Fibrinolytic Parameters, Lipid Status and Lipoprotein(a) in Ischemic Stroke Patients

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SUMMARY

Introduction Ischemic stroke is the third leading cause of mortality and morbidity in most countries in the world. Impaired fibrinolysis, as well as disordered lipid metabolism have been recognized as risk factors for this disease.
Objective To study some of fibrinolytic parameters, lipid status and lipoprotein(a) – Lp(a) in ischemic stroke patients in Serbia and to examine associations between Lp(a) and fibrinolytic parameters.
Methods Sixty ischemic stroke patients (case group, mean age 63.48±9.62 years) and 30 age and sex matched healthy controls (control group, mean age 60.2±7.96 years) were studied.
Results A significantly longer euglobulin clot lysis time (219.7±78,8 min. vs 183.5±58,22 min; p=0.005) and higher levels of plasminogen activator inhibitor-1 (PAI-1) (48.5±17.1 ng/ml vs 27.1±10.1 ng/ml; p=6.2×10^{-11}), tissue-type plasminogen activator antigen (t-PA) (11.1±7.14 ng/ml vs 6,.0±3.66 ng/ml; p=5.2×10^{-5}) and D-dimer (382.27±504.22ng/ml vs 116.12±88.81 ng/ml; p=0.0002) were found in cases compared to controls. There were no significant differences in fibrinogen levels (4.30±0.84 g/l vs 4.09±0.64 g/l; p=0.23) or plasminogen activity (92.67±11.37 % vs 96.87±9.48%; p=0.085). There was no significant difference in Lp(a) concentration between cases and controls (0.15±0.11 g/l vs 0.12±0.11 g/l; p=0.261). However, in the cases, but not in the controls, multivariate analysis of associations between fibrinolytic parameters and Lp(a) showed the highest correlation between t-PA and PAI-1, and the latent effect of Lp(a) on t-PA and PAI-1.
Conclusions Our results show that there are important differences in the characteristics of the fibrinolytic mechanism in ischemic stroke patients compared to healthy population. The major differences are prolonged euglobulin clot lysis time and elevated PAI-1 and t-PA antigen in ischemic stroke patients. In addition, Lp(a) appears to be involved in the inhibition of fibrinolysis in ischemic disease through a mechanism unrelated to its serum concentrations.
Keywords: fibrinolysis; plasminogen activator inhibitor-1; tissue-type plasminogen activator; ischemic stroke

INTRODUCTION

Ischemic stroke is the third leading cause of mortality and morbidity in most countries in the world, as well as in Serbia [1, 2]. This disease that causes long-term and severe disability is increasingly affecting younger populations, producing great social and economic burden. There are therefore continuing efforts to discover biochemical markers that would enable more reliable risk stratification.

Ischemic stroke represents the critical moment of a long and progressive process of atherothrombosis. Lipid disorders have long been recognized as a major risk factor for the development of ischemic stroke. More recently, impaired fibrinolysis, an integral component of the haemostatic mechanism, has been increasingly implicated in the development of cerebral ischemia [3, 4, 5]. Elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) have been found in healthy relatives of persons who suffered ischemic stroke [6]. There is a significant correlation between atherothrombotic stroke and the PAI-1 4G/4G genotype associated with reduced fibrinolysis [7], and in human atherosclerotic arteries increased expression of PAI-1 mRNA has been detected [8, 9]. Patients recovering from ischemic stroke have been reported to have elevated tissue-type plasminogen activator (t-PA) antigen plasma levels [10],

which were, moreover, found to be the risk factor for the development of cerebral ischemia in a prospective study by Ridker et al. [11].

Further research interests have been directed towards determining factors associated with inhibited fibrinolysis in persons with ischemic brain disease. One of the most intriguing factors is lipoprotein(a) – Lp(a), given the structural, immunological and presumably functional homology between apolipoprotein(a) that is uniquely found in Lp(a) particles and a plasminogen molecule [12-15]. However, there are few studies, especially in our region, dealing with the role of Lp(a) in ischemic brain disease, and their results are controversial. While some confirm [16, 17, 18], others dispute the role of Lp(a) in the development of atherothrombotic brain disease [19, 20] or the haemostatic mechanism disorders [21].

OBJECTIVE

The aim of our study was to investigate the role of fibrinolytic factors, lipid parameters and Lp(a) in the development of ischemic stroke, and ascertain whether there is association between Lp(a) and certain components of fibrinolysis in ischemic stroke patients.

METHODS

Study design and subjects

This case-control study was conducted at the Centre for Laboratory Medicine of the Clinical Centre of Vojvodina in Novi Sad, Serbia. A total of 90 subjects of both sexes, aged 46 to 85 years were enrolled.

The case group comprised of 60 ischemic stroke patients (39 male and 21 female), aged 46 to 85 years (mean age ± SD 63.5±9.6 years). In each patient the diagnosis of ischemic stroke was made by computerized tomography or magnetic resonance imaging.

In order to avoid potential influence of acute illness on the studied parameters, only patients who suffered a stroke at least one month prior to enrolment were selected. Similarly, in order to minimize a potential influence of genetic risk factors for early thrombosis, only patients above the age of 45 years were included.

Subjects with a history of verified disturbances of haemostasis verified or treated lipid and lipoprotein disorders, clinical or laboratory evidence of any disorders and conditions that may affect haemostasis or lipid and lipoprotein metabolism, or history of the use of drugs that can affect liver function, lipid metabolism or haemostasis were excluded. At the time of blood sampling none of the subjects had an acute illness that could affect study results.

At the time of enrolment, all cases were on antiplatelet therapy with acetylsalicylic acid to prevent further thromboembolic complications.

The case group was remarkably homogeneous in regard to the time that passed since the stroke; less than a year in as many as 54 (90%) cases, less than 5 years in 5 (8%), and over 5 years in only one (2%).

The control group comprised of 30 age and sex matched healthy subjects with no history or clinical evidence of ischemic brain disease, selected from the general population; 12 female and 18 male, aged 48 to 78 years (mean age ± SD 60.2±8.0 years). Except for stroke, the inclusion and exclusion criteria for the control group were identical to those applied for the case group.

Blood samples were collected after overnight fasting. Serum was separated after centrifugation at 3000 g for 15 minutes. Citrate plasma was also prepared by centrifugation at 3000 g for 15 minutes and stored at -80°C until analyzed.

Ethical consideration

Prior to the study, informed consent was taken from all the subjects. An institutional committee had approved the study protocol.

Laboratory methods

Euglobulin clot lysis time was measured manually in a water bath, according to Macfarlane and Pilling [22]. Plasma D-dimer concentration was measured using a latex agglutination method on a standard automated coagulometer (ACL 9000, IL, Italy). Plasminogen measurements were performed using a chromogen substrate test on an automated coagulometer (ACL 200, IL, Italy). Plasma t-PA antigen and PAI-1 levels were measured by ELISA (Diagnostica Stago, France). Serum levels of total cholesterol, triglycerides and HDL cholesterol were measured by an enzymatic method using commercially available kits (Bio Merieux, France, and Randox, UK for HDL cholesterol) on an automated analyzer (TECHNICON RA-XT , Randox, UK). LDL cholesterol was calculated according to the Friedwald's formula [23], and non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Additionally, LDL/HDL cholesterol and total/HDL cholesterol ratios were calculated. Serum Lp(a) levels were measured using immunoturbidimetry kits (Human, Germany) on an Olympus AU400 autoanalyzer (Olympus Diagnostic, Germany).

Statistical analysis

Data were analyzed using statistical software package SMART LINE (Smart Line Inc., NS). Statistics of all parameters were computed by classifying on the basis of age and gender. Mean values and standard deviations were determined for each fibrinolytic and lipid parameter. The significance of each individual fibrinolytic and lipid parameter was determined by t-test, which is applicable for data with normal distribution. In our study all fibrinolytic and lipid data for the case and control groups were normally distributed. In addition, we applied F test on each pair of case and control groups for all studied fibrinolytic and lipid parameters. This test determines the significance of differences between variances. For some of the studied fibrinolytic parameters, namely euglobulin clot lysis time, D-dimer, PAI-1 and t-PA antigen, there was a significant difference in variances between the case and control groups. For these parameters we applied a modified t-test with Welch's correction. We also used Mann-Whitney U test as a non-parametric test for analysis of non-parametric data. Correlation between different parameters was obtained by calculating correlation coefficients, which theoretically ranged between +1 and -1.

Multivariate analysis was used to determine positive and negative correlations between the studied parameters, as well as major and latent contributions of isolated factors.

RESULTS

Regarding the conventional risk factors for ischemic stroke, we found that systolic and diastolic blood pressure values were significantly higher in cases compared to controls. There was no significant difference in body mass index (BMI) between the groups. Smoking and positive family history of stroke were significantly more frequent among cases than controls (Table 1).

The analyses of fibrinolytic parameters showed a significantly prolonged euglobulin clot lysis time and elevated D-Dimer and PAI-1 and t-PA antigen in cases compared

Table 1. Conventional risk factors in patients and controls

Risk factors		Patients	Control group	*p*
Parametric	BMI (kg/m²)	26.9±4.2	26.0±3.2	0.30
	SBP (mm Hg)	143.8±26.3	128.3±12.4	0.0003*
	DBP (mm Hg)	88.2±12.6	81.9±9.1	0.016*
Nonparametric	Smoking	31	3	<0.001*
	Positive family history	15	3	<0.01*

* statistically significant; BMI – Body Mass Index; SBP – systolic blood pressure; DBP – diastolic blood pressure

Table 2. Fibrinolytic parameters in patients and controls

Parameters	Patients	Control group	*p*
Euglobulin fibrinolysis time (minutes)	219.7±78.8	183.5±58.2	0.005*
D-dimer (µg/ml)	382.3±504.2	116.1±88.8	0.0002*
Fibrinogen (g/l)	4.3±0.8	4.1±0.6	0.23
Plasminogen (%)	62.7±11.4	96.9±9.5	0.085
PAI-1 (ng/ml)	48.5±17.1	27.1±10.1	6.2×10⁻¹¹*
t-PA (ng/ml)	11.1±7.1	6.2±3.7	5.2×10⁻⁵*

* statistically significant; PAI-1 – plasminogen activator inhibitor-1, t-PA – tissue-type plasminogen activator

Table 3. Lipid parameters in patients and controls

Parameters	Patients	Control group	*p*
Total cholesterol (mmol/l)	5.8±1.6	6.4±1.1	0.031*
Triglycerides (mmol/l)	1.7±0.8	2.0±1.4	0.231
LDL cholesterol (mmol/l)	3.9±1.3	4.3±1.0	0.157
HDL cholesterol (mmol/l)	1.2±0.3	1.4±0.3	0.013*
Non-HDL cholesterol (mmol/l)	4.6±1.6	5.0±1.0	0.1
LDL/HDL cholesterol	3.5±1.4	3.2±0.9	0.3
Total/HDL cholesterol	5.1±1.7	4.9±1.3	0.5

* statistically significant; LDL – low-density lipoprotein; HDL – high-density lipoprotein

to controls, whereas there were no significant differences in fibrinogen levels or plasminogen activity (Table 2).

Analyses of lipid parameters produced interesting results. Unexpectedly, total cholesterol levels were significantly higher in the control group. HDL levels were, as anticipated, significantly lower in the case group. There was no significant difference in LDL and non-HDL cholesterol levels and LDL/HDL and total/HDL cholesterol ratios between the groups. Triglyceride levels were, again unexpectedly, higher among controls (Table 3).

No significant difference was found in Lp(a) concentration between cases and controls (0,15±0,11 g/l vs 0,12±0,11 g/l; p=0,261). We therefore divided each group into three subgroups according to Lp(a) concentration: group I – physiological Lp(a) levels, i.e. under 25 g/l; group II – Lp(a) levels 0.26-0.50 g/l; and group III – high risk Lp(a) levels, i.e. above 0.50 g/l. Again, no significant difference in Lp(a) was found between any of the corresponding case and control subgroups.

In the case group, multivariate analysis of associations among studied fibrinolytic parameters and their associations with Lp(a) and D-dimer levels showed the highest positive correlation (r=0,480) between t-PA and PAI-1 and the highest negative correlation (r=-0,308) between Lp(a) and PAI-1. However, neither of these correlations

reached statistical significance. The highest correlation was between t-PA and PAI-1; the greatest contribution of an isolated factor was obtained for PAI-1 (cor=0.636), and t-PA (cor=0.537); whereas Lp(a) showed latent contribution (cor=0.243) (Graphs 1 and 2).

In the control group, the highest positive correlation (r=0.579) was between D-dimer and euglobulin clot lysis time, and the highest negative correlation (r=-0.256) between D-dimer and PAI-1. The strongest mutual associations were found for fibrinogen, D-dimer and Lp(a), whereas the greatest contribution to factorial structure was obtained for D-dimer (cor=0.790), then Lp(a) (cor=0.532), euglobulin clot lysis time (cor=0.53), and fibrinogen (cor=0.527) (Graphs 3 and 4).

DISCUSSION

The present study examined the main characteristics and associations of the fibrinolytic mechanism, lipid status and plasma Lp(a) levels in ischemic stroke patients compared to healthy population.

As regards traditional risk factors for ischemic stroke, we observed significantly higher systolic and diastolic blood pressure values in ischemic stroke patients compared to controls. In recent studies, haemostatic abnormalities have been associated with an increased incidence of cerebral ischemia among hypertensives [24]. Smoking was significantly more frequent in ischemic stroke patients compared to controls. It is also one of the major risk factors for the development of ischemic brain disease [25], and recently it has been suggested that the activation of haemostasis or suppression of fibrinolysis may be potential mechanisms that increase the risk of atherothrombosis in smokers [26]. A positive family history of stroke was significantly more frequent among cases than controls, which corresponds with the well-recognized role of genetic factors in the development of ischemic brain disease [25]. Finally, contrary to anticipated, no significant difference was found in BMI between the patients and controls, which we will discuss later, with the results relating to lipid parameters.

Regarding characteristics of the fibrinolytic mechanism, the case group had a significantly prolonged euglobulin clot lysis time and significantly increased plasma PAI-1 and t-PA antigen levels. Suppression of fibrinolytic activity and elevated plasma PAI-1 were also found in a similar patient population studied by Olah et al. [27]. Yet, previous studies which investigated the role of t-PA and PAI-1 gene polymorphism have not proved association between t-PA and PAI-1 and the risk of cerebral ischemia, hence it has been suggested that t-PA and PAI-1 may have a very complex role in the brain [10]. Indeed, it has been shown that along with inactive t-PA and PAI-1 complexes, brain circulation comprises a pool of free, functional t-PA and PAI-1 secreted in vivo by endothelial cells of cerebral capillaries [28].

As regards lipid parameters, the unexpectedly higher serum cholesterol levels found in controls compared to the cases may be due to the fact that in most study cases lipid parameters were measured several months after an acute ischemic event and those prior to the event were not
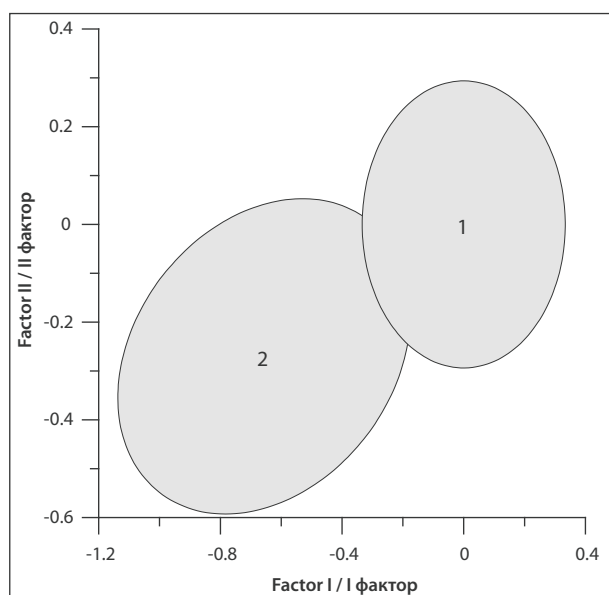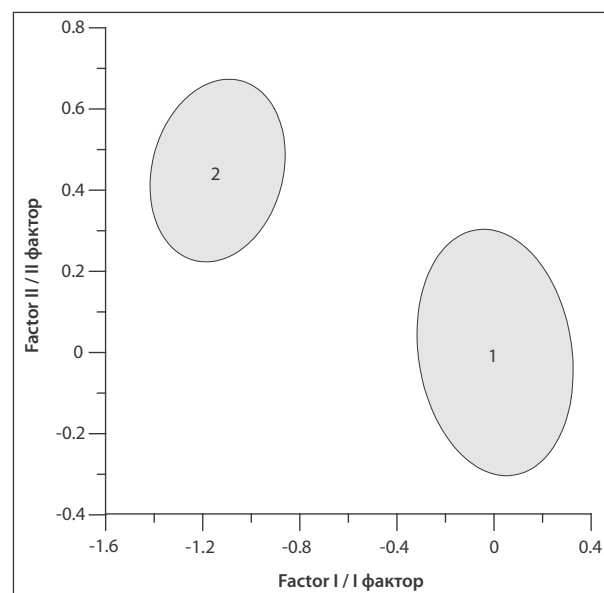
Graph 1. Multivariate analysis of correlation between Lp(a) lipoprotein (1) and PAI-1 (2) levels in the case group
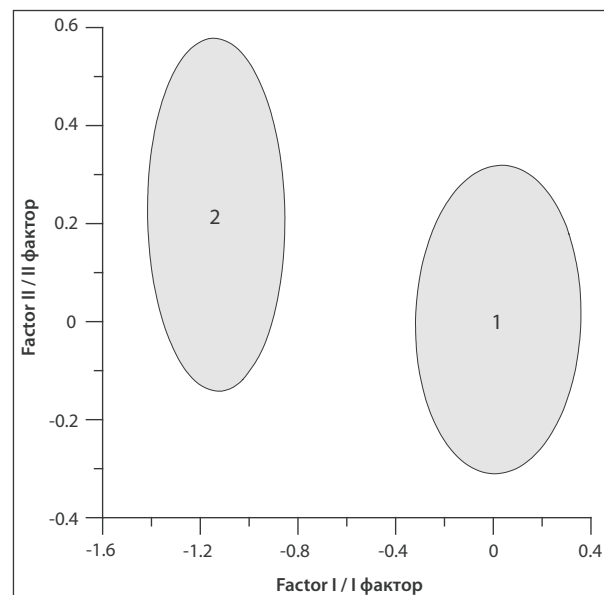
Graph 3. Multivariate analysis of correlation between Lp(a) lipoprotein (1) and PAI-1 (2) levels in the control group
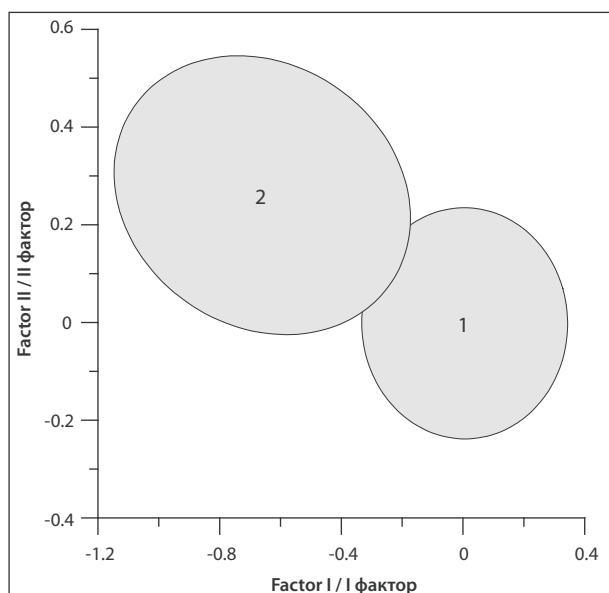
Graph 2. Multivariate analysis of correlation between Lp(a) lipoprotein (1) and t-PA antigen (2) levels in the case group

Graph 4. Multivariate analysis of correlation between Lp(a) lipoprotein (1) and t-PA antigen (2) levels in the control group

available to us. It is similar with BMI. Given that a large percentage of our cases modified their dietary habits and reduced body weight following stroke, we did not have a real picture of their lipid profiles or BMI prior to the clinical event. Contrary to anticipated, serum HDL cholesterol levels were significantly lower in the case group. This is partly due to the fact that stroke patients generally have considerably less physical activity, which is of great importance in keeping HDL cholesterol at desirable levels [29]. In addition, the high percentage of smokers among the cases also contributed to the finding, as smoking is associated with lower levels of HDL cholesterol [30]. Finally, as we found dyslipidemia in as many as 84% of controls, we can conclude that abnormalities of lipid metabolism in healthy population have reached epidemic proportions in our region.

The facts that Lp(a) concentrations did not differ significantly between the cases and controls and that the multivariate analysis of fibrinolytic parameters and Lp(a) showed that this lipoprotein had a latent effect on PAI-1 and t-PA only in the case group, suggest that Lp(a) may affect the fibrinolytic system by a mechanism unrelated to its serum concentration. There is substantial literature suggesting that some differences do exist in the biological potentials of Lp(a) particles that determine their physiological role as well as their role in the processes of atherogenesis and thrombogenesis independently of their serum concentrations. This functional polymorphism is determined primarily by the heterogeneity of Lp(a) particles and polymorphism of apo(a) size, as well as by factors determining the lysine-binding function of Lp(a) [31, 32].

CONCLUSION

Our results show that patients with ischemic stroke have elevated plasma levels of PAI-1 and t-PA antigen, prolonged euglobulin clot lysis time and decreased serum levels of total and HDL cholesterol. Lp(a) appears to have a latent effect on fibrinolytic function through a mechanism that is not associated with its serum concentration.

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Параметри фибринолизе, липидни статус и липопротеин(а) код болесника с исхемијским цереброваскуларним инсултом

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КРАТАК САДРЖАЈ

Увод Исхемијски цереброваскуларни инсулт је трећи водећи узрок морталитета и морбидитета у већини земаља у свету. Смањена фибринолиза и поремећај метаболизма липида сматрају се факторима ризика код овог обољења.

Циљ рада Циљ рада је био да се испитају поједини параметри фибринолизе, липидни статус и липопротеин(а) – $Lp(a)$ код болесника с исхемијским цереброваскуларним инсултом, као и повезаност $Lp(a)$ и параметара фибринолизног механизма.

Методе рада Истраживање је обухватило 60 особа с исхемијским цереброваскуларним инсултом, просечне старости од 63,5±9,62 године, и 30 здравих испитаника (контролна група), просечне старости од 60,2±8,0 година.

Резултати У групи болесника су у поређењу с контролном групом забележени статистички значајно дуже еуглобулинско време лизе коагулума (219,7±78,8 према 183,5±58,22 минута; $p=0,005$) и статистички значајно виши нивои инхибитора активатора плазминогена 1 ($PAI-1$) (48,5±17,1 према 27,1±10,1 ng/ml; $p=6,2 \times 10^{-11}$), антигена ткивног активатора плазминогена ($t-PA$) (11,1±7,14 према 6,20±3,66 ng/ml; $p=5,2 \times 10^{-5}$) и D-димера (382,27±504,22 према 116,12±88,81 ng/ml; $p=0,0002$). Статистички значајне разлике између две групе испитаника није било за ниво фибриногена (4,30±0,84 према 4,09±0,64 g/l; $p=0,23$) и активност плазминогена (92,67±11,37% према 96,87±9,48%; $p=0,085$). Нивои укупног холестерола (5,83±1,56 према 6,44±1,07 $mmol/l$; $p=0,031$) и HDL-холестерола (1,19±0,33 према 1,38±0,36 $mmol/l$; $p=0,013$) били су статистички значајно нижи међу болесницима, док значајнијих разлика у осталим испитиваним параметрима липидног статуса није било. Није било значајне разлике ни у концентрацијама $Lp(a)$ у серуму између болесника и здравих испитаника (0,15±0,11 према 0,12±0,11 g/l; $p=0,261$). Ипак, мултиваријантна анализа међусобне повезаности параметара фибринолизе и $Lp(a)$ открила је латентан утицај $Lp(a)$ на $t-PA$ и $PAI-1$ у групи болесника, али не и у контролној групи.

Закључак Резултати истраживања показују да постоје значајне разлике у одликама фибринолизног механизма код особа које су доживеле исхемијски цереброваскуларни инсулт у односу на здраву популацију. Главне разлике се односе на продужено еуглобулинско време лизе коагулума и повишене нивое $t-PA$ и $PAI-1$ код болесника. Такође, изгледа да $Lp(a)$ има утицаја на инхибицију фибринолизе у исхемијском инсулту преко механизама који нису повезани с његовим концентрацијама у серуму. Посматрајући контролну групу можемо рећи да су дислипопротеинемије достигле епидемијске размере у нашој популацији.

Кључне речи: фибринолиза; инхибитор активатора плазминогена 1 ($PAI-1$); антиген ткивног активатора плазминогена ($t-PA$); исхемијски инсулт

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