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Is the level of C-reactive protein correlated with the extent of carotid atherosclerosis ?

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Abstract

Background : Increased intima-media thickness (IMT) of the common carotid arteries (CCA) and elevated levels of highly sensitive C-reactive protein (hsCRP) are both shown to be associated with the occurrence of stroke. We investigated whether elevated hsCRP level is a risk factor for the increased IMT of the CCA independent of other proven risk factors for the ischemic stroke and studied the interaction between hsCRP level and the extent of carotid atherosclerosis.

Methods and results : We studied 104 patients aged between 30 to 92 years who were admitted to our neurology department with acute ischemic stroke. All patients underwent a clinical evaluation, laboratory investigations, and neuroultrasonographic examination. In 24 patients with normal ultrasonographic examination, mean hsCRP levels was 8.6 + 6.7 mg/L. Mean hsCRP level was 18.0 + 25.6 mg/L in patients having increased intima to media thickness (> 1.2 mm) ; 32.7 + 49.1 mg/L in patients who had atheromatous plaques without significant narrowing ; and 23.9 + 27.3 mg/L in patients with internal carotid artery stenosis more than 50%. hsCRP levels and the extent of the atherosclerosis showed a significant relationship (p = 0.040). In multiple regression analyses, this relationship was found to be independent of other proven risk factors. The only variable that showed a significant relation with the level of hsCRP was the HDL level. A negative correlation was found between hsCRP and HDL levels.

Conclusions : We conclude that elevated hsCRP level is an indirect risk factor for the ischemic stroke through its relation with the extent of the carotid atherosclerosis, and this relation is independent of other known risk factors.

Key words : Carotid artery atherosclerosis ; intima-to-media thickness ; C-reactive protein ; acute ischemic stroke.

Introduction

Cerebrovascular diseases (CVD) are the third most common causes of deaths, following cardiovascular diseases and cancers. It was shown that ischemic events covered 89% of the all cerebrovascular events, 42% of which had an underlying atherosclerotic pathophysiology (American Heart Association, 2000). In a study from Turkey (Bozluolcay M. *et al.*, 2003), patients having ischemic CVD were investigated according to the etiology of the strokes. It was found that 30.9% of the patients with acute ischemic stroke had atherothrombosis, 24.3% had a cardioembolic origin, 18.7% had lacunar infarcts and 5.2% had other infrequent etiologies. In 13.7% of the patients, the etiologies could not be detected. Inflammatory response is also an important component of the complex pathophysiology underlying the ischemic stroke. Inflammation in the vesselwall plays an essential role not only in the initiation and progression of atherosclerosis but also in the erosion or fissuration of plaques and eventually in the rupture of plaques (Di Napoli M. *et al.*, 2001a ; Alexander R. W. *et al.*, 1994). Moreover, C-reactive protein (CRP), a sensitive marker of inflammation, induces vascular thrombosis by stimulating monocytes to express tissue factor, the initiator of the extrinsic pathway of coagulation (Cermak J. *et al.*, 1993). Elevated levels of CRP are found to be related with higher risk of first-ever cardiovascular, cerebrovascular, and peripheral vascular diseases (Kuller L. H. *et al.*, 1996 ; Arenillas J. F. *et al.*, 2003 ; Ridker P. M. *et al.*, 1998). Increased intima-media thickness (IMT) in the carotid arteries and the increased levels of CRP were both shown to be associated with the occurrence of stroke. However, it is not known whether elevated CRP level is an indirect risk factor for the ischemic stroke through its relation with the extent of the carotid atherosclerosis is unknown. In this study, we proposed to survey the relationship between the serum levels of hsCRP and the extent of carotid atherosclerosis.

Method

SUBJECTS AND CLINICAL EVALUATION

In this prospectively designed study, 104 patients (52 females, 52 males) with acute ischemic stroke, consecutively admitted to the

Stroke Unit of the Neurology Department of Cerrahpasa Medical School between January 1, 2003 and January 1, 2004, were included.

Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted more than 24 hours. To indicate the presence of an infarction and also to exclude the hemorrhage, a brain CT and/or MRI were performed for every patient. All participants underwent an evaluation including medical history, physical examination, standardized blood tests, duplex sonography of the carotid arteries, 12-lead ECG, transthoracic echocardiography. The patients were classified according to TOAST criteria, as atherothrombotic, cardioembolic and lacunar strokes ; the patients having infarctions of unknown etiology or caused by an underlying systemic disease were excluded.

Several laboratory parameters and their set values such as hsCRP levels, erythrocyte sedimentation rate (ESR) levels, leukocyte count (wbc), and glucose level as well as the other cardiovascular risk factors including age, sex, dyslipidemia, history of smoking, presence of arterial hypertension, diabetes mellitus, atrial fibrillation, history of the ischemic heart disease (IHD), previous stroke, the presence of the peripheral artery disease, prestroke use of antiaggregants and/or statins were determined. The plasma levels of hsCRP levels were determined in mg/L and cut off point was accepted as 5 mg/L. ESR levels were expressed in mm/hour with a cut off point of 20 mm/hr. Leukocyte number (white blood cells, WBC) was counted per mm^3 and levels higher than 10200 cells per mm^3 were accepted as abnormal. Dyslipidemia was determined by measuring the fasted plasma cholesterol levels. The levels of triglyceride (TG) more than 150 mg/dL, the levels of low-density lipoprotein (LDL) more than 130 mg/dL, and the levels of high-density lipoprotein (HDL) lower than 40 mg/dL for males and lower than 50 mg/dL for females were defined as the criteria for the diagnosis of the dyslipidemia. Patients on medication with the cholesterol-lowering drugs were also accepted as having dyslipidemia. The history of smoking was questioned, and the patients were grouped as non-smoker, quitter, and smoker. The presence of the arterial hypertension was determined if the documented systolic arterial blood pressure was higher than 140 mmHg and/or the diastolic arterial blood pressure was higher than 90 mmHg, or if the patients were on medication with antihypertensive agents. Diabetes mellitus, another known risk factor, was reported in patients having antidiabetic treatment or was diagnosed during hospital (glucose levels higher than 110 mg/dL). Ischemic heart disease (IHD) was reported in the presence of a documented previous myocardial infarction, angina pectoris, bypass surgery, or angiographically documented stenosis of a major coronary artery more than 50%. Body mass index values could not be included in our study, as these informations were not included correctly in the files of the patients.

Patients who had a history of recent infection as outpatients, surgery or trauma in the previous month were excluded from the study. Previous infections were monitored by medical history, chest x-ray, total urine tests, and a complete physical examination within 24 hour of admission. Depending upon the etiology of the ischemic stroke, the patients received anticoagulation and/or antiaggregation therapy as appropriate. To evaluate the secondary stroke complications such as pneumonia or urinary tract infections, the patients received a daily physical examination and a repeated temperature measurement in every 4 hours. If necessary, appropriate antibiotic treatment was then modified according to test results.

Neuroultrasonographic evaluation

All participants underwent an ultrasonographic examination for the determination of the intima to media thickness (IMT) of the carotid arteries. Continuous-wave Doppler and color-flow B-mode ultrasound (model SSA-270A ; Toshiba America Medical Systems) with a high resolution, 7.5 MHz, linear-array probe were used in ultrasonographic evaluation. The same sonographer examined all the subjects who were kept blind about their clinical and biochemical characteristics.

Measurement was performed on the CCAs approximately 1.5 cm proximal to the flow divider using the method of O'Leary *et al.* (1996, 1999). IMT was defined as the mean of the maximum wall thickness for near and far walls on both the left and right sides, and measured at the thickest point, not including plaques on the near and far walls. A plaque was defined as a localized thickening more than 1.2 mm that did not uniformly involve the whole artery (Nicolaides *et al.,* 1996). The presence of plaque was determined regardless of its number or localization. The participants were then divided into four groups, based on their carotid wall thickness ; as (0) normal examination, (1) presence of intimal thickening, (2) presence of plaques with no significant narrowing, and (4) presence of stenosis > 50%.

hsCRP Measurements

The biochemistry laboratory of the University of Istanbul, the Faculty of Cerrahpasa, blind to the status of patients, measured CRP concentrations using a CRP-spesific monoclonal antibody coated to polystyrene particles and fixed-time kinetic nephelometric measurements. The nephelometer (Dade/Behring Marburg GmbH) automatically dilutes the samples as 1:400 (CRP1) or 1:20 in the sensitive assay protocol (CRP2) with N diluent.

The assay protocols, each for serum as well as plasma, are given in the BN System Instruction Manual and software of the instrument. All steps were performed automatically by the system. The analytical sensitivity of the assay is determined by the lower limit of the reference curve and therefore depends upon the concentration of the protein in the N Rheumatology Standart SL. A typical limit for detection for CRP is 0.175 mg/L for measuremets performed using a sample dilution of 1:20. Expected values for healthy individuals as noted in the literature are typically < 3.1 mg/L (9,10). The reference interval of CRP in the serum of healthy individuals using the N High sensitivity CRP assay was found to be 90% 1.69 mg/L, 95% 2.87 mg/L (13). g/dL. Blood samples were taken at admission, within 72 hours after stroke.

Statistical Analysis

Data were first analyzed as to whether a normal distribution was present by means of a Kolmogorov-Smirnov test. Comparisons of the variables were done by paired t-test, the Kruskal Wallis test, or the Jonckheere-Terpstra test as appropriate. Categorical data were compared by Mann-Whitney U test. Spearman's correlation coefficients were used to measure correlations between clinical and laboratory variables. Multiple regression analysis were run to evaluate the independent contribution of clinical and laboratory variables. The threshold level for statistical significance was established at $p < 0.05$. All values were given as mean and 95% CI or median and percentiles.

Results

Subjects and clinical evaluation

One hundred and four patients (52 men and 52 women) were included in this study. The mean age of the patients was 66.7 ± 12.8 years with a range of 30 to 92 years. 22.1% of the patients were still smokers, while 19.2% had been a smoker in their life span before quitting. 85% of all patients had hypertension, 36.5% had diabetes mellitus, 21.2% had atrial fibrillation, 31.7% had a history of IHD, 33.7% had a history of previous stroke, 8.7% had peripheral artery disease, and 55.8% had dyslipidemia, 22% of which were on medications with statins.

Neuroultrasonographic evaluation

24 patients (23.1%) had normal neuroultrasonographic examination, and classified aiming to group patients according to the extent of the carotid atherosclerosis. In 22 patients (21.2%), there was intimal thickening and increased intima to media thickness of the common carotid arteries. 26 patient (25%) revealed the presence of the plaques which did not compromise the blood flow ; and, 32 patient (30.8%) showed plaque formation leading significant stenosis (more than 50%).

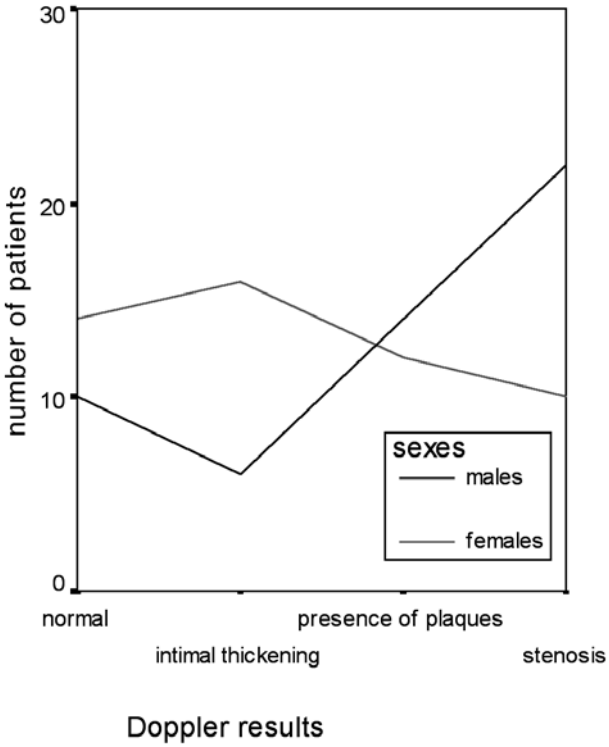

Fig. 1. — The extent of the carotid atherosclerosis between males and females is statistically significant ($p < 0.01$).

Out of 52 males, normal carotid examination was found in 10 patients (19.2%). 6 patients (11.5%) were included in the group 2 – with intimal thickening ; 14 patients (27%) had carotid plaques ; and 22 patients (42.3%) had carotid plaques causing stenosis more than 50%. From 52 female participants, normal carotid examination was found in 27% of them (14 patients). In 16 patients (30.7%), carotid ultrasound examination revealed intimal thickening. 12 patients (23%) had carotid plaques, and 10 of them (19.3%) had plaques leading to stenosis. The extent of the carotid atherosclerosis was found to be significantly higher in males, and lower in females ($p = 0.01$) (Fig. 1).

Mean age of the patients with normal neuroultrasonographic examination was found 57.1 + 7.9 years ; it was 68.0 + 4.0 years in patients with intimal thickening and increased intima to media thickness of the common carotid arteries ; 69.9 + 3.2 years in patients with carotid plaques but no significant narrowing ; and 70.0 + 6.0 years in patients with carotid stenosis more than fifty percent. The difference between the second, third and forth groups were not significant statistically ($p = 0.684$), but the mean age of the normal

Table 1

The odd's ratios of all variables

Variables	Value	95% Confidence Interval	
		Lower	Upper
Sex	0,646	0,257	1,626
Age	7,824	2,056	29,768
CRP	2,377	0,924	6,115
ESR	1,332	0,529	3,350
wbc	2,968	0,634	13,894
HT	1,255	0,360	4,370
DM	1,536	0,572	4,129
AF	1,025	0,334	3,147
IHD	4,200	1,154	15,282
Previous stroke	1,019	0,387	2,680
PAD	0,568	0,131	2,464
Smoking	1,232	0,482	3,147
Glucose	2,037	0,799	5,196
TG	0,571	0,224	1,454
LDL	0,553	0,213	1,437
HDL	0,921	0,336	2,524
Statin use	1,400	0,557	3,521

neuroultrasonographic examination group was statistically significant in compared to the mean ages of the other groups ($p = 0.011$). Although mean ages did not significantly differ between subgroups, age was found as an independent risk factor for carotid atherosclerosis on multilogistic regression analysis ($p < 0.05$).

The subgroups were comparable with regard to several clinical and laboratory parameters, including the presence of the other known cardiovascular risk factors, such as pack-years of smoking, diabetes mellitus, hypertension, dyslipidemia, and history of previous vascular events. Multiple regression tests revealed no significant differences between the intima to media thickness of the common carotid artery and all of the variables. The odd's ratio for each variable is summarized in table 1.

hsCRP Measurements

The hsCRP determination was performed within 72 hours after admission. The delay of the measurement between four groups did not differ significantly ($p > 0.05$). In 30 patients (30%) the hsCRP concentrations were not increased. The mean hsCRP level was 21.3 mg/L.

In 24 patients with normal ultrasonographic examination, mean hsCRP level was found 8.6 + 6.7 mg/L ; it was found 18.0 + 25.6 mg/L in patients with increased intima to media thickness ; 32.7 + 49.1 mg/L in patients who have atheromatous plaques that do not lead to significant narrowing ; and 23.9 + 27.3 mg/L in patients with carotid artery stenosis more than 50%. The levels of hsCRP showed a significant increase as the extent of the atherosclerosis determined by common carotid artery duplex sonography increased ($p = 0.040$, Jonckheere-Terpstra test) (Fig. 2). The hsCRP levels in patients with stenosis were found to be higher in compared to the patients with unstenotic plaques, but the difference was not statistically significant ($p = 0.875$, Mann-Whitney U test).

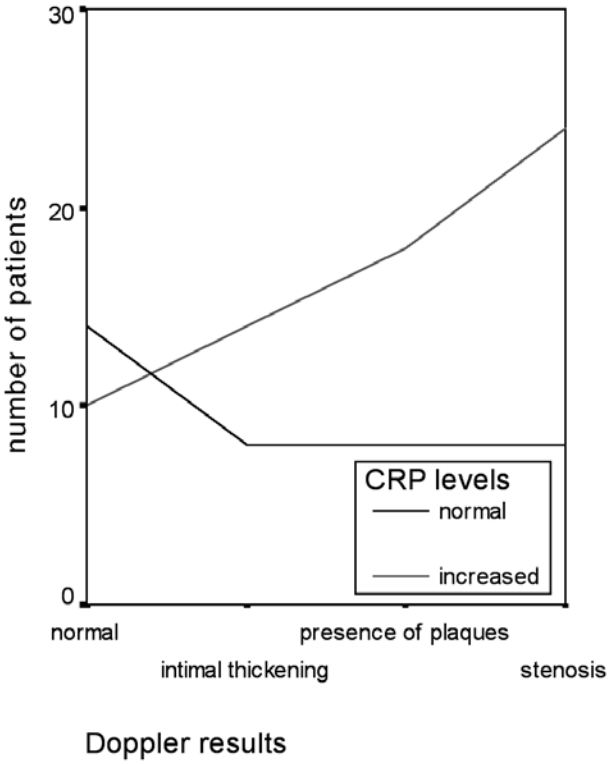

Fig. 2. — The levels of hsCRP showing a significant increase as the extent of the atherosclerosis determined by common carotid artery duplex sonography increased ($p < 0.05$).

When the level of atherosclerosis was correlated with the white blood cell count (wbc) and erythrocyte sedimentation rate (ESR), it was found that no significant relationship existed between these two groups ($p = 0.176$, Kruskal Wallis test, and $p = 0.388$, x^2 test, respectively). The effect of the hsCRP levels on atherosclerosis was examined if it was independent of wbc and ESR by using the multinomial logistic regression tests, which proved the relationship as independent ($p = 0.481$, $p = 0.265$, respectively).

The relationship between the hsCRP level and the other risk factors were also evaluated in our study. All of the variables except HDL levels, failed to show a significant relationship with the hsCRP levels. Only variable that showed a significant relation with the levels of the hsCRP was HDL levels. A negatif correlation between the hsCRP and HDL levels was found that, hsCRP levels decreased as the HDL levels increased. In 75 patients with low HDL levels (HDL < 40 mg/dL for males, < 50 mg/dL for females), the mean hsCRP level was 24.8 + 35.3 mg/L (ranging between 3.0-190.1 mg/L) with a median level of 12.2 mg/L. In

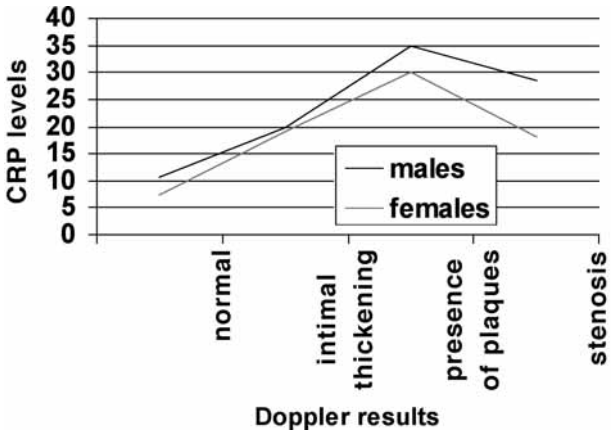

FIG. 3. — The levels of hsCRP in both sexes, showing a significant increase as the extent of the atherosclerosis increased ($p < 0.05$).

patients with normal HDL levels (21 patients), the mean hsCRP level was found 11.3 + 17.8 mg/L (ranging between 3.1-84.9 mg/L, with a median level of 5.4 mg/L). At last, in patients with high HDL levels (8 patients), mean plasma level of hsCRP was 14.6 + 24.0 mg/L (ranging between 3.1-72.7 mg/L ; a median level of 3.9 mg/L). As the number of the patients with high HDL is quite less, the comparison of the median levels of the hsCRP explored the existing relationship between the two variables better ($p = 0.007$, Jonckheere-Terpstra test).

Cerebrovascular diseases (CVD) were classified according to the etiology, as atherothrombotic (51 patients), cardioembolic (26 patients), and lacunar (27 patients) strokes. Mean hsCRP levels in these three groups were 22.8 + 31.3 mg/L, 15.0 + 15.4 mg/L, and 24.7 + 43.6 mg/L, respectively. No significant association was found between the etiology of the CVD and the serum levels of the hsCRP ($p = 0.927$, Kruskal-Wallis test). From the other risk factors , the levels of TG were found incresead in 29 patients out of 51 patients (56.8%) in the atherosclerosis group, 7 patients out of 26 patients (26.9%) in the embolic group, and 18 patients out of 27 patients (66.6%) in the lacunar group ; which was significant as higher levels were associated with lacunar type of infarction ($p = 0.009$; x^2-square test). The HDL were found decresead in 40 patients out of 51 patients (78.48%) in the atherosclerosis group, 16 patients out of 26 patients (61.5%) in the embolic group, and 19 patients out of 27 patients (70.3%) in the lacunar group ; which was significant as lower levels were associated with atherosclerotic type of infarction ($p = 0.011$; Fisher's test). The presence of diabetes mellitus was found in 17 patients out of 51 patients (33.3%) in the atherosclerosis group, 6 patients out of 26 patients (23%) in the embolic group, and 15 patients out of 27 patients (55.5%) in the lacunar group ; which was significantly favored the lacunar type of infarction ($p = 0.039$; x^2-square test). The presence of atrial fibrillation was found in 5 patients out of 51 patients (9.8%) in the atherosclerosis group, 16 patients out of 26 patients (61.5%) in the embolic group, and 1 patients out of 27 patients (3.7%) in the lacunar group ; which was significantly favored the embolic type of infarction ($p < 0.001$; x^2-square test). The other variables failed to show a relationship.

Cerebrovascular diseases were also classified into four groups as total anterior circulation infarctions (17 patients), partial anterior circulation infarctions (55 patients), lacunary infarctions (13 patients), and the posterior circulation infarctions (19 patients). Mean hsCRP levels in these three groups were 28.2 + 36.2 mg/L, 17.7 + 21.5 mg/L, 10.3 + 5.0 mg/L, and 33.2 + 54.7 mg/L, respectively. No significant association was found between the etiology of the CVD and the serum levels of the hsCRP ($p = 0.834$, Kruskal-Wallis test). The other risk factors were analysed and showed no significant association neither. This type of a classification might indicate the size of the infarction ; and the results could be critized as these risk factors are not predictive for the size of the infarction. However, it is known and shown in our study that, at least some of these parameters are risk factors for lacunar infarctions, and some for the atherosclerosis, or embolic enfarctions. Therefore this type of a classification may be insufficient to describe the characteristics of the infarctions.

Discussion

We have demonstrated that elevated hsCRP level is strongly associated with the extent of the atherosclerosis in the carotid arteries. All of the other risk factors failed to show a significant relationship with the atherosclerosis in the carotid arteries. The relationship between the increased serum hsCRP levels and the atherosclerosis in the carotid arteries was found to be independent from the other known risk factors for the atherosclerosis. All of the other risk factors also failed to show a significant relationship with the increased hsCRP levels, except for the HDL levels ; the serum levels of the hsCRP was found to be increased as the levels of the HDL decreased. Cerebrovascular diseases were also classified into four groups according to location of the infarction (as total or partial anterior circulation, lacunar infarction, and the posterior circulation infarctions), and classified into three groups according to the underlying etiology (as atherothrombotic, cardioembolic, and lacunar strokes. No significant association was found between these groups and the serum levels of the hsCRP. Although the number of the patients included in the subgroups may not be sufficient to make conclusions about that type of a relationship, the aim of

our study was beyond this subject, but to investigate if the level of C-reactive protein is correlated with the extent of the carotid atherosclerosis. A correlation between CRP and carotid atherosclerosis in asymptomatic patients, as transient ischaemic attack, would also provide better appreciation of the role of inflammation in atherosclerotic process, as well as in the comprehension of protective treatment, as it might guide to the new studies.

The American Heart Association reported that elevated levels of blood-markers for the inflammation were associated with a significantly increased risk of stroke among the elderly regardless of the amount of the plaques in the arteries supplying the brain. The study found that a high CRP level was an independent risk factor for the stroke regardless of the thickness of carotid artery walls – which indicates the extent of atherosclerotic plaque in the arteries leading to the brain (Cao J. J. *et al.,* 2003). They also found that while C-reactive protein was an independent risk factor for the stroke, it was even more closely related to the stroke in people with thicker arterial walls than in people with thinner walls. Among people with the thinnest carotid walls, there was no significant association between CRP and stroke, whereas, among those people in the second and third tertiles, there was a significant association between CRP and stroke (Cao J. J. *et al.,* 2003). They proposed that their findings raised the possibility that higher levels of CRP are associated with more active or unstable plaque that is more likely to rupture and cause the stroke ; and these findings added to the growing body of evidence that supports the use of CRP measurements in assessing certain individuals' global cardiovascular disease risk (Cao J. J. *et al.,* 2003). In the presented study, the macrostructure of the carotid atheromatous plaques were not classified according to their nature, if they are active or not. Instead, it was aimed to investigate if higher CRP levels were associated with higher IMT levels, or with more advanced carotid atherosclerosis.

CRP levels were associated with the severity of atherosclerosis in our study, as shown by van der Meer *et al.,* 2002). A recent study conducted by Guo *et al.* found significantly elevated CRP levels in ischemic patients with higher IMT values (Guo Y. *et al.,* 2003). Another study carried out by Winbeck *et al.*, reported patients with elevated CRP showed a significantly larger IMT, which was independent of the other proven risk factors (Winbeck K. *et al.,* 2002). In a larger study with 875 men and 948 women, CRP was not strongly and independently associated with prevalent atherosclerosis, and suggested that elevated CRP might be a stronger marker of thrombotic risk than of the degree of atherosclerosis (Folsom A. R. *et al.,* 2001). On the other hand, Sitzer *et al.* (2002) found it unlikely that CRP per se was a major independent cause of early arteriosclerosis, but might mediate the effect of certain conventional risk factors on promoting atherogenesis.

An offspring cohort of the Framingham Heart Study has found elevated CRP levels being associated with carotid atherosclerosis in women but not in men (Wang T. J. *et al.,* 2002). The researchers concluded that a graded association between CRP and carotid atherosclerosis was present in women but not in men and that the significance of this gender difference needed to be studied further. The extent of the carotid atherosclerosis was found to be significantly higher in males in our study.

The association of CRP with the stroke was found significantly different depending on the IMT ($p < 0.02$) ; with no association of CRP with stroke among those in the lowest IMT tertile and with a significant association among those with higher levels of IMT (Cao J. J. *et al.,* 2003). Elevated CRP levels was demonstrated to be a risk factor for the ischemic stroke, independent of the severity of the atherosclerosis as measured by IMT in the carotid arteries. The association of CRP levels with the stroke was more apparent in the presence of a higher IMT. The levels of the CRP and IMT in the carotid arteries might have been independent integrals in determining the risk of the ischemic stroke (Cao J. J. *et al.,* 2003). In a study by Lombardo *et al.*, C-reactive protein levels were higher in patients with complex (7.55 mg/L) than in those with simple (3.94 mg/L ; $P < 0.05$) plaques or without plaques (2.45 mg/L ; $P < 0.05$). On multivariate analysis, higher C-reactive protein levels were independently associated with complex carotid plaques (Lombardo *et al.,* 2004).

It has shown that the major risk factors of the stroke were also associated with the higher levels of CRP (Mendall M. A. *et al.,* 1996 ; Tracy R. P. *et al.,* 1997) ; and the treatment with antiaggregants and statins might have lowered the levels of CRP through their regulatory effects on the inflammation (Cha J. K. *et al.,* 2002 ; Di Napoli M. *et al.,* 2002 ; Jialal I. *et al.,* 2001). In one study with 124 hypertensive patients being managed by drug therapy or lifestyle modification, CRP was shown as an equivalent or superior independent predictor of the progression of carotid atherosclerosis than the pulse pressure or systolic blood pressure (Hashimoto H. *et al.,* 2004). High blood pressure, as well as triglycerides, HDL cholesterol and diabetes were found to be strongly associated with CRP in a study by Blackburn R. *et al.* (2001). In a study by Choi H. *et al.*, 2004), there was no association between hs-CRP and carotid atherosclerosis in subjects with hypertension and normotension. In our study, the relationship between triglycerides, HDL cholesterol and diabetes together with the history of AF were found not to be significantly associated with the levels of CRP. In one study, a significant linear trend for increased carotid artery IMT was found to be associated with increasing

ESR and CRP categories, but these trends were found independent of age, sex, and CV risk factors (Del Rincon I. *et al.*, 2003), as demonstrated in our study. Smokers had higher WBC, fibrinogen, and CRP levels in a study by Magyar *et al.* (2003), which was not significantly associated in our study.

Di Napoli *et al.* (2001a) found that the C reactive protein concentrations increased in about three quarters of patients within 24 hours after ischemic stroke, and higher values were significantly associated with the large infarction size ; smaller increases were reported in patients with small infarctions and deep infarctions (Di Napoli *et al.*, 2001a). On the other hand, we did not find any statistically significant relationship between the serum CRP levels and the type of the stroke that classified as total anterior circulation infarctions, partial anterior circulation infarctions, lacuner infarctions, and posterior circulation infarctions ; which may reflect the size of the ischemic strokes.

Higher CRP concentration was an independent predictor of mortality together with age and the severity of the stroke on the National Institutes of Health Stroke Scale (Muir K. W. *et al.*, 1999). In the same study, it was proposed that the CRP concentration was an independent predictor of the survival after the ischemic stroke which was consistent with the role of the inflammation in acute ischemic stroke, as well as with the hypothesis that elevated CRP might predict the future cardiovascular mortality. Other studies also showed the association between the increased levels of CRP with a worse outcome in patients with ischemic stroke (Di Napoli M. *et al.*, 2001b, Rost N. S. *et al.*, 2001). Morover, one study conducted in an elderly population without preexisting stroke, it has been demonstrated that elevated CRP concentration was an independent risk factor for future ischemic stroke over 10 years of follow-up (Cao J. J. *et al.*, 2003).

We conclude that elevated hsCRP concentration was an independent predictor of atherosclerosis of the carotid arteries in patients with ischemic stroke. All of the other risk factors failed to show any significant relationship with the degree of atherosclerosis and also with the serum levels of hsCRP except HDL levels.

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