



## EVALUATION OF SERUM CHOLESTEROL LEVELS IN PATIENTS WITH HEMORRHAGIC STROKE

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### ABSTRACT

**Introduction:** Cerebrovascular disease is the most common neurological disorder. Many studies have been conducted to investigate the effective mechanisms involved in stroke, however, the main pathomechanism in some patients with hemorrhagic stroke has not been known well. The effect of cholesterol level on ischemic stroke has been somewhat proved and much attention has been paid to the impact of it on hemorrhagic stroke. In this study, serum cholesterol levels in patients with hemorrhagic stroke were evaluated.

**Methods:** The study was cross-sectional and Case-Control. All patients hospitalized with a diagnosis of hemorrhagic stroke in neurology ward of Imam Khomeini Hospital in Urmia Town, Iran, during 2014, were included. Finally, SPSS20 software was used to analyze the data.

**Results:** In this study, 164 patients were placed in the case group and 356 patients were placed in the control group. There is a significant relationship between the case group and the control group in terms of diabetes, hypertension, smoking, oral contraceptive use, hyperlipidemia, which represents the effects of factors examined in the patients of case group (P-value = 0.002, <0.001, <0.001, <0.001, respectively).

**Conclusion:** The results showed that diabetes, hypertension, smoking, and use of oral contraceptives can be as risk factors for hemorrhagic stroke. Also, increase in HDL and decrease in cholesterol levels can be as risk factors for hemorrhagic stroke.

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### Introduction

Cerebrovascular disease is the most common neurological disorder that causes the disease and mortality (1,2). The term of cerebrovascular disease means any brain abnormalities caused by the process of blood vessel damage that its three main processes are: 1. thrombotic occlusion of the arteries, 2. embolic occlusion of the arteries, 3. tearing arteries. Thrombosis and embolism cause ischemic damage or infarction of certain areas of the brain that are irrigated by the vessel. "Stroke" is a clinical schema of all cases, especially when they are started acutely (3,4).

Stroke is caused by two types of vascular disorder in the brain: ischemia or bleeding (5) and ischemic stroke is more common (6). However cerebral hemorrhagic stroke is more prevalent and causes more mortality in developing countries than developed countries (7).

In developing countries, cardiovascular events are the main cause of mortality due to disease (8). In Iran, the prevalence of stroke is 23-139 per 100,000 people which is higher compared to Western countries and the age of onset of the disease is a decade less than the global average (8). The incidence of stroke increases with age, and about two-thirds of all strokes occur in people older than 65 years, it happens more in men than women and it happens more in black people than white ones (1, 3).

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In general, three categories of factors can cause focal ischemia in the brain: vascular disorders, cardiac disorders and hematological disorders (9, 5).

Genetic factors are important in the pathogenesis of ischemic stroke but probably, etiology of the majority of strokes is multi-factor (10, 5).

Bleeding can disrupt brain function through several mechanisms, including the destruction of brain tissue or pressuring on it, and pressuring on the vascular structures results in secondary ischemia and edema. According to the place of bleeding, bleeding is classified into intracranial, subarachnoid, subdural or epidural types that all of them - with the exception of subdural type- are usually caused by arterial bleeding (5).

Risk factors for stroke are hypertension, hypercholesterolemia, smoking and alcohol consumption and use of oral contraceptives (1, 5).

The effect of cholesterol levels on ischemic stroke has been proved somewhat and much attention has been paid to the impact of them on hemorrhagic stroke (9, 10).

Cholesterol is a type of fat that is used in the construction of all cells of the body. The substance may be made from saturated fat in the liver or it enters the body through consumption of meat, eggs and other animal food. Cholesterol is transmitted in various forms in the body. Substances called lipoproteins carry cholesterol in the blood (11).

Different types of cholesterol are VLDL (which carries the molecules of fat from the liver to other parts of the body and after transferring fat to the tissues, it is converted to LDL), LDL (it gets cholesterol from the liver and carries it to the tissues), HDL (remaining cholesterol is carried by HDL and this leads to the use of cholesterol and reduces the risk of cardiovascular diseases. HDL transfers the cholesterol from tissues and leads it towards the liver (11).

In people who have high LDL cholesterol levels, the risk of cardiovascular diseases such as stroke is more (13). Aggressive treatment of dyslipidemia can reduce the risk of stroke (14). In 2002, a review study was not performed in Europe that the results showed a significant relationship between ischemic and hemorrhagic stroke (15). Also, in 2004, another study was conducted on 313 patients with hemorrhagic stroke and results showed that low levels of total cholesterol is associated with an increase in all types of hemorrhagic stroke (16).

More recently, in 2014, a review study has been done in England in which it was stated that Low levels of LDL are associated with the low risk of hemorrhagic stroke and the levels of HDL have a direct relationship with the risk of bleeding into the brain (17).

Given the importance of the issue and the conflicting results obtained in previous studies done in this area and that no study has been done in this field in Iran, it was decided to design a study to examine serum cholesterol levels in patients with hemorrhagic stroke.

## Method

This study is cross-sectional and case-control. All patients hospitalized with a diagnosis of hemorrhagic stroke in neurology ward of Imam Khomeini Hospital in Urmia Town, Iran, during 2014, were included.

The information needed to plan are:

1. Age
2. Gender
3. The serum levels of total cholesterol, HDL and LDL

All the necessary information was extracted from the admission records available in the archives of Imam Khomeini hospital and entered in the self-made forms. Per any patient of case group, two patients admitted to the neurology ward in the period examined in the study and had no history of stroke were selected as control group.

Inclusion criterion for the test(case) group are:

1. Hospitalization for an admitting diagnosis of hemorrhagic stroke

Exclusion criteria for the test group are:

1. History of ischemic stroke
2. Receiving thrombolytic drugs in the last few days

Inclusion criteria for the control group are:

1. Admission in the neurology ward in the period examined in the study
2. Availability of required information in patient's record

Exclusion criteria for the control group are:

1. History of hemorrhagic stroke
2. History of ischemic stroke

Finally, after gathering information from patients using self-made questionnaire. SPSS20 software was used to analyze the data statistically.

## Results

In this study, 520 patients admitted to the neurology ward of Imam Khomeini hospital were examined. 164 (31.5%) and 356 (68.5%) of them were place in case group and control group, respectively.

266 patients (51.2%) were men and 254 patients (48.8%) were women. Mean age $\pm$ SD of patients was 60.6 $\pm$ 17.7 years and it was 61.8 $\pm$ 15.2 years in case group and it was 60 $\pm$ 18.7 years in control group, so, there is no significant difference between these two groups in terms of age (P-value = 0.282).

**Table1. Frequency distribution of gender in two case and control groups**

	Frequency (%)	p-value*
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	Test group	Control group	
Women	88(53.7%)	166(46.6%)	0.081
Men	76(46.3%)	190(53.4%)	

\* Using Chi-Square test

As shown in above table, 88 of 164 patients of case group (53.7%) were women and 76 of them (46.3%) were men and 166 of 356 patients of control group (46.6%) were women and 190 of them (53.4%) were men. So, there is no significant difference between these two groups in terms of gender (P-value = 0.081).

**Table2. Frequency distribution of risk factors in two case and control groups**

	Frequency	Percentage
Diabetes	75	14.4
High blood pressure	203	39
Ischemic heart disease	89	17.1
smoking	87	16.7
Oral contraceptive use	41	7.9
Hyperlipidemia	68	13.1

As shown in table2, the greatest frequency of studied risk factors in test group was related to blood pressure with 203 patient (39%) and after it, ischemic heart disease with 89 patients (17.1%), smoking with 87 patients (16.7%), diabetes with 75 patients (14.4%), history of hyperlipidemia with 68 patients (13.1%), use of oral contraceptives with 41 patients (7.9%) were placed, respectively.

**Table3. Frequency of hemorrhagic stroke types among patients of case group**

	Frequency	Percentage
ICH	207	58.1
SAH	78	21.9
ICH+IVH	51	14.3
SAH+IVH	5	1.4
ICH+SAH+IVH	4	1.1
IVH	11	3.1

As shown in table3, in case group, frequencies of hemorrhagic stroke types were as follows: 207 patients with ICH (58.1%), 78 patients with SAH (21.9%), 51 patients with ICH+IVH (14.3%), 11 patients with IVH (3.1%), 5 patients with SAH+IVH (1.4%) and 4 patients with ICH+SAH+IVH (1.1%).

According to the results of the case conducted for patients, mean ESR  $\pm$  SD of all the patients was  $28 \pm 1.1$ . In case group, it was  $24.1 \pm 1.9$  and in control group, it was  $29.8 \pm 1.3$ . 86 patients of case group (52.4%) and 156 patients of control group (43.8%) had positive CRP.

Following results was obtained in examining the relationship between hemorrhagic stroke and risk factors investigated in the patients:

**Table4. Relationship between hemorrhagic stroke and risk factors investigated in the patients of both groups**

	Frequency		p-value*
	Test group	Control group	
Diabetes	35(21.3%)	40(11.2%)	0.002
High blood pressure	89(54.3%)	114(32%)	<0.001
Ischemic heart disease	27(16.5%)	62(17.4%)	0.447
smoking	45(27.8%)	42(11.8%)	<0.001
Oral contraceptive use	31(18.9%)	10(2.8%)	<0.001
Hyperlipidemia	54(32.9%)	14(3.9%)	<0.001

\* Using Chi-Square test

As shown in table4, there were significant relationships between case and control groups in terms of diabetes, hypertension, smoking, oral contraceptive use and hyperlipidemia. This represents the impact of studied risk factors in the patients of case group (P-value = 0.002, <0.001, <0.001, <0.001, respectively).

For all patients of both groups, the results of lipid profile were as follows:

**Table5. Lipid profile in the studied patents**

	case group	Control group	p-value
LDL	100.9 $\pm$ 29.5	99.6 $\pm$ 33.1	0.690
HDL	47.3 $\pm$ 12.3	41.7 $\pm$ 9.9	<0.001
Cholesterol	167.6 $\pm$ 64.6	165.4 $\pm$ 54.8	0.693
Triglycerides	138.9 $\pm$ 72.7	157.1 $\pm$ 78.7	0.009

As shown in table5, there were significant relationships between control and case groups in terms of triglycerides level (P-value = 0.009) and HDL (P-value <0.001) but there were no significant relationships between them in terms of the level of LDL (P-value = 0.690) and cholesterol (P-value = 0.693).

### Discussion and conclusion

Hypertension and hyperlipidemia are risk factors for ischemic stroke (18) while triglyceride plays no important role as the major risk factors for ischemic stroke (18) but an increase in plasma triglyceride levels after acute ischemic cerebral stroke has been associated with poorer prognosis (19). In a prospective study, it was shown that hyperlipidemia in patients with ischemic stroke who don't receive statins is associated with improved disease prognosis than patients without hyperlipidemia (20). The lower ratio of triglycerides to HDL independently leads to worse prognosis in patients with acute ischemic stroke (21).

In this study, patients of case group had higher HDL than patients of control group, this difference was statistically significant. The amount of triglyceride in case group was lower than control group. The amount of blood LDL didn't have any impact on the incidence of hemorrhagic stroke in the case group compared with the control group. There was no significant difference between the studied and control groups in terms of cholesterol. This indicates that this factor has no impact in the incidence of hemorrhagic stroke.

Bots and colleagues concluded that there are relationships between the levels of HDL and cholesterol ischemic and hemorrhagic strokes and also HDL levels cause different risks of stroke in men and women (15).

In a study by Zhang et al., it was found that there is a positive relationship between total cholesterol and the overall stroke and ischemic stroke in men and there is an inverse relationship between total cholesterol and hemorrhagic stroke in women. The inverse relationship between the increased HDL levels and the risk of ischemic stroke was evident. There is a positive correlation between the increased total cholesterol to HDL ratio and increased risk of ischemic stroke in both men and women (22).

In a prospective study, it was concluded that reducing the levels of LDL in patients who have been hospitalized due to ischemic stroke, increases the risk of hemorrhagic stroke and high levels of LDL, have a protective effect. Therefore, it is suggested that aggressive treatment of dyslipidemia in patients with ischemic stroke who have less LDL, is performed with caution (23 and 24).

In the study by Bharosay A et al., it was found that total cholesterol and triglyceride levels in patients with hemorrhagic stroke and worse prognosis was significantly lower than patients with better prognosis. Also, higher levels of total cholesterol, LDL, HDL and triglycerides in patients with ischemic stroke was associated with worse prognosis (25).

In a study by Trischwell et al., it was found that high levels of total cholesterol and low levels of HDL are associated with the increased risk of ischemic stroke and high levels of total cholesterol is associated with the increased risk of all types of hemorrhagic stroke (16).

Albers JJ. et al. concluded that HDL3-C subtype has protective effect against cardiovascular events, while HDL2-C, HDL-C, LDL-C and LDL-TG subtypes increase the risk of the disease (26).

Wang et al. concluded that low levels of LDL are associated with low risk of hemorrhagic stroke, but cholesterol levels are inversely associated with the risk of hemorrhagic stroke (17).

It seems that high cholesterol can reduce the risk of hemorrhagic stroke. Using statins to reduce the level of cholesterol doesn't increase the risk of non-lobar brain hemorrhage in patients with hypercholesterolemia but in people with genotypes of ApoE4 / E4 and ApoE2 / E4, using statin increases the risk of lobar brain hemorrhage (27). However, recently, it was concluded that prescribing statins with Ezetimibe reduces the risk of death caused by cardiovascular disease, including stroke, in patients with moderate to high risk of these diseases (28).

According to the findings of this study and similar articles, it was concluded that diabetes, hypertension, smoking, use of oral contraceptives can be as risk factors for hemorrhagic stroke. Also, increased level of HDL and reduced level of triglyceride can be as risk factors for hemorrhagic stroke.

### Suggestions

Finally, it is suggested the patients under the treatment of hyperlipidemia are accurately examined with considering the factors of diabetes and high blood pressure in shorter time periods and given that the influence of genetic factors in the development of this disease has been confirmed, screening the first degree relatives of patients is conducted at younger age. Also, future studies will be done with considering greater number of risk factors to clarify the impact of effective factors on hemorrhagic stroke and follow up studies will be planned to evaluate the impact of these factors on the prognosis of patients with the disease.

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