Original Research Article

Study of lipid peroxidation and antioxidant status in ischemic stroke patients

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Abstract

Background: Oxidative stress is probably one of the mechanisms involved in neuronal damage induced by ischemia. During ischemia, high amounts of free radical formation together with reduced antioxidant defense causes oxidative stress that may play a role in the pathogenesis of stroke associated neuronal injury**. Aim and objectives:** To study the correlation between lipid peroxidation and antioxidant status in ischemic stroke patients in comparison with normal controls. **Materials and Methods:** Cross sectional study includes 50 Ischemic stroke cases and 50 healthy controls. Fasting Venous blood samples were collected in ischemic stroke patients within 24hours from the time of onset of stroke and blood levels of Lipid profile, Malondialdehyde, Vitamin C, Vitamin E and Uric acid are estimated in both cases and controls. **Results:** In the Ischemic stroke group total cholesterol, triglycerides and LDL levels were significantly increased and HDL level was significantly decreased. Malondialdehyde a lipid peroxidation product was significantly increased, while antioxidants Vitamin C and Vitamin E were significantly decreased. The other antioxidant Uric acid has increased significantly in cases when compared to controls. **Conclusion:** This study showed an altered antioxidant status in ischemic stroke patients, which may be an indirect proof for the existence of Lipid Peroxidation.

Key words: Lipid peroxidation, Antioxidants, Ischemic stroke. Malondialdehyde, HDL

Introduction

Stroke is a medical emergency situation that may lead to loss of brain function and even death. It is the second most common cause of death and the most common cause of impairment in the world [1].

The world health organization defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24hours or longer or leading to death, with no apparent cause other than vascular origin".

The national institute of neurological disorders and stroke (NINDS) apply the term stroke to any one or all of a group of disorder including cerebral infarction, intra cerebral hemorrhage or subarachnoid hemorrhage [2].

Stroke is basically classified in to two categories, ischemic and hemorrhagic. Ischemic stroke constitute 85-87% of all strokes. Ischemic stroke is mainly caused by thrombosis, embolism and focal hypo perfusion, all of which can lead to a reduction or an interruption in cerebral blood flow that affect neurological function [3].

In hemorrhagic stroke, bleeding can occur within the cerebral parenchyma or within the meninges. Intra cerebral hemorrhage is defined as bleeding in to brain parenchyma [4].

The common risk factors of stroke are modifiable and non modifiable. Modifiable risk factors include hypertension, diabetes, smoking, lipid disorders, alcohol intoxication and physical inactivity where as non modifiable risk factors include age, gender, positive family history, previous transient ischemic attack [5].

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The symptoms of stroke include vertigo, sensory loss, nystagmus, facial numbness, ataxia, dysphasia, opthalmoplegia, hemi paresis, upper and lower limb paralysis, urinary incontinence and coma [6].

Oxidative stress is probably one of the mechanisms involved in neuronal damage induced by ischemia. During ischemia, high amounts of free radical formation together with reduced antioxidant defense causes oxidative stress that may play a role in the pathogenesis of stroke associated neuronal injury [7].

The brain contains high levels of polyunsaturated fatty acids in membrane lipid; therefore lipid peroxidation is one of the major consequences of free radical mediated injury to brain [10]. Lipid Peroxidation is a free chain reaction, which arises from the oxidative conversion of polyunsaturated fatty acids by HO to lipid peroxides, which in turn can damage biological membranes. MDA level is widely utilized as a marker of lipid peroxidation in states of elevated oxidative stress [9].

Some studies found increased risk of ischemic stroke is associated with increased total cholesterol and triglyceride levels. Triglycerides concentration was 2- 3 times higher in ischemic stroke group. Patients with highest levels of triglycerides were 2-7 times more likely to suffer from atherosclerotic stroke than those with lower levels. HDL cholesterol concentration is markedly reduced in patients with stroke [8].

Studies had shown that there is a decreased level of antioxidant's during Lipid Peroxidation. The antioxidant system includes enzymatic and non-enzymatic antioxidants. The enzymatic system includes superoxide dismutase, catalase, glutathione peroxidase and non-enzymatic system includes Vitamin C (Ascorbic acid) and Vitamin E (Tocopherol) [10].

Vitamin C represents the major water-soluble antioxidant in the human body. Many studies show that reduced Vitamin C levels are associated with increased risk of both ischemic and hemorrhagic strokes [11].

Vitamin E a potent chain breaking lipid soluble antioxidant reacts with lipid peroxyl radicals eventually terminating the peroxidation chain reaction and thereby reducing oxidative damage. Low serum Vitamin E levels in stroke patients may be due to high lesion volume resulting in production of more number of free radicals from a large ischemic injury [12].

Uric Acid is the most abundant endogenous aqueous antioxidant in humans. It may protect against oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation during oxidative stress.

Several studies have shown that increased oxidative stress is associated with high circulating uric acid levels due to elevation of xanthine oxidase in stroke inducedbrain damage [13].

This study has been undertaken to understand the significant role of lipid peroxidation and antioxidants in stroke. Since stroke is the second most common cause of death and disability in the world and oxidative stress is evident in the first 24 hours of stroke, antioxidants and lipid peroxidation signifies it.

Aim & Objectives

1. To observe the lipid peroxidation and antioxidant status in Ischemic strokepatients.
2. To determine lipid peroxidation by measuring the levels of Serum Malondialdehyde in Ischemic stroke patients in comparison with controls.
3. To determine the antioxidant status by measuring Vitamin C, Vitamin E, Uric acid levels in ischemic stroke patients in comparison with controls.

Materials and methods

The study was carried out in 50 ischemic stroke patients who attend asinpatient in the department of Neurology and 50 normal Controls at NRI Institute of Medical Sciences, AP during the year 2013-15. The institutional ethical committee approved the study protocol.

Sources of data

Inclusion criteria

By including healthy controls, cases clinically diagnosed as ischemic stroke of less than 24hours duration after the onset of symptoms and conformed by detailed neurological examination and computerized tomography are involved in the study.

Exclusion criteria

Patients with any other neurological diseases or those who were on iron or antioxidant supplements during preceding month, those who are using vasodilators containing nitrates or releasing nitrates as end products are excluded from the study.

Method of collection of data

Informed consent was taken from patients and controls. A structured proforma was used to collect the data. Baseline data including age and detailed medical history, clinical examinations and relevant investigations were included as part of the methodology.

Specimen collection

Under aseptic conditions 6ml of plain venous blood sample was obtained by venepuncture from both cases and controls. The sample was allowed to clot and centrifuged for 5minutes at 3500rpm and the serum was separated. Serum lipid Profile, serum Malondialdehyde, serum Ascorbic acid, serum Vitamin E and serum Uric acid were performed using the serum.

Estimation of serum malondialdehyde by tba method [14]

Estimation of serum ascorbic acid [15]

Determination of serum tocopherol: [16]

Results

The present study is undertaken to observe the lipid peroxidation and antioxidant status in ischemic stroke patients. Fifty [50] ischemic stroke cases were considered for the study. Fifty [50] healthy persons are chosen as controls.

Statistical Analysis used

Arithmetic mean, standard deviation, z test of difference between two independent means, $\chi 2$ test of association, z test of difference between two proportions, Karl Pearson correlation coefficient

Comparison of cases in <55 age group and >55 age group

There is a statistically significant difference between proportion of cases in <55 age group and >55 age group (z test value -5.2, p value < 0.0001).

Persons with age less than 55 in cases 12
Persons with age more than 55 in cases 38

Comparison of Blood Pressure between cases and controls

The mean value of systolic blood pressure among cases as compared to controls was statistically significant, (z test value 11.95, p value < 0.0001) and mean value of diastolic blood pressure among cases as compared to controls was statistically significant, (p value < 0.0001, z test value 6.42).

Table 5. Distribution of cases and controls according to systolic blood pressure and diastolic bloodpressure

PARAMETER	MEAN	SD	MEAN	SD	Z-TESTVALUE	P-VALUE
SBP	163.40	25.20	119.20	6.95	11.95	<0.0001
DBP	96.00	12.94	83.00	6.14	6.42	<0.0001

Association of smoking in ischemic stroke cases and controls

The $\chi 2$ value shows significant association between the habit of smoking and presence of disease ($\chi 2$ value 21.4, p value < 0.0001). Distribution of cases and controls based on smoking habit is graphically represented inAssociation of alcohol in ischemic stroke cases and controls

The $\chi 2$ value shows significant association between the habit of alcohol and presence of disease ($\chi 2$ value 46.9, p value < 0.0001). Distribution of cases and controls based on alcohol consumption habit is graphically represented in

Table: 6 Comparison of Lipid Profile between cases and controls

	cases		control			
Parameter	**Mean**	SD	Mean	SD	**Z-test Value**	**P-Value**
TC	178.74	37.42	152.08	31.67	3.85	0.0001
TG	192.90	110.02	100.98	43.27	5.50	<0.0001
HDL	31.16	4.94	41.06	9.43	-6.58	<0.0001
LDL	107.76	35.68	91.08	27.87	2.61	0.0090

The mean serum total cholesterol level is higher among cases as compared to controls and statistically significant (z test value 3.85, p value < 0.0001).

The mean serum triglycerides level is higher among cases as compared to controls and statistically significant (z test value 5.50 p value <

0.0001).
The mean serum HDL level is lower among cases as compared to controls and is statistically significant (z test value -6.575, p value < 0.0001).
The mean serum LDL level is higher among cases as compared to controls and is statistically significant (z test value 2.6051, p value < 0.009).

Table: 7: Comparison of Biochemical parameters to assess lipid peroxidation and antioxidant status between cases andcontrols

	cases		control			
Parameter	**Mean**	SD	Mean	SD	**Z-test Value**	**P-Value**
MDA	609.36	104.28	196.36	19.07	27.55	<0.0001
UA	6.25	1.27	3.32	0.92	13.27	<0.0001
VIT-E	6.24	1.18	10.52	2.65	-10.44	<0.0001
VIT-C	0.35	0.08	1.47	0.38	-20.39	<0.0001

The mean serum malondialdehyde levels are higher among cases as compared to controls and statistically significant (z test value 27.55, p value < 0.0001).
The mean serum ascorbic acid levels are lower among cases as compared to controls and statistically significant (z test value -20.39, p value < 0.0001).
The mean serum vitamin 'E' levels are lower among cases as compared to controls and statically significant (z test value -10.44, p value < 0.0001).
The mean serum Uric acid levels are higher among cases as compared to controls and statistically significant (z test value 13.27, p value < 0.0001).

Correlation between MDA and Lipid profile
The following Scatter diagram explains the relationship between MDA andTotal cholesterol

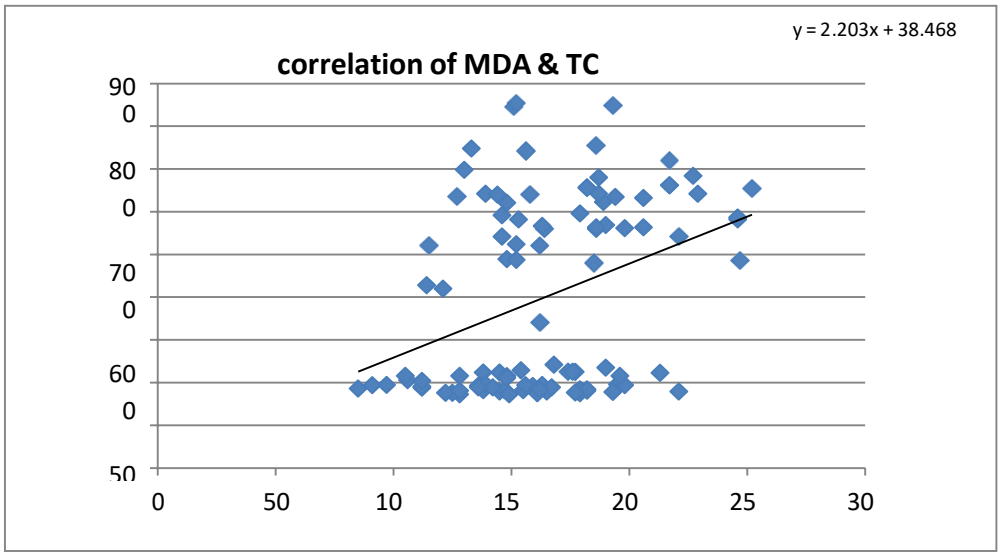

Figure: 11

There is a possitive co-relation between serum MDA and serum Total cholesterol in ischemic stroke cases and is statistically significant (t value 4.38, p value < 0.00002).
There is a possitive co-relation between serum MDA and serum Triglycerides in ischemic stroke cases and is statistically significant (t value 5.24, p value < 0.0000009).
There is a negative co-relation between serum MDA and serum HDL in ischemic stroke cases and is statistically significant (t value -4.093, p value < 0.00008).
There is a possitive co-relation between serum MDA and serum LDL in ischemic stroke cases and is statistically significant (t value 3.066, p value < 0.002).
There is a significant negative co-relation between serum MDA and serum ascorbic acid and is statistically significant (t value 12.973, p value < 0.0001).
There is a significant negative co-relation between serum MDA and serum vitamin 'E' and is statistically significant (t value -7.44, p value < 0.0001).
There is significant positive co-relation between serum MDA and serum uric acid and is statistically significant (t value 10.333, p value < 0.0001).

Discussion
Stroke is defined as an "acute neurological dysfunction of vascular origin with sudden or rapid occurrence of signs and symptoms corresponding to the involvement of focal areas in the brain. The two main types of stroke are ischemic and haemorrhagic accounting for approximately 85% and 15% respectively [17].

Age, gender, heredity, hypertension, atrial fibrillation, diabetes, lipids, cigarette smoking, alcohol consumption, life factors like obesity, physical activity, diet are the major risk factors of stroke [18].
Age is the single most important risk factor for stroke. For each successive ten years after the age of 55, the risk factor of stroke doubles in both men and women. In the present study there is a

statistically significant difference between proportion of cases in >55 age group and <55 age group.

According to Philip A. Wolf the stroke incidence rates are 1.25 times greater in men than women [19].

primary and environmental tobacco smoke exposure can increase the risk of stroke and heart disease are numerous and include carboxyhemoglobinemia, increased platelet agreeability, increased fibrinogen levels, reduced HDL-cholesterol, and direct toxic effects of compounds such as 1,3-butadiene, a vapor phase constituent of environmental tobacco smoke has been shown to accelerate atherosclerosis [20].

In the present study the association of smoking between ischemic stroke cases and controls shows significant association between smoking andpresence of disease (p value < 0.0001, $\chi 2$ value 21.4).

According to the study conducted by Reena S Shah and John W Cole there is a strong association between smoking and stroke risk, with current

Smokers having at least a two- to fourfold increased risk of stroke compared with lifelong nonsmokers or individuals who had quit smoking more than 10 years prior [20].

Drinking large amounts of alcohol can raise blood pressure consistently to higher levels. Hypertension is one of the important modifiable risk factor for ischemic stroke [20].

In the present study the association of alcohol consumption between ischemic stroke cases and controls shows significant association between the alcohol consumption and presence of disease (p value < 0.0001, $\chi 2$ value 46.9).

According to the study conducted by Hillbom.M heavy drinking of alcohol increases the risk for both hemorrhagic and ischemic strokes [21].

Hypertension can cause stroke through many mechanisms. A high intraluminal pressure will lead to extensive alteration in endothelium and smooth muscle function in intracerebral arteries. The increased stress on the endothelium can increase permeability over the blood-brain barrier and local or multifocal brain edema. Endothelial damage and altered blood cell- endothelium interaction can lead to local thrombi formation and ischemic lesions. Mostly systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg is indicative for relative risk of stroke. Mostly systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg is indicative for relative risk of stroke [22].

In the present study the systolic blood pressure among cases as compared to controls was statistically significant (p value < 0.0001, z test value 11.95) and the diastolic blood pressure among cases as compared to controls was statistically significant, (p value < 0.0001, z test value 6.42).

According to the study conducted by Johansson.BB it is well established that hypertension is the main risk factor for ischemic stroke [22].

The term lipids include cholesterol, triglycerides, LDL (low density lipoproteins) and HDL (high density lipoproteins). Hyperlipidemia refers to increased levels of lipids (fats) in the blood. Findings revealed a significant relation between hyperlipidemia and the occurrence of the ischemic stroke. Different findings were reported that increased serum cholesterol, triglycerides, LDL cholesterol and decreased HDL cholesterol is a risk factor for ischemic stroke.

In the present study we had estimated the lipid profile level in ischemic stroke patients in first 24-hours from the time of onset of stroke and compared these levels with healthy controls.

There is a distinct epidemiological association between serum total cholesterol levels and the risk of coronary heart disease. Various clinical trials demonstrated a link between high concentrations of serum total cholesterol and ischemic stroke. [23].

In the present study there is significant increase in serum total cholesterol level (p value < 0.0001, z test value 3.85), triglycerides (p value < 0.0001, z test value 5.50) and LDL cholesterol (p value < 0.0001, z test value 3.85) and there is significant decrease in HDL cholesterol (p value < 0.0001, z test value 5.50) in first 24hours from the time of onset in ischemic stroke cases when compared to normal controls.

Study by Mansoureh Togha, Mohamad Reza Gheini etal, showed higher levels of total cholesterol in patients with ischemic stroke comparedwith the control group [24].

According to David Tanne, Nira Koren-Morag etal, the study showed that higher levels of triglycerides constitute an independent risk factor for ischemic stroke and transient ischemic attack [25].

Denti et al reported that LDL-C concentrations over 100 mg/dl along with low HDL-C levels were associated with higher stroke risk [26].

In the present study there is significant co-relation in ischemic stroke cases between serum MDA and serum Total cholesterol (t value 4.38, p value < 0.00002), serum Triglycerides (t value 5.24, p value < 0.0000009), serum LDL (t value 3.066, p value < 0.002), and there is a significant negative co- relation between serum MDA and serum HDL cholesterol in ischemic stroke cases (t value -4.093, p value < 0.00008).

According to Jaspreet Kaur, Sarika Arora etal, there is significant positive correlation between serum MDA and serum total cholesterol as well serum LDL cholesterol [27].

According to Natheer H Al-Rawi serum triglycerides concentrations were 2-3 times higher in ischemic stroke group than in control group, moreover, serum levels of triglycerides were directly correlated with MDA, LDL-C and inversely correlated with HDL-C. [8].

Oxidative stress is an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage. The increased production of free radicals in the setting of cerebral ischemia, with or without reperfusion, will arise from several mechanisms: glutamate stimulation of NMDA receptors, mitochondrial dysfunction, activation of neuronal nitric oxide synthase, induction of nitric oxide synthetase or cyclooxygenase 2, autooxidation of catecholamines, metabolism of free fatty acids, particularly arachidonic acid which released during ischemia, migration of neutrophils and leukocytes able to generate superoxide anions, the conversion of xanthine dehydrogenase to xanthine oxidase. Lipid peroxidation, with accumulation of both conjugated dienes and thiobarbiturate-reactive material, is consistently found when cerebral ischemia is followed by reperfusion. Hydroxyl radicals (formed from hydrogen peroxide), peroxinitrite and superoxide are powerful radicals that can cause lipid peroxidation, a self propagating chain reaction, that irreversibly damages plasma and mitochondrial membranes. Malondialdehyde product of lipid peroxidation irreversibly disrupts enzymes, receptors and membrane transport mechanisms. The concentrations of MDA were significantly increased in stroke patients, arising from excess free radical activity [28].

In the present study there is significant increase in serum levels of malondialdehyde (p value < 0.0001, z test value 27.55) in first 24 hours in ischemic stroke cases when compared to normal controls.

According to M Beg, S Ahmad, S Gandhi, N Akhtar, Z Ahmad there is a significant increase in serum MDA levels in cases than controls suggesting an increase in the level of lipid peroxides [29].

According to Demirkaya S, Topcuoglu MA et.al there was a significant raise in MDA levels in ischemic stroke patients when compared with controls [30].

In this study we estimated the antioxidant levels of Vitamin C and Vitamin E and Uric Acid in ischemic stroke patients.

Vitamin C, also known as ascorbic acid, is a water-soluble nutrient found in some foods. In the body, it acts as an antioxidant, helping to protect cells from the damage caused by free radicals. The functions of ascorbate in the CNS and brain are numerous. Regarding antioxidant functions, ascorbate directly acts to scavenge oxygen- or nitrogen based radical species generated during normal cellular metabolism. At the millimolar concentrations present in neurons in vivo, ascorbate will effectively scavenge superoxide, a major diffusible byproduct of rapid neuronal mitochondrial metabolism. Ascorbate in aqueous compartments can also recycle α-tocopherol in membranes by reducing the α- tocopheroxyl radical back to α-tocopherol. Ascorbate hasbeen shown to spare/recycle α- tocopherol in lipid bilayers and in erythrocytes. Ascorbate prevents lipid peroxidation induced by various oxidizing agents especially in

combination with α-tocopherol [31].

In the present study there is a significant decrease in serum levels of ascorbic acid (z test value -20.39, p value < 0.0001) in first 24 hours from the time of onset of stroke in Ischemic stroke cases when compared to normal controls.

Concepción Sánchez-Moreno, John F. Dashe, etal have shown that ischemic stroke cases had lower levels of plasma vit-C and higher levels of inflammatory markers than controls suggesting that ischemic stroke may be accompanied by a reduction in vit-C concentration and elevated levels of inflammatory markers [32].

In the present study there is significant negative co-relation in ischemic stroke cases between serum MDA and serum ascorbic acid and is statistically significant (t value 12.973, p value < 0.0001).

Some studies stated that ischemic stroke patients in the early post ischaemic period (before starting therapy) had significantly higher levels of serum MDA and hsCRP, and significantly lower total antioxidant status than controls. Evaluations of antioxidants in blood, urine, or cerebrospinal fluid of ischemic stroke patients revealed lower levels of serum vitamin C [32].

In the present study there is a significant decrease in serum levels of Vitamin E (z test value -10.44, p value < 0.0001) in first 24 hours from the time of stroke in ischemic stroke cases when compared to normal controls.

Antonio Cherubini, Maria Cristina Polidori etal, found that stroke patients had lower levels of vitamin E than controls on admission, reaching plasma concentrations similar to those of controls 1 week after stroke [33].

In the present study there is significant negative co-relation in ischemic stroke cases between serum MDA and Serum Vitamin E and is statistically significant (t value -7.44, p value < 0.0001).

According to Jaspreet Kaur , Sarika Arora etal, a significantly increased levels of MDA and decreased level of serum Vitamin E and SOD were observed in stroke and TIA cases as compared to controls in this study [27].

In the present study there is a significant increase in serum levels of uric acid (z test value 13.27, p value < 0.0001) in first 24 hours from the time of onset of stroke in ischemic stroke cases when compared to normal controls.

Inimoria Mihaela Cojocaru, M.Cojocaru etal, stated that uric acid is a powerful radical scavenger and its antioxidant properties could be expected to offer a number of benefits in humans. They also stated that increased oxidative stress is associated with high circulating uric acid levels and that uric acid may protect against oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress [34].

In the present study there is significant co-relation in ischemic stroke cases between serum MDA and serum levels of Uric acid (t value 10.333, p value < 0.0001).

Conclusion

Measurement of antioxidant status may have important diagnostic and therapeutic implications in ischemic stroke cases. Intake of antioxidant rich diet can minimize the risk of ischemic stroke and supplementation of antioxidants for ischemic stroke patients can minimize the disease.

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