	1.00
Serum MDA	Healthy control	Stroke group	-0.23	0.00
		Stoke risk group	0.10	0.35
Abbreviations: BMI: Body mass index; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TAC: Total antioxidant capacity; MDA: Malondialdehyde.				
*P-values calculated using one-way ANOVA test.				

Predictors of stroke development

No significant association was found between quartiles of serum TAC and odds of stroke neither without adjustment for confounding factors nor after adjustment for them (P = 0.12 without adjustment; P = 0.14 after adjustment). While, levels of serum MDA were significantly associated with development of stroke

before and after adjustment for confounding factors. Looking at the quartiles of dietary TCA showed that participants in the second quartile had a reduced odds of stroke by 71% (odds ratio (OR) = 0.29; 95% confidence interval (CI): 0.09–0.94)). Moreover, increasing the levels of serum MDA was associated with increasing risk of stroke development. In this regard, after adjustment for age, sex, and BMI, the third and fourth quartile had ORs of 7.98 (95% CI: 1.94, 32.80) and 11.97 (95% CI: 2.74, 52.35), respectively (Table 3).

Table 3

Odds ratios (ORs) (95% confidence interval) for stroke according to the quartiles of serum total antioxidant capacity (TAC) and malondialdehyde (MDA).

Quartiles of TAC					
Variable	1st quartile	2nd quartile	3rd quartile	4th quartile	P-trend [§]
Serum TAC [¥] (µmol/L)	2939.00	2453.00	4102.00	4916.50	
No. cases/ controls	72/ 32	40/59	44/62	60/35	
Model ¹	1	0.29 (0.09–0.94)	0.34 (0.11–1.10)	0.66 (0.21–2.11)	0.12
Model ²	1	0.37 (0.10–1.25)	0.32 (0.09–1.96)	0.75 (0.23–2.48)	0.14
Quartiles of MDA					
Variable	1st quartile	2nd quartile	3rd quartile	4th quartile	P-trend [§]
Serum MDA [¥] (µmol/L)	1.44	1.91	2.06	2.29	
No. cases/ controls	16/ 60	48/ 72	72/ 32	80/ 24	
Model ¹	1	2.50 (0.66–9.38)	8.43 (2.11–33.60)	12.50 (2.98–52.30)	0.00
Model ²	1	2.12 (0.54–8.31)	7.98 (1.94–32.80)	11.97 (2.74–52.35)	0.00
¥ These value is presented as median					
§ P-trend was calculated using logistic regression model by considering the median of each quartile of TAC or MDA as a continuous variable.					
¹ regression model without adjustment.					
² regression model adjusted for age, gender, and body mass index (BMI).					

Predictors of having risk factors for stroke

No significant association was found between serum levels of TAC and MDA with having risk factors for stroke. Lower levels of MDA were associated with reduced risk for developing stroke risk factors. However, fourth quartile level of serum TAC had lower risk for having stroke risk factors than the third quartile (OR = 0.50 (95% CI: 0.14, 1.79) vs. 0.80 (95% CI: 0.22, 2.93) in the adjusted model). The second quartile of MDA levels had almost the most significant association with not having risk factors for stroke compared to other quartiles of MDA and TCA levels (OR = 0.32 (95% CI: 0.10–1.01) (Table 4).

Table 4

Odds ratios (ORs) (95% confidence interval) for having risk factors of stroke according to the quartiles of serum total antioxidant capacity (TAC) and malondialdehyde (MDA).

Quartiles of TAC					
Variable	1st quartile	2nd quartile	3rd quartile	4th quartile	P-trend [§]
Serum TAC [¥] (µmol/L)	2939.00	2453.00	4102.00	4916.50	
No. cases/ controls	40/ 32	36/ 60	40/ 40	36/ 64	
Model ¹	1	0.4 (0.13–1.66)	0.80 (0.22–2.87)	0.51 (0.14–1.79)	0.98
Model ²	1	0.49 (0.14–1.76)	0.80 (0.22–2.93)	0.50 (0.14–1.79)	1.00
Quartiles of MDA					
Variable	1st quartile	2nd quartile	3rd quartile	4th quartile	P-trend [§]
Serum MDA [¥] (µmol/L)	1.44	1.91	2.06	2.29	
No. cases/ controls	68/ 60	28/ 72	32/ 32	24/ 24	
Model ¹	1	0.34 (0.11–1.04)	0.88 (0.26–2.93)	0.88 (0.23–3.32)	0.30
Model ²	1	0.32 (0.10–1.01)	0.92 (0.27–3.12)	1.03 (0.26–4.06)	0.27
¥ These value is presented as median					
§ P-trend was calculated using logistic regression model by considering the median of each quartile of TAC or MDA as a continuous variable.					
¹ regression model without adjustment.					
² regression model adjusted for age, gender, and body mass index (BMI).					

Correlation between chemical and clinical assessments

We found statistically significant negative correlation between baseline and follow-up levels of NIHSS and TAC ($\rho = -0.28$ ($P = 0.04$) and -0.31 ($P = 0.03$), respectively) and between levels of mRS in follow-up and MDA ($\rho = -0.26$; $P = 0.04$) (Table 5).

Table 5

The correlation between TAC or MDA and NIHSS-baseline, NIHSS-follow-up, mRS-discharge, and mRS-follow-up among patients with stroke.

	NIHSS-baseline	NIHSS-follow-up	mRS-discharge	mRS-follow-up
TAC	-0.28 (0.04)	-0.31 (0.03)	-0.12 (0.37)	-0.17 (0.21)
MDA	-0.09 (0.48)	-0.29 (0.07)	-0.16 (0.23)	-0.26 (0.04)
Values are presented as Spearman's rho (P-value).				
Abbreviations: TAC: Total antioxidant capacity; MDA: Malondialdehyde; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale.				

Discussion

Findings of this hospital-based case control study demonstrated that TAC levels despite MDA levels, which were higher in patients with stroke, were lower in this group. Also, it showed that MDA levels is a better predictor of stroke development than TCA, while none of these measures was significantly associated with having risk factors for stroke. Furthermore, we found a negative correlation between clinical tools, NIHSS and mRS, and chemical measures, TAC and MDA.

Numerous studies have investigated the TAC and MDA levels in stroke patients and showed that serum TAC levels in stroke cases were significantly lower (20, 21) and MDA levels were higher than the control group (22, 23). A case-control study on 195 hospitalized cases with stroke and 195 healthy controls in Iranian populations which were categorized into three groups showed that the top tertile of dietary TAC had lower chance to have stroke than the bottom tertile (OR = 0.49 (95% CI: 0.23, 1.00)), although our study revealed a significant protective association between the bottom quartile of TCA and stroke (OR = 0.29 (95% CI: 0.09–0.94)) (24). The discrepancy might be due to different methods for determining categories. Moreover, the article by Guldiken et al. which categorized participants into diabetic stroke, non-diabetic stroke, and healthy controls showed that TAC levels were significantly higher in diabetic acute stroke patients than in non-diabetic ones (10.03 vs. 5.97 mM; $P < 0.001$) and was higher in diabetic patients with stroke compared to control group (10.03 vs. 5.44 mM; $P < 0.001$) (25). Opara et al. found that the total antioxidant capacity was depleted in the diabetic patients compared to normal subjects (26). On the contrary, Savu et al. showed that the TAC of plasma, despite of high oxidative stress levels, was increased in patients with uncomplicated type 2 diabetes (27). In the present study, the TAC levels of the patient at risk of stroke did not show any significant difference from control group, whereas it was higher than the stroke patients and healthy group, which might be due to the different assays for determination of TAC.

The study by Al-Rawi et al. conducted on 50 patients with ischemic stroke, 75 participants with a risk factor for stroke, including diabetes, hypertension, and ischemic heart disease, and 25 healthy individuals. MDA levels were measured in the serum and saliva of subjects and showed that MDA levels

in both groups were significantly higher than the healthy group ($P < 0.001$) (28). Our findings confirmed that MDA has a significant increasing association with stroke occurrence, while this association was not significant in patients who were at risk of stroke. We propose that significant increase in MDA level in stroke is a reflection of increased MDA production and oxidative stress in cerebral ischemia since the top quartile of MDA was in higher risk of stroke compared to the bottom quartile, although they were not significant.

A case-control study on 50 patients with stroke and 50 healthy controls represented higher levels of MDA in cases than controls (3.31 vs. 1.62 nmol/ml; $P < 0.0001$) (29). In this regard, the article by Bir et al. showed significantly greater MDA values in both atherothrombotic ischemic stroke and with lacunar infarction compared to healthy controls ($P < 0.001$) (30). It has been suggested that blood or neural lipids may be the source of lipid peroxidation caused by ischemia. In addition, during ischemia, increased cytosolic calcium leads to the activation of phospholipases and proteases, which leading to conversion of xanthine dehydrogenase to xanthine oxidase or activation of protein kinase. Consequently, these activated enzymes can also be the cause of the increased free radicals (31).

This study also compared the correlation between TAC or MDA with NIHSS-baseline, NIHSS-follow-up, mRS-discharge, and mRS-follow-up. A cohort study on 42 patients with acute ischemic stroke found no significant association between severity of stroke based on baseline NIHSS and level of MDA ($P = 0.60$), whereas there was a significant positive correlation between level of MDA and mRS after three months of follow-up ($r = 0.54$; $P = 0.001$) (32). In addition, Yaseen et al. revealed that level of MDA on the 7th day had a positive correlation with NIHSS and mRS scores at 7th day ($r = 0.335$; $P = 0.024$ for NIHSS and $r = 0.342$; $P = 0.022$) (33). We found a negative correlation between levels of MDA and TAC and NIHSS and mRS. Our findings is in accordance with a study on 34 ischemic stroke patients and 34 healthy controls that showed a negative correlation between total antioxidant status (TAS) and NIHSS values, even though it was not significant ($r = -0.17$; $P = 0.34$) (34). Moreover, another study on acute ischemic stroke patients and healthy controls showed that TAC levels were negatively correlated with NIHSS scores ($r = -0.38$; $P = 0.02$) (21). The differences in results of our study with mentioned articles can be due to differences in methods of measurement of factors, especially oxidative stress parameters, time to assess the values, and study participants.

The strength of this study is that it is among pioneer studies which included a group of participants who were potentially at risk of having stroke, while several previous studies compared serum levels of oxidative markers only between stroke cases and healthy controls. However, our study had some limitations. First, we adjusted multiple logistic regression test by age, sex, and BMI, while other potential confounding and risk factors, especially atrial fibrillation for stroke were not included in our analysis (35). Second, selection and recall bias could have influenced the results because of susceptibility of case-control studies. Third, we could not reach to a cause-effect relationship because of observational design of this study. Fourth, body composition might have effects on inflammatory factors (36), while the study did not include data on some body composition components measures such as fat mass.

Conclusions

In the light of present findings, it seems that MDA is a better predictor of stroke than TCA, while both TCA and MDA might not be recommended to use for prediction of having stroke risk factors. In addition, TCA and MDA had negative association with severity and disability of stroke. Altogether, it will be worthwhile to pursue oxidative stress role in stroke pathogenesis and it is needed to be design further large-scale studies to investigate TAC and MDA role in stroke patient clearly.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Tabriz University of Medical Sciences (Ethics number: TBZMED 94/3-4/3). Our study was implemented in accordance with the ethical standards of the 1964 Declaration of Helsinki and its lateral amendments. All participants had been given the written informed consent.

Consent for publication

Written informed consent was obtained from all of the participants at the beginning of the study.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due for they are personal data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflicts of interests.

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None.

Authors' contributions

S.S., M.K.: designed the study. F.H., M.M., H.R., M.K.: patient data acquisition, statistical analysis, and interpretation of data. S.A.N., M.M., H.R.: preparation and critically revision of the manuscript. All the authors have read and approved the final version of the manuscript.

Acknowledgments

None.

Abbreviations

GBD: Global Burden of Disease

DALY: Disability-adjusted life-year

UI: Uncertainty interval

ROS: Reactive oxygen species

DNA: Deoxyribonucleic acid

MDA: Malondialdehyde

TAC: Total antioxidant capacity

MRI: Magnetic resonance imaging

DWI: Diffusion-weighted imaging

mRS: modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

TBARS: Thiobarbituric acid reactive substance

FRAP: Ferric-reducing antioxidant power

ANOVA: Analysis of variance

BMI: Body mass index

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

TG: Triglyceride

OR: Odds ratio

CI: Confidence interval

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