

Carotid Intimomedia Complex Thickening in Patients with Stroke: A Case Control Study

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According to World Health Report 2001 stroke^{7,13} is the second leading cause of death in the world second only after ischemic heart disease and is responsible for a high percentage of major disability, requiring substantial resources spent on care and rehabilitation. Existing evidences suggest that this trend will remain for some time to come and the global pattern of death will increasingly be dominated by non-communicable diseases; by 2020, heart disease and stroke are expected to be the leading causes of death and loss of disability-adjusted life years.⁷ Among multiple causes atherosclerosis due to lipid accumulation in the vessel wall with formation of atheromatous plaques in the carotid artery is an important cause of stroke.

The carotid arteries are readily accessible to ultrasound imaging, non-invasively, and predict the risk of stroke as well as delineate the further management guidelines.

There are no data regarding the extent of the disease, causes of the stroke, definition of risk factors associated with stroke and contribution of atherosclerosis of carotid artery for the stroke in Nepalese population. Exploration of these factors would help in prediction, prevention and treatment of stroke. This study is designed to find out the status of carotid artery IMT in stroke patients, find out

Increase in the thickness of intima-media of the carotid artery has been associated with an increased risk of stroke. No such information exists for Nepalese population. The present study was undertaken to find out the status of carotid artery in patients with stroke and examine relationship between intimomedia thickness (IMT) with stroke.

High-resolution ultrasonography evaluation of carotid arteries was performed in 97 stroke patients and 114 control individuals. Maximal IMT of common carotid artery (CCA) was recorded. We examined the association of IMT with stroke and association of various potential vascular risk factors with IMT. A significant difference in IMT was found between stroke patients and control individuals along with significant relationship of IMT with smoking in both groups. Mean IMT was greater in cases compared to control group (Right, IMT=0.94 & left, IMT= 0.99 in cases vs. right, IMT=0.73 & left, IMT=0.77 in controls, $p<0.0005$). IMT strongly correlated with stroke in Nepali population. Smoking was found to be a major risk factor for stroke and increase in IMT. The present study indicates that a non-invasive ultrasonic measurement of IMT is a helpful tool to identify individuals at risk for stroke.

Key Words: carotid artery, intimomedia thickness, stroke

contribution of known risk factors to stroke and other associated cause of stroke in Nepalese patients.

Materials and Methods

This was a case control study using Convenience sampling method. A total of 129 patients with stroke were examined from September 2003 to September 2004. Out of 129 patients 23 patients were excluded from the study according to exclusion criteria (vide infra). Nine were further excluded due to incomplete clinical workup. Thus 97 patients constitute the basis for this study. One hundred and fourteen individuals were included in the control group.

Patients were consecutively recruited, who were visiting our hospital, if they fulfilled the following criteria: a) Clinical symptoms suggestive of stroke or TIA as ascertained by neurologists, b) Infarction or hemorrhage on CT scan, c) Infarct proven by MRI, d) 40- 80 years old. Cases were included in the study within a month after the event. Patients with the following findings were excluded from the study: a) Hemorrhage due to rupture of an AVM and aneurysm, b) Infarction due to other known cardiac causes identified by echocardiography, c) Tumor bleed or bleed attributable to trauma.

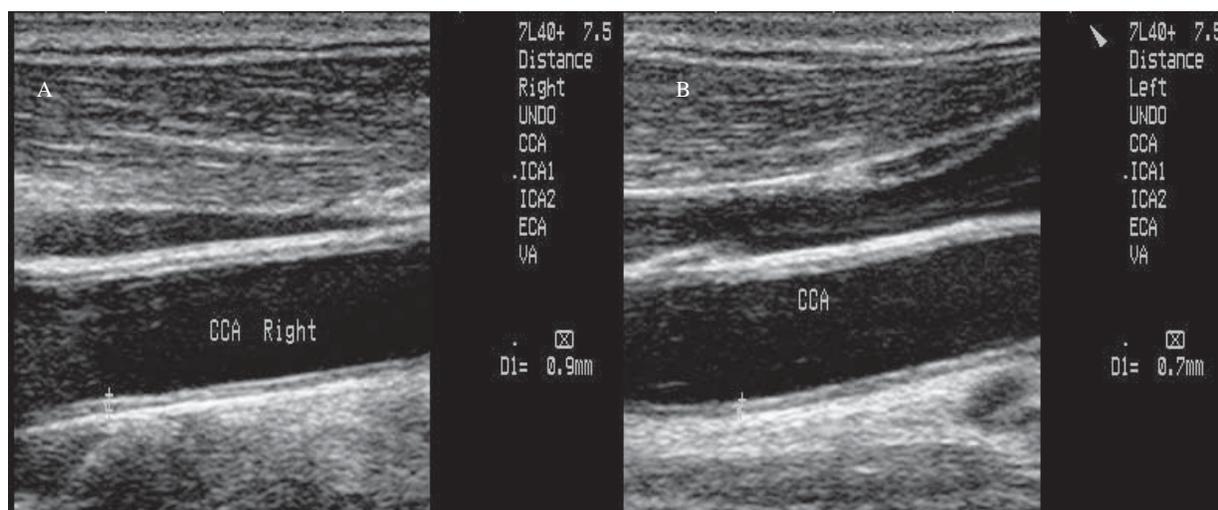


Figure 1. High resolution grey-mode ultrasonography showing intimo-medial complex thickness measurement in (A) right and (B) left CCA. Abbreviation, CCA= common carotid artery.

Controls were recruited among individuals hospitalized or visiting the out patients, general health check up clinic at our hospital and Shahid Ganga Lal National Heart Center for reasons other than neurological diseases. Control were matched by sex and age (± 5 years). History of stroke or other cardiovascular diseases was elicited. Individuals reporting a positive history of stroke were not eligible to participate in the study.

All individuals underwent high-resolution carotid ultrasound examination with 7.5 MHz linear probe to evaluate the morphology and velciometric characteristics. Two commercially available ultrasound (Medison- Korea and Aloka- Japan) machines with Doppler capability were used for carotid evaluation. The author himself did the ultrasound evaluation in all cases. An IMT measurement was taken at the far wall of both common carotid arteries (Figure 1). An informed consent was obtained from all individuals participating in the study.

Results

General Characteristics

The general characteristics of the study population is presented in the Table 1. The mean age of cases was 64 years and control was 62 years ($p < 0.133$). The mean age for male cases was 62 years and for male controls 61 years. Similarly mean age for female cases was 68 years and female controls was 63 years.

The majority of the patients with stroke were male comprising 70.1% of cases. In control group 60% of the individuals were male. Number of cases in case and control group according to sex was not statistically significant. The majority of patients with stroke were 60-69 years of age comprising 29.9% of the stroke patients. Out of them 70.1% were male. Left side was involved in 53% of cases. Ischaemic stroke was the predominant subtype of stroke comprising 69%, which was followed by haemorrhagic (16%), TIA (11%) and lacunar infarction (3%).

Parameters	Cases	Controls
Mean age (years)	64	62
Mean age for Male (years)	62	61
Mean age for Female (years)	68	63
Female (%)	29	46
Smoking (%)	53	33
Alcohol (%)	36	28
Hypertension (%)	61	47
Diabetes (%)	24	21
IMT (right) (mm)	0.94	0.73
IMT (left) (mm)	0.99	0.77

Table 1. General characteristics of study population

Prevalence of Risk Factors

11% of the patients with stroke didn't have any risk factor. In control group 78% of the patient had one to four risk factors. 53% of the cases and 33% of control group individuals were smoker. There was a statistically significant difference in the history of smoking between stroke patients and control group ($p < 0.005$) (Tables 2 & 3). In both groups

	Smoking	No. of Patients	Mean	SD	p
Right IMT (mm)	Yes	51	0.99	0.27	0.96
	No	46	0.89	0.32	
Left IMT (mm)	Yes	51	1.03	0.31	0.296
	No	46	0.95	0.41	

Table 2. IMT and Smoking in Stroke Patients

IMT was thicker in smoker compared to nonsmokers. No significant difference was observed in the history of alcohol intake in stroke and control groups. Approximately 60% of patients with stroke had history of treated hypertension, while 47% of control group had this history. There were marginally more patients with diabetes in stroke

	Smoking	No. of Patients	Mean	SD	P
Right IMT (mm)	Yes	54	0.83	0.23	0.0001
	No	60	0.65	0.14	
Left IMT (mm)	Yes	54	0.79	0.21	0.721
	No	60	0.75	0.70	

Table 3. Table showing IMT and smoking in control group.

cases compared to control group (24.7 % Vs 21.9%), however this was not statistically significant. Serum lipid profile level in both case and control group was analyzed and no significant difference was found in both groups.

Intima-media Thickness

Mean intimomedia thickness on the right side was 0.94 mm in cases and 0.73 in controls with a statistically significant difference between the groups. Mean intimomedia thickness on the left side was 0.99 mm in the case and 0.77 mm in control group (p <0.0005) (Figures 2 & 3). Analyzing the IMT in stroke cases no statistical difference was observed among male and female patients. Mean IMT in smokers was higher than in nonsmoker in both stroke and control groups.

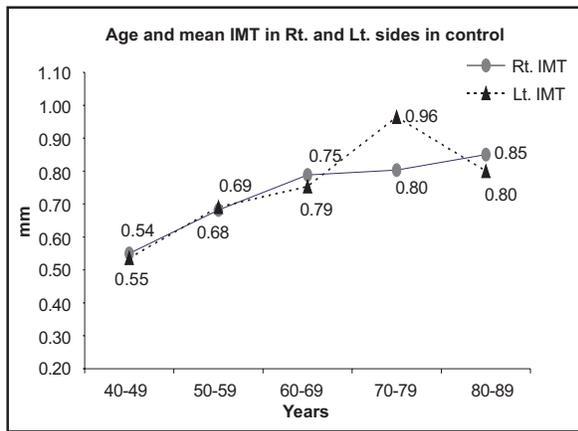


Figure 2. Graph showing mean CCA IMT in right and left side in case in relation to age. CCA= common carotid artery.

In both males and females IMT was thicker in stroke patients compared to control group. (Tables 4 & 5)

IMT was thickest in patients with ischemic type of stroke followed by in patients with hemorrhagic stroke.

Discussion

This study revealed increased IMT in patients with stroke, which was statistically significant, compared to control group. Various studies have shown association between IMT and stroke. Bots, et al., found a graded association of common carotid intima-media thickness with stroke. IMT was measured in 1373 subjects free from myocardial infarction and stroke that were followed up for 2.7 years. Stroke risk increased gradually with increasing

IMT. The odds ratio for stroke per standard deviation increase (0.163 mm) was 1.41 (95% CI, 1.25 to 1.82). This study indicated that an increased common carotid intima-media thickness is associated with future cerebrovascular and cardiovascular events in older subjects. These associations were independent of age, sex, and history of myocardial infarction or stroke.²

Touboul, et al., observed that an increased CCA IMT was associated with brain infarctions both overall and in the main subtypes. They found a slight but significantly higher IMT even in lacunar infarcts compared with control subjects¹¹, however Cupini, et al. did not find a significant difference in IMT between control subjects and patients with lacunar infarcts.³

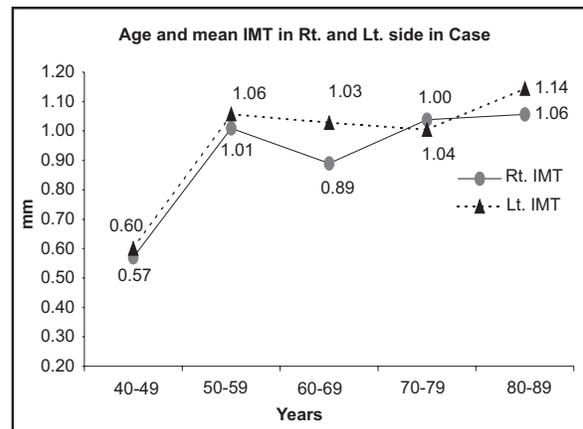


Figure 3. Graph showing mean CCA IMT in right and left side in control in relation to age. Abbreviation: CCA= common carotid artery.

Kitamura, et al.,⁶ examined the relationship of carotid IMT and the surface, morphology, and calcification of carotid plaques with the incidence of stroke among 1289 Japanese men aged 60 to 74 years without history of previous stroke or coronary heart disease. In this cohort 34 strokes occurred in 4.5-year follow-up. The multivariate-adjusted relative risk (95% CI) for the highest versus lowest quartiles of maximum IMT of the common carotid artery (CCA; ³1.07 versus d³0.77 mm) was 3.0 (1.1 to 8.3) for stroke.

O’Leary, et al.,⁸ measured intima and media of the common and internal carotid artery with high-resolution ultrasonography in 5858 subjects (65 years of age or older) and followed over a median period of 6.2 years. Cardiovascular events (new myocardial infarction or stroke) served as outcome variables in subjects without clinical cardiovascular disease. The relative risk of myocardial infarction or stroke increased with intima-media thickness

	Male	No. of Patients	Mean	SD	p
Rt IMT (mm)	Case	68	0.91	0.30	0.004
	Control	68	0.78	0.22	
Lt IMT (mm)	Case	68	1.01	0.36	0.000001
	Control	68	0.74	0.19	

Table 4. IMT and Male Sex in Case & Control Group

	Male	No. of Patients	Mean	SD	p
Rt IMT (mm)	Case	29	1.00	0.30	0.000002
	Control	46	0.66	0.17	
Lt IMT (mm)	Case	29	0.97	0.37	0.322
	Control	46	0.81	0.80	

Table 5. IMT and Female Sex in Case & Control Group

($P < 0.001$). The relative risk of myocardial infarction or stroke (adjusted for age and sex) for the quintile with the highest thickness as compared with the lowest quintile was 3.87 (95 percent confidence interval, 2.72 to 5.51). The relative risk increased in a linear fashion with increasing IMT. They concluded that the IMT of the common carotid artery and the internal carotid artery is strongly associated with the risk of myocardial infarction and stroke in asymptomatic older adults. Moreover, such measurements seem more powerful predictors than traditional risk factors for CV disease. In the present study also except smoking only IMT showed a strong correlation with stroke event. Other risk factors were not statistically significant to show the relationship with stroke. All these findings in the literature and findings of the present study confirm that increased IMT is associated with stroke event and IMT can be taken as an independent risk factor for the development of stroke.

Analyzing the subtypes of stroke it was found that IMT was thickest in Ischemic type of stroke followed by hemorrhagic stroke. As most of the hemorrhagic stroke occurred in patient with hypertension, thickening of IMT partly can be explained by hemodynamic stress.

This study showed a strong correlation between smoking and IMT in both stroke and control group. Atherosclerosis Risk in Communities (ARIC)¹ and Cardiovascular Health Study (CHS)¹⁰ studies found that increased exposure to cigarette smoking is significantly related to increased carotid artery IMT.¹⁰ Both active and passive smoking are associated with increased carotid wall thickness. Howard et al⁵ found the evidence that passive smoking exposure is related to greater IMT in general population. They found that among past and current smokers, increased pack-years of exposure were associated with increased IMT. We did not quantified level of exposure in our study. Among nonsmoking men exposed to environmental tobacco smoking (ETS), there was a significant increase in IMT with increasing number of hours per week of ETS exposure. These data confirm the strong relationship between active smoking and carotid artery IMT. It was not possible to qualify and quantify the ETS in our study group due to status of patient's condition and reliability of response. Robbins, et al.,⁹ in a clinical cohort study of U.S. Male Physicians correlating Cigarette Smoking and Stroke found that with never-smokers as the reference group (relative risk, 1.00), relative risks for total nonfatal stroke (n = 312) were as follows: former smoking, 1.20 (95% CI, 0.94 to 1.53); currently smoking fewer than 20 cigarettes daily, 2.02 (CI, 1.23 to 3.31); and currently smoking 20 or more cigarettes daily, 2.52 (CI, 1.75 to 3.61) (P for trend, < 0.0001). These findings suggest

that smoking is strongly related to risk for stroke.¹⁰² Diez-Roux et al⁴ found lowest mean IMT among never smokers who had never been exposed to ETS (mean +/- standard error: 0.706 +/- 0.013 mm). Exposure to ETS was associated with increased IMT among never smokers. Active smoking in the past was also associated with increased IMT. Diez-roux, et al., concluded that both past and current passive and active smoking is associated with and increased carotid intimal-medial wall thickness. van den Berkortel, et al.,¹² found that the posterior walls of both carotid bulbs (right: $P = 0.0005$; left: $P = 0.02$) and of the internal carotid arteries (right: $P = 0.004$; left: $P = 0.003$) as well as the posterior wall of the right common carotid artery ($P = 0.02$) and of the right common femoral artery ($P < 0.0001$) were thicker in smokers. All these research data and the findings of the present study confirm the strong relationship between smoking and carotid artery IMT.

This was a single institution based case control study with convenience sampling and was limited in time frame and resources. Although, the patients enrolled in the study were from different parts of the country, majority of the patients were from Kathmandu Valley. This might not represent the true picture of the patients from all part of the Nepal. There was also limitation in number of cases enrolled in the study.

Conclusions

Carotid ultrasonography is a non-invasive tool to evaluate atherosclerosis. CCA IMT appears to be a surrogate marker of generalized atherosclerosis process. This is the first case series of patients reported evaluating the status of carotid artery in the Nepalese population. This study showed that IMT is thicker in stroke patients and thus appears to be a strong predictor of stroke. It was also found that smoking is strongly associated with increased IMT and plaque formation. No significant association was found between serum lipid levels and IMT and carotid plaque. This study shows that carotid ultrasound can be used for evaluation of middle age and elderly individuals for potential risk of stroke.

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