

## ORIGINAL ARTICLE

# Prevalence and Predictors of Carotid Artery Stenosis in Patients with Critical Limb Ischemia

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- Background** Patients referred to the hospital with symptomatic peripheral vascular disease often have symptomatic or asymptomatic manifestations of atherosclerosis elsewhere in vascular systems because atherosclerosis is a generalized and progressive process, the risk of premature death in patients who have peripheral arterial disease is three times the risk in subjects without that disease, possibly be due to myocardial infarction, and/or stroke.
- Aim of work** Estimate the prevalence of carotid stenosis in patients presenting with critical limb ischemia and define the predictors of carotid stenosis in this group of patients.
- Methods** One hundred and ten patients presenting with critical limb ischemia were evaluated for carotid stenosis using carotid duplex, peripheral angiography, and laboratory tests; including (liver functions, kidney functions, serum uric acid, fasting, post-prandial blood sugar, and lipid profile) and ECG.
- Results** 29% of the patients had significant carotid artery stenosis  $\geq 70\%$ , 35% had  $<70\%$  stenosis and 35% had normal duplex. Ischemic heart disease, history of heart failure, diabetes mellitus, impaired kidney function, hyperuricemia, hypoalbuminemia, dyslipidemia, prevalence of affected segments (more than one segment) and level of obstruction in the arteries are predictors for severity of stenotic lesion between carotid stenosis and critical limb ischemia. According to Significance of stenotic lesion of carotid artery, carotid Duplex patients' findings were divided into three groups: normal, insignificant, and significant lesions. There was no statistically significant difference between the three groups as regards the age, sex, family history of cerebrovascular stroke and peripheral vascular disease, smoking, hypertension, history of cerebrovascular stroke and liver Function Tests. However, there was a statistically significant difference concerning the presence of carotid artery bruit, ischemic heart disease, history of heart failure, diabetes mellitus, impaired kidney function, hyperuricemia, hypoalbuminemia, dyslipidemia, prevalence of affected segments (more than one segment) and level of obstruction in the arteries.
- Conclusion** Our study confirmed that 29% of the patients had significant carotid artery stenosis  $\geq 70\%$ , 35% had stenosis  $< 70\%$  and 35% had normal duplex, The study also concluded that ischemic heart disease, history of heart failure, diabetes mellitus, impaired kidney function, hyperuricemia, hypoalbuminemia, dyslipidemia, prevalence of affected segments (more than one segment) and level of obstruction in the arteries are predictors for severity of stenotic lesion between carotid stenosis and critical limb ischemia.
- Keywords** Carotid stenosis, peripheral vascular diseases, ultrasound, angiography  
(Heart Mirror J 2008; 2(2): 74-79)

## INTRODUCTION

Arterial occlusive disease is a systemic phenomenon frequently coexisting in more than one arterial bed (1,2). Atherosclerosis underlies most peripheral arterial disease. Narrowed vessels that cannot supply sufficient blood flow to exercising leg muscle may cause claudication which is brought on by exercise and relieved by rest (3). As vessel narrowing increases critical limb ischemia occurs (4). Critical limb ischemia is the end result of arterial occlusive disease most commonly secondary to atherosclerosis in association with hypertension, hyperlipidemia, smoking and diabetes

mellitus (5). Critical limb ischemia usually manifests by pain at rest and/or unresolved limb infection and/or non-healing wound and/or gangrene (3).

Patients referred to the hospital with symptomatic peripheral vascular disease often have symptomatic or asymptomatic manifestation of atherosclerosis elsewhere in vascular systems. The risk of premature death in patients who have peripheral arterial disease is three times the risk in subjects without that disease (6). Carotid atherosclerosis is associated

**Abbreviations and Acronyms**

PVD = Peripheral Vascular Disease  
LDL = Low Density Lipoprotein  
HDL = High Density Lipoprotein  
CAS = Carotid artery stenosis  
CLI = Critical limb Ischemia  
PAOD = Peripheral Artery Occlusive Disease

with the risk of stroke that increases with the severity of stenosis (7). Stroke remains the third most common cause of death in the United States and survivors have significant residual morbidity rate. More than 500,000 new strokes occur annually. An estimated 20% to 50% of these strokes are caused by extra-cranial carotid artery disease and therefore are potentially preventable (8,9).

**PATIENTS AND METHODS**

This study was conducted on 110 patients suffering from critical limb ischemia from Sidnawy Hospital in the period of February 2003 to December 2003. All patients were subjected to the following:

**I- Thorough clinical assessment including:**

History taking and Clinical examination Careful history taking from the patient for assessment of risk factors including age, sex, smoking, hypertension, diabetes, previous history of Transient ischemic attacks (TIAs) or stroke, cardiac symptoms, family history of dyslipidmia and any symptoms of any associated disease. All patients were subjected to full clinical examination with special emphasis on; complexion for xanthomata, xanthelasma, blood pressure for the presence of hypertension, palpation of pulse for abnormal rhythm, cardiac examination, neurological examination to detect any neurological deficits.**II-Laboratory Examinations:**

All patients were subjected to the following investigations:

- Fasting and post-prandial blood sugar to diagnosis DM
- Kidney function tests including plasma urea, serum creatinine, serum sodium and potassium.
- Liver function tests including ALT, AST, bilirubin (total and direct), albumin, total protein and ALP.
- Lipid Profile tests including cholesterol, triglycerides, LDL and HDL.
- Resting ECG to detect left ventricular hypertrophy, presence of ischemic heart disease. And presence of Arrhythmias.

**III-Imaging**

**1- Peripheral angiography**

It was performed using computerized digitalized angiography (Technix TCA 4R Plus). Peripheral angiography was the definitive examination for decision making in PVD, as it gave important information regarding the quality of inflow and runoff, and the character and abundance of the collateral arterial supply to the extremity, begun with a complete study of the abdominal aorta to assess both the aorta and its major visceral branches, performed using computerized digitalized angiography. Non-ionic

contrast was used in patients who were elderly or had renal impairment while ionic contrast was used in young patients who had no cardiac or renal diseases.

**2- Carotid Duplex**

Carotid Duplex Ultrasound is a safe and accurate method for identifying significance of carotid artery stenosis. All patients were subjected to carotid duplex (core-version Toshiba set, duplex) using B-mode and Doppler mode.

**RESULTS**

According to Carotid Duplex patients findings were divided into three groups: those with normal carotid artery (Group A), those with diseased but insignificantly stenosed carotid artery (Group B) and those with diseased and significantly stenosed carotid artery (Group C).

Regarding age and the sex; there was no statistically significant difference between the three groups (Table 1). Regarding smoking, history of hypertension, family history of cerebrovascular stroke, peripheral vascular disease and history of cerebrovascular stroke: there was no statistically significant difference between the three groups between the three groups (Table 2). Regarding carotid artery bruit, history of ischemic heart disease, and history of heart failure, there was statistically significant difference in the carotid artery bruit between the three groups (Table 2).

**Laboratory Data**

As regards Blood Sugar, kidney function tests (urea, creatinine, and serum uric acid), albumin, lipid Profile (Cholesterol Level, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), and Triglycerides), there was a statistically significant increase in the group C when compared to both group A and group B. At the same time, there was a statistically significant increase in fasting blood sugar in the group B when compared to group A (Table 3).

**7- Peripheral Angiography**

Regarding the prevalence of affected segments (more than one segment) and the level of obstruction in critical lesions was increased significantly in both group C and group B when compared to group A. While one segment vessel stenosed was more predominant in the group B followed by the group C and finally group A (Figure 1, 2).

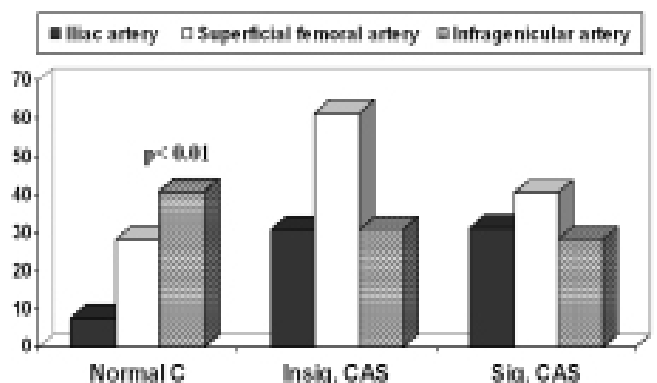
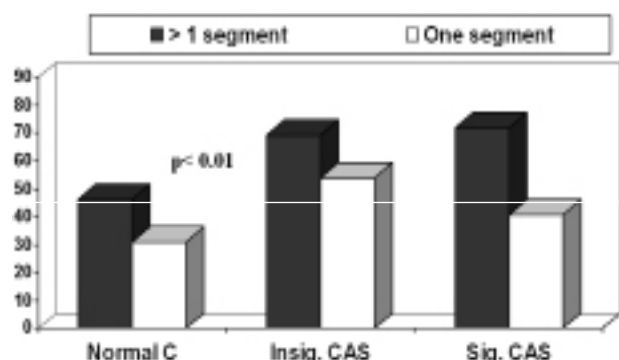


Figure 1: Prevalence of stenotic arterial segment in the lower limb arteries among the studied groups.



**Figure 2:** Prevalence of affected number of segments in the lower limb arteries among the studied groups.

### 8-Carotid Duplex

Nine patients had hypoechoic plaques, 3 of them were in group B and 6 in group C. Calcific plaques were found in 62 patients, while the prevalence of increased intimal-medial thickness in group A was 3 patients out of 39.

**Table 1:** Demographic features of the studied groups

	Normal CA (n= 39)	Insig. CAS (n= 39)	Sig. CAS (n= 32)	p value
Age				
Range	43-75	38-82	41-83	
Mean	60.36 ± 6.94	62.21 ± 7.59	62.78 ± 14.27	NS
Sex				
Male	33/39 (84.6%)	35/39 (89.7%)	29/32 (90.6%)	NS
Female	6/39 (15.4%)	4/39 (10.3%)	3/32 (9.4%)	NS

**Table 3:** Laboratory data of the studied groups.

	Normal CA (n= 39)	Insig. CAS (n= 39)	Sig. CAS (n= 32)	P value
FBS	145.2 ± 77.2	192.3 ± 72.3 <sup>a</sup>	239.7 ± 88.7 <sup>b,c</sup>	<sup>a</sup> p< 0.05 vs control <sup>b</sup> p< 0.01 vs control <sup>c</sup> p< 0.05 vs Insig.
PP	213.1 ± 62.9	274.9 ± 101.2 <sup>a</sup>	346.6 ± 151.0 <sup>b,c</sup>	<sup>a</sup> p< 0.05 vs control <sup>b</sup> p< 0.01 vs control <sup>c</sup> p< 0.05 vs Insig.
Na	139.2 ± 11.6	138.5 ± 6.3	138.8 ± 8.3	NS
K	4.3 ± 0.6	4.3 ± 0.4	4.6 ± 1.2	NS
Urea	37.4 ± 12.9	50.6 ± 33.9	56.0 ± 34.8 <sup>a</sup>	<sup>a</sup> p< 0.05 vs control
Creatinine	1.2 ± 0.4	1.45 ± 0.6	2.35 ± 2.8 <sup>a</sup>	<sup>a</sup> p< 0.05 vs control
Uric acid	6.3 ± 1.9	6.9 ± 2.1	7.6 ± 1.9 <sup>a</sup>	<sup>a</sup> p< 0.05 vs control
SGOT	27.7 ± 20.3	25.2 ± 13.6	30.4 ± 2.24	NS
SGPT	26.3 ± 17.2	25.2 ± 18.1	27.7 ± 30.2	NS
Albumin	2.37 ± 1.28	2.83 ± 0.72	1.9 ± 0.67 <sup>a</sup>	<sup>a</sup> p< 0.05 vs Insig.
Total protein	6.97 ± 0.52	7.27 ± 0.63	7.07 ± 0.67	NS
ALP	76.13 ± 47.69	71.28 ± 21.81	85.84 ± 55.09	NS
Total bilirubin	0.48 ± 0.25	0.55 ± 0.31	0.68 ± 0.63	NS
Direct bilirubin	0.15 ± 0.06	0.21 ± 0.14	0.23 ± 0.23	NS
Cholesterol	184.39 ± 30.6	227.63 ± 63.2 <sup>a</sup>	274.1 ± 93.15 <sup>b,c</sup>	<sup>a</sup> p< 0.05 vs control <sup>b</sup> p< 0.01 vs control <sup>c</sup> p< 0.05 vs Insig.
TG	151.78 ± 101.6	215.9 ± 107.9 <sup>a</sup>	227.9 ± 110.0 <sup>b,c</sup>	<sup>a</sup> p< 0.05 vs control <sup>b</sup> p< 0.01 vs control <sup>c</sup> p< 0.05 vs Insig.
LDL	87.67 ± 27.69	110.31±37.25 <sup>a</sup>	134.53±57.89 <sup>b,c</sup>	<sup>a</sup> p< 0.05 vs control <sup>b</sup> p< 0.01 vs control <sup>c</sup> p< 0.05 vs Insig.
HDL	49.53 ± 25.35	66.95±22.45 <sup>a</sup>	86.0±38.9 <sup>b,c</sup>	<sup>a</sup> p< 0.05 vs control <sup>b</sup> p< 0.01 vs control <sup>c</sup> p< 0.05 vs Insig.

**Table 2:** Prevalence of risk factors among different studied groups.

	Normal CA (n= 39)	Insig. CAS (n= 39)	Sig. CAS (n= 32)	p value
Cerebral manifestation				
-ve	38/39 (97.4%)	34/39 (87.2%)	26/32 (81.3%)	
+ve	1/39 (2.6%)	5/39 (12.8%)	6/32 (18.7%)	NS
Carotid bruit				
-ve	36/39 (92.3%)	30/39 (76.9%)	20/32 (62.5%)	
+ve	3/39 (7.7%)	9/39 (23.1%)	12/32 (37.5%)	< 0.01
Neck veins congestion				
-ve	37/39 (94.9%)	37/39 (94.9%)	24/32 (75%)	
+ve	2/39 (5.1%)	2/39 (5.1%)	8/32 (25%)	< 0.01
S3				
-ve	37/39 (94.9%)	37/39 (94.9%)	24/32 (75%)	
+ve	2/39 (5.1%)	2/39 (5.1%)	8/32 (25%)	< 0.01
ECG				
-ve	16/39 (41.0%)	25/39 (64.1%)	12/32 (37.5%)	
+ve	23/39 (59.0%)	14/39 (35.9%)	20/32 (62.5%)	< 0.05
Hypertension				
-ve	9/39 (23.1%)	5/39 (12.8%)	6/32 (18.7%)	
+ve	30/39 (76.9%)	34/39 (87.2%)	26/32 (81.3%)	NS
Smoking				
-ve	8/39 (20.5%)	5/39 (12.8%)	7/32 (21.9%)	
+ve	31/39 (79.5%)	34/39 (87.2%)	25/32 (78.1%)	NS
Family history				
-ve	29/39 (74.4%)	22/39 (56.4%)	18/32 (56.3%)	
+ve	10/39 (25.6%)	17/39 (43.4%)	14/32 (43.7%)	NS

## DISCUSSION

Atherosclerosis is still the leading cause of death in the world. It is universally accepted that atherosclerosis is a systemic disease involving the large and medium-sized arteries (10). Peripheral vascular disease (PVD) is common, with an age adjusted prevalence of 12% to 20% of adult<sup>6</sup>, 20% of claudicates progress to critical limb Ischemia (CLI) with one fourth of them resulting in Amputation (11). The mortality rates increase with the severity of PVD as assessed by symptoms (6), critical limb Ischemia carries at least 30% risk of death within 5 years and almost 50% within 10 years, primarily due to myocardial Infarction (60%) or stroke (12%) (12). Stroke is currently the third leading cause of death in the developed countries, preceded by heart disease and cancer (13). Furthermore, many of stroke victims who are alive today suffer severe disability (14) and require continued medical care when they are discharged from hospital.

The risk of ischemic stroke distal to an atherothrombotic carotid stenosis increases with the degree of stenosis. The main mechanism of stroke is thought to be embolism from fissured or ruptured plaque (15). In the Egyptians population the prevalence of significant cervical carotid artery stenosis was 18% among patients with ischemic strokes (16). There was a difference between Egyptians and Caucasians concerning distribution of cervical and cerebral atherosclerotic lesions (17,18,19). Stroke risk factors are classified as nonmodifiable and modifiable. Fortunately the list of nonmodifiable risk factors is small: advanced age, male gender. Conversely, the modifiable risk factors for stroke are more extensive hypertension, smoking, diabetes, hypercholesterolemia, heart disease, peripheral artery occlusive disease (PAOD).

In the current study, there was no statistically significant difference in the age of the three studied groups. This may be attributed to that all patients suffering from critical limb ischemia were relatively old (mean age of most of them was more than 60 years old) so age is a risk factor for all patients who had arterial atherosclerosis. This result was in agreement with those who reported that age is a powerful independent risk factor for arterial atherosclerosis and there was a strong relationship between mortality rates and the age of the patients (20,21). In the current study we found that the prevalence of hypertension in patients with Critical Limb Ischemia was a statistically no significant difference in blood pressure (hypertension) between the three groups. 75% of patients in the three groups had hypertension. This result was in agreement with those McMahon et al. (1994) who reported that hypertension is the most powerful and prevalent risk factor. And the decrease in DBP of 7.5 mm hg over time was associated with a 46% decline in stroke risk (22,23). In the current study, the prevalence of smoking in patient groups was more than 78%, but there were no statistically significant difference between them. Smoking is closely related to the top four leading causes of death, and has been clearly established as a biologically plausible and independent determinant of stroke through epidemiologic data and observational studies and remains a significant

determinant of atherosclerosis after adjusting for other factors (24). In a prospective, cohort study, middle-aged men who smoked more than 21 cigarettes per day were found to have a fourfold greater risk of stroke as compared with nonsmokers (25).

In the current study, we found the prevalence of diabetes mellitus to be more than 80% and there was a statistically significant increase in both fasting and post-prandial blood sugar in group C when compared to both group A and group B, At the same time, there was a statistical significant increase in fasting and post-prandial blood sugar in the group B when compared to group A (Table2).

Atherosclerosis and vasculopathy of the coronary, peripheral, and cerebral arteries are frequent complications of diabetes (26,27). The main source of thromboembolic stroke in patients with diabetes is the internal carotid artery (28). Furthermore, cohort studies have demonstrated an independent effect of diabetes on stroke risk factor after controlling for other risk factors, with relative risk ranging from 1.5 to 3.0 folds (29). This result was in agreement with those who reported that diabetes is high risk factor for CLI as prevalence of amputation increased eight folds than non diabetic patients (30). World Health Organization (WHO) reported that prevalence of diabetes among Arabian in stroke patients 14%-20% while in Europeans varied between 3%-10%. This result was in agreement with those who reported that found the prevalence of diabetes mellitus in stroke victims was 18% (31).

In the current study, carotid bruits was more prevalent in Group C (37.5%) ( $p < 0.01$ ), followed by Group B (23.1%) and finally Group A (7.7%). These results were in harmony with those of NASCET (1991) that reported the presence of cervical bruit had an approximately 60% sensitivity and specificity for high-grade carotid stenosis. In the presence of a carotid bruit in asymptomatic patients doubled the risk of stroke, the presence of a bruit may be a general marker for patients at higher risk of cerebrovascular events and majority of patients with carotid artery bruit have stenosis more than 50% (32).

In the current study, we observed that renal impairment was associated with significant lesion of carotid artery stenosis, these results were in agreement with those of who reported that high lipid level might promote the progress of the renal disease and uremic patients had accelerated atherosclerosis as incidence of IHD had two and half times more than non-uremic (33). In the current study we observed that hypoalbuminemia was significantly associated with carotid artery stenosis ( $P < 0.05$ ). This was in agreement with some investigators that reported an inverse association between serum albumin and carotid atherosclerosis among subjects with renal disease. Specifically, albumin was inversely related to carotid plaques among dialysis patients (34). These reports were in agreement with those of who reported that no association between serum albumin and carotid artery

in a community based population (35), and did not find an association between serum albumin and the prevalence of carotid plaque among subjects with chronic renal failure (36). Thus, although an inverse relation has been observed between albumin and carotid atherosclerosis among subjects with impaired renal function, no such relation has been reported in a community-based cohort.

In the current study, we have found the prevalence of dyslipidemia in our patients was to be more than 80%, in patients with CLI, there was statistically significant correlation between hypercholesterolemia, hypertriglyceridemia, LDL and HDL and carotid artery stenosis. Abnormalities of serum lipid have been regarded more as risk factors for coronary artery disease than for cerebrovascular disease. However, most prospective studies have found no association between serum cholesterol, PVD and cerebral infarction, although some have demonstrated a relationship (37). This was in agreement with some investigators that reported that have found that 38% of PVD and stroke victims had high cholesterol levels (38), while found the prevalence was 85% (31).

In patients with hyperuricemia, there was significantly more in group C than group A ( $P < 0.05$ ). This was in contradictory with the results of the (The Atherosclerosis Risk in Communities) ARIC study (1996). Several studies have not found association between hyperuricemia and atherosclerosis (25).

In the current study we found the prevalence ischemic heart disease was to be more than (55%).by using history and an ECG abnormality for IHD. The presence of IHD and heart failure were significantly correlated with the presence of carotid artery stenosis and its severity, these were that reported some investigators that 27% of their Egyptians patients with stroke and cervical carotid artery stenosis had history of IHD (17).

In patients with critical limb ischemia, both the number of stenosed arterial segments as well as the level of critical stenosed arteries (iliac versus superficial femoral artery versus infra-genicular) significantly correlated with the presence of carotid artery stenosis and its severity. This may be explained due to more progression of atherosclerosis process among patients with group B and C. This was concordant with who reported that peripheral arteries occlusive disease may be helpful to identify patients at high risk for sever carotid stenosis and have found the prevalence of PVD with stroke victims was 31% (31,39).

In conclusion: age is considered one of the risk factors for patients who had arterial atherosclerosis because all patients suffering from critical limb ischemia were relatively old. Smoking and hypertension was prevalent in more than 75% of patient groups, so it could be considered to be associated with an elevated risk of atherosclerosis. Diabetes mellitus, dyslipidemia, renal impairment, hyperuricemia, ischemic heart disease, hypoalbuminemia, auscultation of neck bruit,

site of stenotic limb artery and numbers of stenotic segments of limb artery were more prominent in a significant group so they may be used as predictors for carotid artery stenosis.

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