# C-reactive protein, fibrinogen, lipoprotein (a), and lipid profile levels and platelet counts in ischemic stroke patients

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## ABSTRACT

**Objective:** To ascertain the most prevalent risk factor for stroke.

**Methods:** We performed a descriptive and analytical prospective study on patients with stroke admitted to the neurology wards of Imam Hospital, Tabriz, Iran during 2004 and 2005. The study comprised 100 ischemic stroke (IS) patients consisting of 46 men and 54 women with a mean age of 67 ± 15, and 100 age and gender matched apparently healthy subjects. Plasma levels of C-Reactive protein (CRP), fibrinogen, platelet counts, lipoprotein (a) (LP (a)), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total cholesterol (TC), and triglycerides (TG) were measured in both patients and controls. Background disease was also investigated in the patients. Hemorrhagic and embolic stroke patients were excluded from the study.

**Results:** We found no significant difference in serum fibrinogen, HDL-c levels, and platelet counts between patients and control subjects, however, levels of LP (a), TG, LDH-c, and CRP were significantly higher in patients than controls. Among the predisposing background illnesses, the most common risk factors were hypertension and hyperlipidemia. The frequency of studied risk factors among patients was: no risk factors (20%), one risk factor (32%), 2 risk factors (36%), and 3 risk factors (12%).

**Conclusion:** Hypertension was the most prevalent background disease in IS patients. We also found that although there is close relationship in the incidence of IS with levels of LP (a), TC, TG, LDL-c, and CRP, the cutoff point frequency of fibrinogen, CRP, LP (a), and platelet counts was variable from patient to patient.

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Stroke is the most common life-threatening neurologic disease, which is more often disabling than lethal. In the past 3 decades, different risk factors including dyslipidemia, fibrinogen, platelet aggregation, and inflammation of sensitive plasma proteins, and cigarette smoking in association with stroke has been studied. However, the association of these risk factors combined or alone with stroke remains controversial. Although some investigator based cohort studies suggest that dyslipidemia, including high serum cholesterol, triglycerides (TG) and low-density lipoprotein cholesterol (LDL-c) levels, and low high-density lipoprotein cholesterol (HDL-c) have not predicated cerebral infarction in several populations,[1-5] others suggested that not only total cholesterol (TC) and LDL-c, but also HDL-c, and TG levels predict the risk of a cerebrovascular accident (CVA).[6,7] Lipoprotein (a) (LP (a)) is a complex macromolecule that consists of LDL-like particles and apoprotein (a), which has a close structural homology to plasminogen.[8] Elevated serum LP (a) levels have been found in association with stroke,[9,10] and its significance is likely age related.[11] Fibrinogen is an independent risk factor for atherosclerosis with a synergistic effect on classical risk factors,[12,13] however, there is little data available on its association with stroke. There is evidence that plasma fibrinogen is a strong predictor of, instead of a direct causative factor for subsequent stroke among patients at increased risks owing to manifest coronary heart disease.[14] It has been suggested that C-reactive protein (CRP) as a marker of the inflammatory process has a predictive value in coronary events.[15,16] In this respect, the prognostic importance of CRP in ischemic stroke (IS) has been postulated.[17] Antiplatelet therapy has been found useful in prevention of further ischemic attack or stroke,[18,19] therefore, it should be considered whether a high platelet count may be a dependent or independent risk factor for stroke. However, these risk factors are often studied independently and there is still much controversy on the significance of each as a risk factor for stoke. The aim of the present study was to evaluate these risk factors in patients with

stroke compared with healthy controls, and also with a definition of the cutoff point for each of the risk factors to find out their importance individually or combined; underlying diseases were also considered in this study.

**Methods.** The study population comprised 100 Iranian IS patients from the Department of Neurology, consisting of 46 men, and 54 women with a mean age of 67±15, and 100 apparently healthy persons who were age and gender matched selected from outpatients admitted to hospital for checkup. The study was carried out at Imam Hospital, Tabriz University, Iran from April 2004 to September 2005, after permission from the the institutes ethics committee. All patients gave their informed consent. All ischemic stroke patients were included, and hemorrhagic stroke and other neurological disease patients were excluded. The clinical diagnosis was confirmed by CT scan and MRI examination. Each patient was questioned for previous stroke, underlying disease, and smoking status. Ten-milliliter blood samples were obtained from patients and control subjects at the time of admission. For measuring hematological parameters including hemoglobin, hematocrit, platelet counts, and fibrinogen, 2 cc, and 1.8 cc blood were located in EDTA and 3.8% ± trisodium citrate containing tubes. The remaining blood was centrifuged at 4000 g for 10 minutes at room temperature within one hour of collection. The serum was subsequently separated and divided in 2 parts; one part was stored at -60°C until measurement of CRP and LP (a) were performed, and other part was delivered to the laboratory to determine TG, cholesterol, HDL-c, LDL-c, and fasting blood sugar (FBS) on the day of blood collection. Assay procedures for TC, TG, HDL-c, HDL-c, and FBS levels in serum were measured on a Kone specific model analyzer by the enzymatic procedure (using Raudox kit). Fibrinogen levels were determined with a one-stage clothing assay kit (Mahsa Yaran). Serum LP (a) and CRP were measured by immunoturbidimetric assay kits (Pars Azmon Iran) on a Kone specific model analyzer. Hemoglobin, hematocrit, and platelet counts were determined on a Sysmex K 1000 cell counter. Samples were analyzed in duplicate and in random order to reduce systemic bias and interassay variation.

Data are shown as mean ±SD, one-way analysis of variance, and t test was used for comparison of the mean values in independent groups. In addition, using Microsoft Excel 2 event's test, and Pearson's correlation coefficients were calculated for the different variables. A *p*-value of <0.05 was considered statistically significant. A cutoff point was also defined for each variable to find out how many patients lie outside the normal range.

**Results.** We found that the prevalence of IS was highest in patients in their 70's. There was no significant difference in serum fibrinogen, HDL-c levels, and platelet counts between patients and control subjects ($p>0.05$), however, levels of LP (a), TG, LDL-c, and CRP were significantly higher in patients than controls ($p<0.05$) (**Table 1**). A positive correlation was found between TG and cholesterol and LDL-c, however, the correlation between platelets and LP (a) was negative. We did not find a significant correlation between other parameters (**Table 2**). In exploring any predisposing background illness, the most common risk factors were hypertension (78 cases), hyperlipidemia (62 cases), cardio-vascular disease (38 cases), history of smoking (20 cases), and previous stroke (18 cases). With respect to finding a cutoff point for the following parameters, namely, LP(a), TG, cholesterol, LDL-c, HDL-c, CRP, fibrinogen, and platelets, any value occurring with increasing distance from the point was considered abnormal. For the cutoff point of each parameter, we tried to find out the independent frequency of each risk factor in patients. According to these criteria, patients

**Table 1 -** Plasma levels of lipids, C-reactive protein (CRP), and fibrinogen and platelet counts in ischemic stroke patients and controls.

| Variable | Ischemic stroke patients | Control group | *P*-value |
|---|---|---|---|
| Lipoprotein (a) (mg/dl) | 19.02±10.94 | 15.46±8.9 | $p<0.05$ |
| Triglyceride (mg/dl) | 147±75.95 | 120.10±34.83 | $p<0.05$ |
| Total cholesterol (mg/dl) | 196.97±52.4 | 150.36±23.69 | $p<0.05$ |
| LDL-C (mg/dl) | 128.32±44.04 | 86.00±23.48 | $p<0.05$ |
| HDL-C (mg/dl) | 38.88±7.31 | 40.64±7.09 | $p>0.05$ |
| CRP (mg/dl) | 35.35±22.31 | 16.65±22.16 | $p<0.01$ |
| Fibrinogen (mg/dl) | 334.67±85.56 | 333.35±55.98 | $p>0.05$ |
| Platelets (mm³) | 216617.75±80455.5 | 207622.5±65218.2 | $p>0.05$ |

LDL-C - low density lipoprotein cholesterol, HDL-C - high density lipoprotein cholesterol, *p*-value > 0.05 indicates a non significant relation

**Table 2 -** Correlation between different studied parameters in the ischemic stroke patients.

| Studied parameters | *P*-value | Correlation value |
|---|---|---|
| Platelets & LP (a) | <0.05 | -0.562 |
| Triglycerides & cholesterol | <0.05 | 0.529 |
| Triglycerides & LDL-C | <0.05 | 0.375 |
| Cholesterol & LDL-C | <0.05 | 0.844 |

LP (a) - Lipoprotein (a), LDL-C - low density lipoprotein cholesterol

**Table 3 -** Frequency of risk factors according to cutoff points of studied parameters in ischemic stroke (IS) patients.

| Risk factors | No. of IS patients | Gender | |
|---|---|---|---|
| | | Male | Female |
| *No risk factors* | 20 | 10 | 10 |
| | | | |
| *One risk factor* | 32 | | |
| CRP | | 5 | 6 |
| PLT | | 1 | 3 |
| LP (a) | | 4 | 3 |
| Fib | | 6 | 4 |
| | | | |
| *Two risk factors* | 36 | | |
| LP (a), Fib | | 3 | 6 |
| Fib, CRP | | 4 | 4 |
| Fib, PLT | | 3 | 3 |
| LP (a), CRP | | 4 | 5 |
| LP (a), PLT | | 1 | 3 |
| | | | |
| *Three risk factors* | 12 | | |
| LP (a), CRP, Fib | | 5 | 7 |

CRP – C-Reactive protein, PLT – platelet, LP (a) – lipoprotein a, Fib – Fibrinogen

were classified as having no risk factor (20%), one risk factor (32%), 2 risk factors (36%), and 3 risk factors (12%) (**Table 3**). The background disease and lipid profile were excluded in this classification.

**Discussion.** Different environmental factors, genetic influences, and aging are operating in the occurrence of stroke. In our study, stroke had the highest prevalence in the 70-80 years age group. An association between increasing carotid artery intima-media thickness and decreasing elasticity of the brain's vascular system with elevation of age has been reported.[20] In this context, as Kroger et al[21] has shown, our results also revealed a strong relationship between age and stroke. The mean value of TG, TC, LDL-c, and LP (a) were significantly higher in stroke patients than controls. However, no significant difference was found in HDL-c levels between patients and controls. Despite these associations between IS and dyslipidemia, controversy still exists. Velcheva et al[22] reported high levels of TC, TG, and LDL-c, and low levels of HDL-c in cerebrovascular disease. Scherle et al[23] found levels of TG and LP (a) greater in IS patients than controls, but no significant difference was observed for TC, HDL-c, LDL-c, and very LDL-c. Also, some cohort studies[24,25] suggested that increased lipid levels have not predicated cerebral infarction in several populations. However, our results, excluding HDL-c, are in agreement with those who found that dyslipidemia was a significant risk factor for stroke event. In this study, in contrast to some other studies,[22,26] we could not establish HDL-c as a risk factor for stroke. Since age, sample size, and severity of disease are important factors[27,28] that influence the results when the association of serum lipid levels with stroke are investigated, our adverse results for HDL-c could be a consequence of the above parameters that was unfortunately not considered.

There is more controversy about LP (a) as a risk factor for stroke than other lipids. It has been suggested that LP (a) may be an independent risk factor for stroke.[29] However, LP (a) concentration in other studies failed to independently predict stroke-related events.[30,31] The LP (a) was considered a weak risk factor for stroke in men, and was not considered a significant risk factor for stroke in women,[32] however, our results were in favor of some studies,[23,33,34] that found a high level of plasma LP (a) might be a risk factor for stroke.

With the recognition that atherosclerosis is an inflammatory process,[35] several plasma markers of inflammation have been studied as a potential for prediction of the risk of coronary events. Among different markers measured, CRP was found the strongest predictor.[36] However, for stroke there is no clear or consistent relationship to plasma CRP level. Ford et al[37] suggested that CRP concentration may be a risk factor or marker in the U.S. population. Another study purposed that CRP was a strong, but nonspecific risk factor of fatal stroke in older persons.[38] Di Napoli et al[39] concluded that increased levels of CRP were associated with a poorer outcome in patients with IS, but whether it was an independent risk factor for stroke was not clear. In our study, increased base line CRP levels in stroke patients compared to controls may indicate its significance as a risk factor for stroke patients.

In the present study, we found that the mean level of fibrinogen, and platelet counts in stroke patients was not significantly different from controls (p>0.05). Atherothrombosis is the major underling cause of IS,[40] and in this respect platelet count and blood fibrinogen levels have been widely investigated. Zhu et al[41] indicated that plasma fibrinogen levels and platelet counts increased and decreased respectively 3 and 9 days after onset of stroke, and this confirmed that the platelet aggregation process is strictly dependent on fibrinogen concentration. Different studies also suggested that an increased plasma level of fibrinogen was the cause of an inflammatory reaction during cerebral vasculopathies, and a strong predictor of subsequent stroke among patients.[42-44] The role of platelets in stroke events has long been recognized and different antiplatelet therapies alone, or combined with thrombolytic agents have been used.[45-47] However, these studies have mostly emphasized on platelet function rather than their counts. Thus, our finding of no difference between patients and controls for fibrinogen or platelet counts could imply that they were more predictors rather than risk factors.

Aside from those isolated parameters, we also assessed the prevalence of some background diseases and smoking as other risks factors. The most important risk factors prevalent in our patients were found to be hypertension, hyperlipidemia, heart disease, diabetes mellitus type II, smoking, and previous CVA, in agreement with many other studies. In this respect, Sacco[48] divided these risk factors into 2 nonmodifable and modifiable categories and recommended ramipril to prevent stroke in patients with diabetes and hypertension. Leys et al[49] reported that medication for high blood pressure, hypercholesterolemia, ceasing smoking, and increasing physical activity reduced the risks of first ever stroke, recurrent stroke, any vascular event after stroke, and vascular death. Hypertension and hyperlipidemia among these risk factors were found most important, similar to other studies.[50,51] Our study showed that some of the studied risk factors for stroke are more important than others, contrary to other studies. We did not find a significant change for some of these risk factors such as HDL-c in our stroke patients compared with controls. There were reports that some of these factors could intensify the effect of each other as shown for CRP, the coagulation/fibrinolysis system, and platelet function.[52] Also, some investigators believe that instead of one risk factor, the combination of multiple risk factors were associated with the development of stroke.[6,13]

As we composed a mean value of risk factors in our study, we could not classify the patients regarding severity of disease, so we tired to find a cutoff point for CRP, platelets, LP (a),  and fibrinogen, and then indicated the frequency of these risk factors in each patient. As a result of our attempts, we found that 20% of the patients had none, 19% had 3, and the rest of the patients had 1-2 of these risk factors. Of course, it should be emphasized that as there are many risk factors associated with stroke events, thus, the absence of any of the above mentioned risk factors in the patients, do not exclude other risk factors that were not included in this study.

In conclusion, as stroke results from a number of pathologic processes, so the predisposing conditions and risk factors must be considered. We must also remembered that genetic, ethnic, age variation, life style, and background diseases could make some determinants as important risk factors in some patients, with others in other patients. However, it is generally believed that identification and modification of risk factors can prevent stroke occurrence.

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