

Prevalence of Significant Carotid Artery Stenosis in Patients with Significant Atherosclerotic Peripheral Arterial Disease

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Abstract

Background: Peripheral arterial disease (PAD) and carotid occlusive disease (COD) are both known to be specific manifestations of atherosclerosis so can be correlated to each other. An important area of investigation is to identify those with significant carotid artery stenosis (CAS) to reduce the risk of cerebrovascular events. Duplex ultrasound scanning (DUS) is considered a valuable imaging modality to evaluate carotid arteries with high sensitivity and specificity and virtually non-existent hazards.

Objectives: We investigated the prevalence of significant CAS among patients with severe peripheral vascular disease (PVD) using carotid duplex.

Methods: A total of 50 patients with PVD diagnosed as having significant PAD by peripheral angiography (PA) underwent carotid duplex scanning. Data were collected concerning known risk factors. Significant CAS was defined as a stenosis of 70% or greater.

Results: The mean age was 61.6 ± 8.5 years, male (88%). Out of the 50 patients with significant PAD, 7 patients (14%) had significant Carotid Stenosis of which 6 patients (12%) had severe stenosis and 1 patient (2%) had totally occluded carotid artery. CAS was correlated with diabetes, hypertension, dyslipidemia, smoking, coronary artery disease and severity of symptoms. On multivariate analysis, Diabetes and Dyslipidemia seemed to have independent influence.

Conclusion: Significant CAS is prevalent among patients having significant PVD. Patients with PAD may be a suitable subgroup for screening for CAS using Carotid duplex, especially those with diabetes, dyslipidemia and positive CRP.

Keywords: Carotid artery stenosis; Carotid duplex; peripheral Arterial disease

Introduction

Atherosclerosis is a systemic disease; peripheral arterial disease (PAD) and carotid occlusive disease (COD) are both known to be specific manifestations of atherosclerosis. Given the common etiology of peripheral atherosclerosis occurring at different vascular sites, the presence of disease at one site increases the frequency of symptomatic and asymptomatic disease at another [1]. Because they both have a common cause, it is reasonable to hypothesize that they should correlate with each other to a certain extent, and previous studies have shown that there is a correlation between the prevalence of PAD and COD [2-5].

Carotid artery stenosis (CAS) is usually caused by an atherosclerotic process and is one of the major causes of cerebrovascular stroke (CVS) and transient ischemic attack (TIA) [6]. Ischaemic stroke has a major public health impact as the first cause of long-term disability and the third leading cause of death. Large artery atherosclerosis and specifically internal carotid artery stenosis, accounts for ~20% of all ischaemic strokes [7]. In the vast majority of cases, carotid artery stenosis is caused by atherosclerosis.

Carotid stenosis is usually diagnosed by carotid duplex scanning of both carotid arteries. Early detection of carotid occlusive disease will help in controlling cerebrovascular events as for each 10% increase in the degree of carotid stenosis [8].

The association between manifestations of atherosclerotic disease in various arterial beds has been evaluated in numerous studies employing several types of study design. The rationale for expecting a correlation among different arterial beds is the systemic nature of atherosclerosis.

Specifically, peripheral arterial disease (PAD) and carotid occlusive disease (COD) have been evaluated to determine how they correlate with each other and with other manifestations of atherosclerosis [9].

An important area of investigation is to identify those with significant carotid artery stenosis (CAS) to reduce the risk of cerebrovascular events [10]. Carotid Duplex ultrasound scanning (DUS) is considered a valuable imaging modality to evaluate carotid arteries with high sensitivity and specificity and virtually non-existent hazards [11].

In this study, we performed carotid DUS on patients having significant atherosclerotic symptomatic PAD by peripheral angiography aiming to detect the prevalence of significant asymptomatic carotid artery stenosis.

Methods

Study subjects

The study was conducted on 50 patients who did peripheral

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Received February 03, 2017; Accepted March 21, 2017; Published March 24, 2017

Citation: Abu Arab TM, Ramzy AAEW, Ghareeb M (2017) Prevalence of Significant Carotid Artery Stenosis in Patients with Significant Atherosclerotic Peripheral Arterial Disease. J Cardiovasc Dis Diagn 5: 265. doi: [10.4172/2329-9517.1000265](https://doi.org/10.4172/2329-9517.1000265)

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Degree of stenosis (%)	Primary Parameters		Additional Parameters	
	ICA PSV (cm/sec)	Plaque estimate (%)*	ICA/CCA PSV Ratio	ICA EDV (cm/sec)
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50-69	125-230	≥ 50	2.0-4.0	40-100
≥ 70 but less than near occlusion	>230	≥ 50	>4.0	>100
Near occlusion	High, low, or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	Not applicable	Not applicable

Table 1: Spectral Doppler velocities and plaque estimate correlated with degree of ICA stenosis [13].

Variable	Study population (with significant PAD) (n=50)
Age (years), mean ± SD	61.6 ± 8.5
Male gender, no (%)	44 (88%)
Hypertension, no (%)	26 (52%)
Diabetes, no (%)	27 (54%)
Dyslipidemia, no (%)	23 (46%)
Smoking, no (%)	39 (78%)
FH of premature atherosclerosis, no (%)	20 (40%)
IHD, no (%)	24 (48%)
CRP>6mg/L, no (%)	8 (16%)
Clinical manifestation of PVD	
Limiting claudication, no (%)	45 (90%)
Rest pain, no (%)	
Night cramps, no (%)	32 (64%)
Skin changes, no (%)	12 (24%)
Ulcer, no (%)	6 (12%)
Gangrene, no (%)	3 (6%)
Amputation, no (%)	1 (2%)
Site of PAD affection	
Iliac, no (%)	1 (2%)
Superficial femoral, no (%)	29 (58%)
Popliteal, no (%)	11 (22%)
Infragenicular, no (%)	36 (72%)
Degree of stenosis found in peripheral angiography	
70%-79%, no (%)	6 (12%)
80%-89%, no (%)	35 (70%)
90%-99, no (%)	5 (10%)
Total occlusion, no (%)	28 (56%)
Unilateral affection, no (%)	44 (88%)
Bilateral affection, no (%)	6 (12%)

Table 2: Basic characteristics of the study population.

angiography in our center during the period from October 2014 to April 2015 and diagnosed as having significant peripheral arterial disease. The included patients were referred to our center complaining of symptoms and signs of PAD as limiting claudications, rest pain, ulceration, amputation, gangrene in lower limbs or necessitating limb salvage and peripheral angiography was done for each of them. Those patients with significant PAD underwent duplex scanning of their carotid arteries to detect asymptomatic significant carotid artery stenosis.

Patients with previous history of carotid artery stenosis, carotid endarterectomy, history of cerebrovascular stroke or TIA, patients having Contraindications to peripheral angiography such as renal impairment and patients with non-significant PAD were excluded from the study.

The study was approved by the local ethics committee; as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013 and all patients signed a written informed consent

for peripheral angiography, carotid duplex scanning and inclusion in a study.

Study methods

All patients were subjected to full medical history, clinical examination and laboratory assessment for age, gender, risk factors including hypertension, diabetes, dyslipidemia, smoking, family history of premature atherosclerosis (<55 years in males and 65 years in female), and history of ischemic heart disease (IHD). Symptoms and signs of PAD including limiting claudications, night cramps, rest pain, skin changes (hair loss, thickened brittle nails, shiny smooth skin, color and temperature changes), muscular atrophy, ulceration, gangrene and amputations. Symptoms and signs of neurological affection as lateralization, weakness, power and sensory affection were tested for exclusion from the study. Serum CRP was measured.

Peripheral angiography: All patients underwent peripheral angiography for visualization and assessment of both lower limb arteries starting from lower aorta down to dorsalis pedis and posterior tibial arteries. Each arterial level was examined for the degree of lumen stenosis, laterality whether it is unilateral or bilateral limb affection, Site of arterial affection (iliac, superficial femoral, popliteal, infra-genicular) and whether it is single or multiple lesions.

Only patients with significant peripheral arterial disease were included in the study with degree of stenosis ≥ 70% or total occlusion at single or multiple arterial levels.

Carotid duplex ultrasound: All patients with significant PAD underwent duplex scanning of their carotid arteries to detect significant internal carotid artery stenosis.

Standard protocols included carotid examination with a high-resolution linear array transducer (7 MHz or broad spectrum 5 MHz to 12 MHz). Three modalities were used: B-mode gray scale imaging, color flow Doppler, both on transverse and longitudinal planes, and spectral Doppler velocities on longitudinal planes. The study was started low in the neck by visualizing the common carotid artery along its longitudinal axis followed by examination of the internal carotid artery. The intima media thickness was measured and recorded at each level. The B-mode images were inspected for acoustic shadowing, bright echoes from plaques and regions of calcification, with plaques defined as echo structures encroaching into the lumen of the vessel and detecting the degree of stenosis as <50% mild stenosis, 50% to 69% moderate stenosis, 69% to 99% severe stenosis and >99% totally occluded [12,13]. The pulsed Doppler sample volume at each point was positioned either in the center of the artery or at the point that provides the greatest audible velocity change. During the examination, the audible characteristics of the velocity signals are noted. These characteristics are useful in detecting velocity changes associated with flow disturbances. Peak systolic velocity (PSV) was measured at common carotid, external and internal carotid arteries to detect the significance of CAS (Table 1) [13]. Significant carotid stenosis was defined as a stenosis of 70% or more of internal carotid artery [13].

Statistical analysis

Data was collected, revised, coded and entered to the statistical package for social science (SPSS) version 20 and the following was done: Qualitative data was presented as number and percentages while quantitative data was presented as mean, standard deviations, median and interquartile range. The comparison between two groups with qualitative data was done by using Chi-square test. Receiver operating characteristic curve was used to assess the best cut off point with a sensitivity, specificity, positive predictive value and negative predictive value.

The confidence interval was set to 95% and the margin of error accepted was set to 5% so the p-value was considered significant as the following, P>0.05: non-significant, P<0.05: significant and P<0.01: highly significant.

Results

The study included 50 patients who presented to our center with symptoms and signs of PAD. Peripheral angiography was done for each patient to prove significant PAD at least in one vessel. All patients underwent carotid duplex scanning to study the extent of carotid arteries affection and prevalence of significant carotid artery stenosis.

The mean age of the studied patients was 61.6 ± 8.5 years, 44 (88%) of them were males. Patients had multiple risk factors with more prevalence of Smoking (78%), Diabetes (54%) and HTN (52%) and about 50% of them had history of IHD. The main presenting complaint was limiting claudications (90%) followed by rest pain (64%) and night cramps (24%) (Table 2).

Peripheral angiography

It revealed significant multiple lesions with stenosis ranging from 70% to 100% with mean stenosis of 92.6% ± 9.27%, the most common affected site was infra-genicular (72%) followed by superficial femoral arteries (58%) then popliteal (22%) then iliac (2%). Six patients (12%) had bilateral peripheral affection and 56% had total occlusion of at least one vessel (Table 2).

Carotid duplex US scanning

It was done for all the studied Patients with significant PAD with almost all of them (48 patients (96%)) had increased IMT reaching to carotid artery plaques in 24 patients (48%) causing different degree of stenosis. 17 patients (71%) out of the 24 with carotid plaques had bilateral carotid affection indicating that bilateral carotid artery stenosis (CAS) is more prevalent than unilateral affection. Using PSV and

Variable	Study population (n=50)
Patients with normal carotid duplex, no (%)	2 (4%)
Patients with increased intima-media thickness (IMT), no (%)	24 (48%)
Patients with increased IMT and carotid plaques, no (%)	24 (48%)
Unilateral carotid plaque, no (%)	7 (14%)
Bilateral carotid plaques, no (%)	14 (28%)
Degree of carotid stenosis, no (%)	
Mild <50%	14 (28%)
Moderate 50%-69%	3 (6%)
Severe 70%-99%	6 (12%)
Total occlusion	1 (2%)
Peak systolic velocity (PSV) in patients with significant CAS cut-off value of 230 cm/sec (mean ± SD)	243 ± 9.75

Table 3: Carotid duplex data.

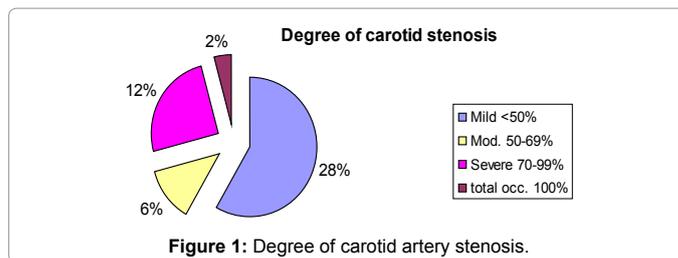


Figure 1: Degree of carotid artery stenosis.

Variable	Number of patients with carotid artery stenosis (CAS) (24 patients with carotid stenosis, 7 patients with ≥ 70% stenosis)	P-value
Prevalence of risk factors in relation to CAS, no (%)	(no=24)	
Hypertension (26)	15 (62.5%)	
Diabetes (27)	18 (75%)	
Smoking (39)	21 (87.5%)	
Dyslipidemia (23)	14 (58.3)	
FH of atherosclerosis (20)	10 (41.6%)	
IHD (24)	17 (70.8%)	
Risk factors in relation to laterality of CAS, no (%)	Unilateral (no=7)	Bilateral (no=17)
Hypertension (26)	4 (57.1%)	11 (64.7%)
Diabetes (27)	4 (57.1%)	14 (82.4%)
Smoking (39)	5 (71.4%)	16 (94.1%)
Dyslipidemia (23)	2 (28.6%)	12 (70.6%)
FH of atherosclerosis (20)	2 (28.6%)	8 (47.1%)
IHD (24)	4 (57.1)	13 (76.5%)
Number of risk factors to number of patients with carotid stenosis, no (%)	(no=24)	
1 risk factor	0 (0%)	
2 risk factors	3 (12.5%)	
3 risk factors	4 (16.7%)	
4 risk factors	8 (33.3)	
≥ 5 risk factors	9 (37.5%)	
Risk factors in relation to significant CAS, no (%)	(no=7)	
Hypertension (26)	6 (85.7%)	0.05
Diabetes (27)	7 (100%)	0.012
Smoking (39)	7 (100%)	0.17
Dyslipidemia (23)	7 (100%)	0.016
FH of atherosclerosis (20)	3 (42.8%)	0.86
IHD (24)	6 (85.7%)	0.041
Relation to PAD affection, no (%)	(no=7)	
Unilateral affection	5 (71.4%)	
Bilateral affection	2 (28.6%)	
Iliac affection	0 (0%)	
Superficial femoral affection	6 (85.7%)	
Popliteal affection	3 (42.8%)	
Infragenicular affection	4 (57.1%)	
Relation to carotid plaque laterality, no (%)	(no=7)	
Unilateral carotid affection	0 (0%)	
Bilateral carotid affection	7 (100%)	

Table 4: Correlation between carotid artery stenosis and other parameters in patients with significant PAD.

plaque volume estimate as primary parameters to estimate the degree of carotid artery stenosis we diagnosed 7 patients (14%) having significant CAS (6 patients (12%) with $\geq 70\%$ stenosis and one patient (2%) had totally occluded carotid artery) with mean PSV of $243 \text{ cm/sec} \pm 9.75 \text{ cm/sec}$, so the prevalence of significant carotid artery stenosis in those patients with significant PAD in our study is 14% and if we added the group of patients that had $\geq 50\%$ carotid artery stenosis the prevalence will be 20% (Table 3 and Figure 1).

Carotid artery stenosis in relation to other parameters

All the 7 patients with significant CAS were males with mean age of 69.1 ± 4.02 years and had bilateral carotid affection. We found that most of the patients had multiple risk factors with smoking present in about 90% of the patients with CAS and 100% of patients with significant CAS, more than 70% of them had IHD and it was evident that adding risk factors increased the number of patients who had CAS. Moreover diabetes, dyslipidemia and hypertension were significantly prevalent in patients with significant CAS ($P=0.012, 0.016$ and 0.05 respectively).

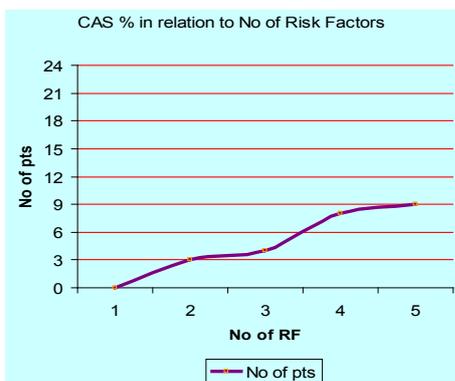


Figure 2: Carotid Stenosis in relation to number of risk factors.

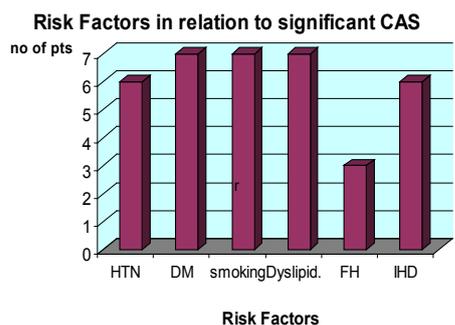


Figure 3: Risk factors in relation to significant CAS.

Also, risk factors were more profound in bilateral carotid affection (Table 4 and Figures 2 and 3).

The main presenting complaint that is significantly correlated with significant CAS was limiting claudication (P -value 0.008) and the most common affected site was superficial femoral artery in 6 (85.7%) out of 7 patients and this might be related to the size of arterial affection together with carotid arteries (Table 4).

Eight patients (16%) of the study group had high CRP more than 6 mg/L, studying those patients in depth revealed that all of them had bilateral carotid affection with 5 (62.5%) patients had significant CAS, 6 (75%) patients had total occlusion in their peripheral arteries, 6 (75%) patients had ≥ 4 risk factors and 6 (75%) patients had IHD indicating that those patients with high CRP represent the highest risk group of patients with extensive atherosclerosis in all vascular beds (Table 5).

Discussion

Peripheral arterial disease (PAD) and carotid occlusive disease (COD) are both known to be specific manifestations of atherosclerosis which is a generalized and progressive process. Because they both have a common etiology, it is reasonable to hypothesize that they should correlate with each other to a certain degree, and previous studies have shown that there is a correlation between the prevalence of PAD and COD. Patients referred to hospitals with symptomatic PAD often have symptomatic or asymptomatic manifestations of atherosclerosis elsewhere in the vascular system.

The risk of premature death in patients who have PAD is three times the risk in subjects without the disease [14]. The presence of co-existing cerebro-cardio-vascular disease increases the mortality in those patients with PAD, approximately 50% of the deaths are caused by myocardial ischemia, and 15% are caused by CVS [12].

We investigated the prevalence of significant carotid artery stenosis (CAS) in patients who had significant PAD and who were not yet known to have symptomatic carotid disease and who never had sustained (transient) cerebral ischemia. We also investigated which patient characteristics were associated with the presence of CAS.

An overall of 50 patients with significant PAD diagnosed by peripheral angiography were consecutively recruited into our study and carotid duplex scanning was done for all of them to detect the prevalence of significant CAS. Their mean age was 61.6 ± 8.5 years and most of them (88%) were males.

While analyzing the data obtained from the current study it is important to keep in mind the study population characteristics and the small number of the studied patients.

Carotid duplex scanning of our 50 patients with significant PAD revealed that 7 patients (14%) had significant CAS (6 patients (12%) had

HTN	DM	Smoking	Dyslip	FH	IHD	PAD		
						Degree of stenosis	Degree of stenosis	Laterality
Negative	Positive	Positive	Positive	Negative	Positive	100	100	Bilateral
Positive	Positive	Positive	Positive	Positive	Positive	100	76	Bilateral
Negative	Negative	Positive	Positive	Positive	Negative	100	30	Bilateral
Positive	Positive	Positive	Positive	Positive	Positive	100	70	Bilateral
Positive	Positive	Positive	Positive	Negative	Positive	85	73	Bilateral
Negative	Positive	Positive	Positive	Positive	Negative	100	30	Bilateral
Positive	Positive	Positive	Positive	Negative	Positive	80	30	Bilateral
Positive	Positive	Positive	Positive	Negative	Positive	100	72	Bilateral

Table 5: Criteria of the eight patients with high CRP level among study group.

severe $\geq 70\%$ carotid stenosis and one patient (2%) had total occlusion of one carotid artery) i.e., the prevalence of asymptomatic significant ($\geq 70\%$) CAS in patients with significant PAD in our study is 14% and if we added those three patients (6%) with 50-69 stenosis, the prevalence of $\geq 50\%$ CAS will be 20%.

The results of the correlation analysis comparing the severity of PAD with COD showed a modest but significant correlation between the two disease processes, which was hypothesized based on the amount of evidence demonstrating an overlap in the prevalence of PAD and COD. The findings of our study were also reported in other studies with similar design.

Mirsharifi et al. studied 54 consecutive patients with severe PVD admitted at a vascular surgery unit and underwent carotid duplex scanning in a prospective study. 17% of the patients had Significant CAS which was defined as a stenosis of $\geq 70\%$ and concluded that the prevalence of significant asymptomatic carotid artery stenosis (ACAS) is higher among patients with severe PVD, especially when hypercholesterolemia is present [3].

House et al. showed ACAS of $>50\%$ in 35% and $>70\%$ in 18% of patients with PVD of which 5% had an occluded carotid vessel at first presentation [15].

Klop et al. performed DUS to assess ICA disease in 416 consecutive patients with PVD. Major ICA disease, meaning $>70\%$ stenosis was found in about 15% [4].

Pilcher et al. conducted a study on 200 patients with PVD but no previous cerebrovascular history to determine the prevalence and severity of ACAS. A total of 50 patients (25%) were found to have CAS $>50\%$, with 27 (13.5%) of those having $>70\%$ stenosis. Bilateral CAS $>50\%$ was seen in 21 (10.5%) patients, of which 10 patients (5%) had bilateral stenosis of $>70\%$. No correlation was found between the significant CAS and severity of PVD or individual atherosclerotic risk factors [16].

Our Study revealed that 28% of patients with significant PAD were also having bilateral COD and significant CAS was more relevant in patients having superficial femoral arteries involved in the PAD which could be related to the size of the affected arteries. Also, limiting claudication was significantly correlated to significant CAS ($P=0.008$).

Inger et al. performed DUS on 53 patients with multiple risk factors of atherosclerosis and the results showed a clear relationship between the thickness of the intima-media complex in the common carotid artery and the prevalence of plaque in the carotid and femoral arteries. This may be interpreted as an expression of a generalized atherosclerotic process [17].

In our study, we also measured CRP level in patients with significant PAD and found that 8 patients (16%) had elevated CRP (>6 mg/L) of which 5 patients (62.5%) had significant carotid stenosis, those patients were having multiple risk factors, severe PAD with multiple lesions, bilateral carotid affection and IHD as well indicating advanced atherosclerosis in those highest risk group with positive inflammatory marker.

Jenkins et al. concluded that CRP may be predictive of the risk of developing symptomatic PAD independent of conventional risk factors [18] but further studies are needed to confirm its clinical utility in this regard with greater clinical relevance. Infact the circulating CRP levels appear to be of predictive value for cardiovascular events and mortality in patients with known PAD and may also be associated with disease progression and functional decline.

In our results, we studied the correlation between different risk factors present in patients with significant PAD and significant CAS; risk factors included (age, sex, HTN, DM, smoking, dyslipidemia and FH of premature atherosclerosis and IHD), we have found that DM ($P=0.012$), dyslipidemia ($P=0.016$), HTN ($P=0.05$) and IHD ($P=0.041$) were independently associated with significant CAS.

Cina et al. studied 620 neurologically free patients having PVD by carotid duplex. An occluded ICA was found in 4.8% of patients. The prevalence of CAS $>50\%$ was 33%. Age of more than 70 years ($p=0.007$), diabetes mellitus ($p=0.042$) were independently associated with CAS $>50\%$. They concluded that screening for CAS in asymptomatic patients with PVD is justifiable, but not mandatory, when two or more risk factors are present [19].

A study done by Rancic et al. on 109 patients with symptomatic lower extremities atherosclerosis underwent routine carotid DUS to detect the presence of ACAS. Forty patients (36.69%) had significant CAS $>60\%$, and 32 patients (29%) had CAS $>70\%$. They found that significant CAS was prevalent in hypertensive patients and those over 60 years [20].

Another study done by Ascher et al. they examined findings of carotid DUS in 307 patients aged 65 years and older referred to a vascular surgeon for problems other than carotid disease [21]. They found that more than 20% has asymptomatic significant CAS and this finding was evident in elder males, smokers and diabetics.

Kurvers et al. conducted a study to answer an important question about the candidate patients who need screening for CAS and abdominal aortic aneurysm (AAA), they concluded that the prevalence of CAS $>70\%$ was low in patients with risk factors for atherosclerosis (only 1.8% to 2.3%), intermediate in patients with coronary artery disease (3.1%), and highest in patients with PVD (12.5%) or AAA (8.8%). They concluded that screening for CAS should be limited to patients referred with PVD or AAA, especially those with advanced age or with low diastolic blood pressure [22].

Our finding of significant CAS in about 14% of patients with PVD is similar to other studies. The correlation between diabetes, hypertension, Dyslipidemia, FH of atherosclerosis, Smoking and IHD and the presence of significant CAS among our patients was done. Of these factors, Dyslipidemia, HTN, Diabetes and IHD showed independent influence. We believe that the results of this study support the idea that patients with severe PVD may be a suitable population to screen for CAS, especially in subgroups with multiple risk factors especially Dyslipidemia, Diabetes and positive CRP.

An important final issue to know is what to do further when we find significant CAS in order to prevent future cerebrovascular events, but actually the answer for this question is beyond the scope of this diagnostic study and a question should be raised to be answered in prospective clinical interventional trial for such patients. To our knowledge different guidelines for management of asymptomatic significant CAS state that those patients with more than 70% stenosis can be treated with carotid endarterectomy or stenting [23]. So, early diagnosis and treatment of asymptomatic significant CAS may help in preventing future CVS.

Study Limitations

The study is a single center with a small sample size. Tortuosity of the ICA due to kinking and coiling secondary to atherosclerosis may deliver a high PSV in carotid artery. In such cases, the absence of plaques

as a source of increased velocities must be confirmed on gray scale and color flow imaging. Heavily calcified plaques may act as a barrier to the ultrasound waves and may cause posterior acoustic shadowing, flow patterns immediately distal to the lesion should be observed.

Conclusion

Significant CAS is prevalent among patients having significant PVD. Our data and literature research emphasize that patients with PAD should undergo this quick, available and safe carotid artery ultrasound examination to detect (even asymptomatic) significant CAS, especially those with diabetes, dyslipidemia and positive CRP.

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