

*Original Article***Comparison of carotid artery intima - media thickness and risk factors of atherosclerosis in lacunar versus non-lacunar cerebral infarcts***Seyed Ali Mousavi\*, Seyed Payam Mirabdolbaghi\*\****Abstract**

**BACKGROUND:** Increases in the thickness of the intima-media of the carotid artery have been associated with an increased risk of myocardial infarction and stroke in subjects without a history of cardiovascular disease. Lacunar infarcts, one of the most common subtypes of ischemic stroke, show unique pathological and clinicoradiological characteristics. The present study examined the relationship between the vascular risk factors, including carotid artery intima-media thickness (IMT), and lacunar versus non-lacunar infarcts.

**METHODS:** We collected data from patients admitted to hospital with acute ischemic stroke. 195 Patients and 96 control subjects underwent B-mode ultrasonographic measurements of IMT of the common carotid artery. We examined the association of lacunar and non-lacunar infarcts with age, sex, and potential vascular risk factors.

**RESULTS:** Of 195 adult patients with acute ischemic stroke, 87 were considered lacunar and 108 were considered non-lacunar strokes. Between these two groups of patients, we did not find a significantly different percentage of diabetes, smoking, hypertension, dyslipidemia, myocardial infarction, or previous history of ischemic stroke, alcohol, obesity, atherogen diet, exercise, and IMT. However, patients with lacunar infarct, diabetes mellitus ( $P = 0.02$ ), and hypertension ( $P = 0.02$ ) had a significantly higher percentage of history of prior CVA ( $P = 0.03$ ) and a significantly higher percentage of non-lacunar infarct.

**CONCLUSIONS:** The present results indicated that diabetes mellitus and hypertension are more common in patients with lacunar infarcts, and history of CVA is more common in patients with non-lacunar infarcts. We further concluded that IMT cannot differentiate subtypes of ischemic stroke. Because risk factors and clinical presentation of ischemic stroke differ among races, more national studies should be done in our country to find ways to prevent stroke and its complications.

**KEY WORDS:** Lacunar infarction, risk factors, ultrasonography.

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Every year, at least 750,000 Americans experience a new or recurrent stroke, causing stroke to remain the third leading cause of death in the United States<sup>1</sup>. Cardiovascular disease is one of the most common causes of premature death or disability in developed societies, and atherosclerosis remains

the major cause of such disorders in these societies<sup>2</sup>. High-resolution B-mode ultrasonography provides a noninvasive method of quantifying sub-clinical arterial wall thickening and atherosclerotic progression<sup>3</sup>. In addition, carotid artery intima-media thickness (IMT) has been found to be strongly associated with cardiovascular risk factors<sup>4,5</sup>.

\* Associate Professor, Department of Neurology, Isfahan University of Medical Science, Isfahan, Iran. e-mail: a-mousavi@med.mui-ac.ir (Corresponding Author)

\*\* Clinical Resident, Department of Neurology, Isfahan University of Medical Science, Isfahan, Iran.

Please review the singular versus plural uses of this word throughout the text. I aimed primarily at consistency in its use, but may have misinterpreted its idiomatic application in some instances.

Several studies have shown an association between carotid artery IMT, incidence of myocardial infarction<sup>6,7</sup>, and stroke<sup>7-9</sup>. Measurements at different sites of the carotid artery have been performed by different groups<sup>7,8</sup>. It has been shown that common carotid artery (CCA) IMT is a good predictor of stroke incidence, whereas internal carotid artery (ICA) IMT measurement has a greater power of prediction for myocardial infarction<sup>8</sup>. Similarly, CCA IMT has been shown to be strongly associated with risk factors for stroke, whereas IMT bifurcation and plaque were more directly related to ischemic heart disease and its risk factors<sup>10</sup>. Risk factors of atherosclerosis include smoking, hypertension (BP>14/9), age (>45years), diabetes, hyperlipidemia, obesity (BMI>30), myocardial infarction, and previous stroke<sup>2</sup>. Those for ischemic stroke include lacunar infarction, large artery infarction, and embolism. Lacunar infarction, one of the most common causes of ischemic stroke, is presumed to result from the occlusion of single perforating arteries. Clinical presentation (lacunar syndrome), history of diabetes and hypertension, previous lacunes on baseline early CT, and the absence of cardiac sources of embolism have been investigated as predicting variables of lacunar infarcts<sup>1,11</sup>. The purpose of the present study was to assess the relationship between the vascular risk factors in our society, including CCA IMT, and both lacunar and non-lacunar infarcts, because IMT and risk factors of stroke differ among races and major ethnic groups<sup>1,12</sup>.

## Methods

We prospectively collected data from 195 consecutive patients with acute ischemic stroke admitted to our neurology ward from April 2004 to September 2005, and from control subjects recruited during the same period. A stroke was defined as rapidly developing signs of focal or global disturbance of cerebral function lasting >24 hours with no apparent cause other than vascular etiologies. Exclusion criteria were age (<45 years), and isolated transient ischemic attacks (TIAs). All patients underwent a CT scan without contrast on admission as part of standard stroke patient care. MRI with DWI sequences (or CT when MRI was contradicted because of the presence of a metal implant, or if the patient refused or was claustrophobic) was performed within 1 week from the onset of symptoms. Images were evaluated at a central reading center by neuroradiologists. To check the reliability of the

radiological definitions, 2 observers (1 neuroradiologist and 1 neurologist who were unaware of patients' vascular risk factors) re-examined the images for this study. The carotid arteries were evaluated with a high-resolution ultrasound equipped with a linear transducer with 5 MHz in B mode. The carotid arteries were evaluated for the presence of atherosclerotic lesions. All patients and 96 control subjects underwent B-mode ultrasonographic measurements of CCA IMT. Control subjects were recruited among individuals who consecutively underwent ultrasound examination at the same institution for any reason other than cerebrovascular disease. Subjects complaining of symptoms such as tension-type headache, dizziness, and hypoacusia, and who were subsequently shown to be disease free, were included in the present study. The subjects were examined in the supine position with the head turned 45° to the left or right. Longitudinal images of the left and right CCAs were acquired. Like other standardized studies, far-wall measurement was considered<sup>13-15</sup>. Two frozen images of IMT from the far wall on both the right and left CCAs were acquired. IMT of the far wall was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface. The measurement of IMT in the CCA was made 1 cm proximal to the carotid bulb. The number of measurements ranged from 3 to 5 for each frozen image. The sonographers were unaware of the clinical and radiological information about the participants. Information on demographic characteristics, previous diseases, habits, and cardiovascular risk factors was collected from both patients and control subjects with a structured medical history.

Traditional risk factors for cerebrovascular disease were evaluated. Height and weight were measured. Age, sex, diabetes, history of smoking (current smokers), alcohol consumption, history of hypertension (previously diagnosed and treated, or systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg persistently observed during admission and after the acute phase), low-density and high-density lipoprotein cholesterol levels, presence or absence of atrial fibrillation (AF; history of AF confirmed by previous ECG examination, or AF diagnosed at the time of admission and/or during the hospital stay), cardiovascular diseases, and history of previous CVA were recorded. Brain imaging was classified as lacunar or non-lacunar infarcts. Lacunar infarcts were defined by a combination of

symptoms or signs and radiological criteria. Patients with a clinical presentation consistent with 1 of the 5 classic lacunar syndromes (primary motor, primary sensory, or sensory motor symptoms, the dysarthria clumsy hand syndrome or the ataxia-hemiparesis syndrome) were included. Rarer lacunar syndromes, such as subthalamic infarction causing hemiballismus, were included only if there was MRI documentation of the site and size of infarct. In all cases, MRI excluded causes other than cerebral infarction. To be defined as a lacunar lesion by MRI, the following criteria had to be met: (1) be round or oval in shape, (2) measure  $\leq 1.5$  cm in diameter, (3) be located in the typical territory supplied by deep or superficial small perforating arteries, (4) not be in cortical territories, and (5) not have the morphological and topographical distribution consistent with partial internal border-zone infarcts. Patients with a clinical presentation consistent with a lacunar syndrome, and with neuroimaging confirmation of  $>1$  lacunar lesions located in the appropriate area of the brain to explain the symptoms were classified as having lacunar infarcts. Patients were subdivided into 2 groups, lacunar and non-lacunar infarctions, for further statistical analysis. The association of the IMT with lacunar and non-lacunar infarcts was examined before and after control for the potential risk factors. Data on controls' and patients' clinical characteristics and presence of cerebrovascular risk factors were kept in a SPSS 9 software package.  $\chi^2$  test was performed for statistical analysis and  $P < 0.05$  was declared as significant for presentation, results of investigations, and demographic characteristics.

## Results

Among 237 adult patients consecutively recruited during the study period, 20 subjects were excluded because they were  $<45$  years of age, and also 22 subjects were excluded because they were diagnosed as having had emboli of cardiac source. Among the patients who entered the present study, 87 were considered to have had lacunar, and 108 to have had non-lacunar strokes. The 5 classic lacunar syndromes accounted for 97% of the lacunar infarctions; other lacunar syndromes accounted for only 3%. The average of left and right IMTs was considered for statistical analysis as a parameter of atherosclerosis. Table-1 summarizes the descriptive statistics of the 3 groups, findings for the demographic and vascular risk factor characteristics. The overall tests indicated that hypertension, diabetes mellitus,

and history of previous CVA were able to discriminate between the 3 groups. Among 195 adult patients with acute ischemic stroke, 87 subjects were considered lacunar and 108 patients were considered non-lacunar strokes. Between these two groups of patients, we did not find a significantly different percentage of diabetes, smoking, hypertension, dyslipidemia, myocardial infarction, or previous history of ischemic stroke, alcohol, obesity, atherogen diet, exercise, and IMT. However, patients with lacunar infarcts had a significantly higher percentage of diabetes mellitus ( $P = 0.02$ ), and hypertension ( $P = 0.02$ ) while patients with non-lacunar infarcts had a significantly higher percentage of history of prior CVA ( $P = 0.03$ ).

## Discussion

Lacunar infarcts, one of the most common subtypes of ischemic stroke, show unique clinical, pathophysiological, and radiological characteristics. When a stroke occurs, the ultimate outcome differs with the subtype of stroke and is influenced by patient comorbidities. Patients with lacunar stroke have the best short- and long-term prognoses and the highest survival rates. In addition, lacunar patients have the lowest risk for both early and late recurrence<sup>16</sup>. Lacunes are considered to account for between 12% and 30% of all cases of ischemic stroke. The higher proportion of patients with lacunar infarct in our population (44.6%) could be due to selection factors inherent in the referral of patients to our neurological department. In fact, stroke patients who present large hemispheric strokes and thus require an intensive care unit are admitted to a special department; for this reason they were not able to be included in the present study. Moreover, because we excluded stroke patients  $<45$  years of age, a group of mostly non-lacunar strokes did not enter the present study. According to the lacunar hypothesis, small-vessel disease (from lipohyalinosis and fibrinoid degeneration) is the most important cause of lacunar infarction<sup>17</sup>, whereas atherosclerosis and embolism are less important. Nevertheless, both cardiac embolism and large-artery atherosclerosis have been increasingly recognized and described as potential causes of lacunar stroke<sup>18-20</sup>. In our study, patients with acute ischemic stroke were considered lacunar and non-lacunar strokes. Between these two groups, we did not find a significantly different percentage of diabetes, smoking, hypertension, dyslipidemia, myocardial infarction, previous history of ischemic stroke, alcohol, obesity, atherogen diet, exercise,

and IMT. However, patients with lacunar infarcts, had a significantly higher percentage of diabetes mellitus and hypertension while patients with non-lacunar infarcts had significantly higher percentage of history of prior CVA. A study done by BILLER J et al concluded that lacunes usually occur in patients with hypertension, current cigarette smoking habit, and diabetes mellitus<sup>1</sup>. Thereby, diabetes and hypertension are compatible with our study. In the present study, we observed that CCA (IMT) cannot differentiate lacunar and non-lacunar infarcts in our patients and that our control subjects had high normal IMT ( $1 \pm 0.2$ ). Conversely, in the study by Touboul et al in developed societies, he observed a slight but significantly higher IMT even in lacunar infarcts compared with control subjects<sup>21</sup>. Another study by SACCO et al found races to have different

patterns of atherosclerotic occlusive disease; blacks in particular have higher rates of intracranial atherosclerotic occlusion. Additionally, the study of BONITA et al concluded that clinical characteristics are also markedly different among the major ethnic groups<sup>1,12</sup>.

In conclusion, the present results indicate that diabetes mellitus and hypertension are more common in patients with lacunar infarcts, and history of CVA is more common in patients with non-lacunar infarcts. We further concluded that IMT cannot differentiate subtypes of ischemic stroke. Because risk factors and clinical presentation of ischemic stroke differ among races, more national studies should be done in our country to find ways to prevent stroke and its complications.

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