Is peripheral arterial disease associated with carotid artery disease in Egyptians? A pilot study

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Background
Atherosclerosis involves various vascular segments. The association of carotid artery disease (CAD) to peripheral arterial disease (PAD) is not well investigated in Egyptian patients.

Objective
In this pilot study, our aim was to examine the relationship between PAD and CAD in an Egyptian population.

Patients and methods
We examined 37 consecutive patients with PAD for the presence of CAD. Vascular and neurologic examination and duplex assessment of extracranial and intracranial carotid system and ankle–brachial index measurement were carried out to determine whether CAD is symptomatic or not.

Results
CAD was found in 20 (54.1%) patients. Eight (21.6%) patients had significant extracranial internal carotid stenosis and 13(37%) had intracranial stenosis and were more significantly above the age of 60 years. All patients with intracranial stenosis were men. PAD with RC6 was significantly associated with cerebrovascular events ($P = 0.001$) and significant extracranial stenosis ($P = 0.013$) and intracranial internal carotid stenosis ($P = 0.001$).

Conclusion
Intracranial and extracranial carotid stenoses are commonly present in patients with critical PAD. Duplex ultrasound screening for CAD presence and severity may be of great benefit, especially in the elderly and patients with critical limb ischemia. These findings need to be further confirmed in a study on larger population of Egyptians.

Keywords:
carotid stenosis, intracranial stenosis, peripheral arterial disease

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Introduction

Atherosclerosis is a complex disease that may involve multiple vascular segments and blood vessels such as the carotid, coronary, and peripheral arteries, and is the leading causes of morbidity and mortality all over the world. In the USA, almost 800 000 deaths are reported annually in relation to vascular events [1]. Atherosclerotic diseases are expected to be the leading cause of death in developing countries in the future [2].

Atherosclerotic changes in the carotid artery mirrors general atherosclerosis. Carotid artery disease (CAD) has been linked to increased risk for stroke, myocardial infarction, and death from coronary artery disease, which may occur alone or simultaneously [3]. Carotid artery evaluation using B-mode ultrasound and duplex imaging can relate to cardiovascular disease events, and the progression of atherosclerosis, measuring not only carotid structural alterations but also reflecting the severity of arterial damage in other vascular territories such as the peripheral arterial system [4].

This pilot study aimed to examine the relationship between peripheral arterial disease (PAD) and cerebrovascular disease in an Egyptian population.

Patients and methods

In this pilot study, we prospectively included 37 patients presenting to the Vascular Surgery Division, Kasr Al-Ainy University Hospitals with PAD. Patients with PAD due to causes other then atherosclerosis were excluded. This study was approved by the Cairo University research committee and all patients signed informed consent before enrollment.

Among clinical parameters recorded were age, sex, risk factors (smoking, diabetes mellitus, hypertension,

hyperlipidemia, obesity), prior history of stroke, transient ischemic attack (TIA) or neurological deficit by clinical examination (due to a cerebrovascular event), or ischemic heart disease. Patients with PAD were classified according to Rutherford categories (RCs) [5] (Table 1).

Doppler ultrasound evaluation included the following:

Duplex ultrasonography

All patients underwent duplex ultrasound examination of both extracranial and intracranial carotid systems by a single operator blinded to the clinical data. Cerebrovascular ultrasound examination was carried out using Philips HD15000 (Philips Healthcare, Amsterdam, The Netherlands) as follows:

(1) Extracranial carotid system [common carotid, internal carotid (ICA), and external carotid arteries] was examined using the linear array transducer of multifrequency (5–10 MHz), real time, sagittal, coronal, and axial views. Carotid system was examined by using the following:
(a) B-mode imaging of the arterial wall (intimal–medial thickness, plaque, stenosis, obstruction, or other pathologies).
(b) Color-coded B-mode imaging for further analysis of pathology.
(c) Doppler flow analysis:

According to the clinical significance of the duplex findings, we divided our patients into three groups [6]:

(i) Group 1: normal, mild increased intima-media thickness (IMT), stenosis less than 50% (provided the plaque was not complicated).
(ii) Group 2: stenosis 50–69%.
(iii) Group 3: stenosis greater than 70%.

(2) Intracranial carotid system was examined using the transcranial color-coded duplex examination (Philips HD15000).

Ankle–brachial index measurement

Ankle-brachial index (ABI) is an easy way to compare the systolic pressure of the upper extremity with that of the affected lower extremity. The systolic pressure in the pedal arteries (dorsalis pedis or posterior tibial) was measured using a handheld 5-MHz Doppler probe and a blood pressure cuff. The higher of these two measurements was compared with a similarly taken brachial artery systolic pressure. A ratio (ankle/brachial) of 0.9 or less is considered a sign of impaired flow to the extremity [7]. A normal resting ABI does not exclude PAD. In patients with mild or very proximal occlusive lesions, pulses may be palpable at rest. Exercise testing increases the sensitivity of the ABI [8]. Patients were classified according to ABI into four categories:

(1) I < 0.9–0.7 (mild PAD).
(2) II < 0.7–0.5 (moderate PAD).
(3) III < 0.5–0.3 (severe PAD).
(4) VI < 0.3–0 (impending gangrene).

Management of CAD was in accordance to the international guidelines based on the data from NASCET [9], ECST [10], ACAS [11], where asymptomatic patients with ICA stenosis greater than 70% and symptomatic patients with ICA stenosis greater than 50% underwent carotid revascularization by carotid endarterectomy or carotid stenting. Patients with lesser degrees of stenosis received best medical treatment in the form of antiplatelet therapy, lipid-lowering agents, and control of blood pressure and diabetes mellitus. PAD was managed with an open surgery or endovascular interventions according to lesion morphology and patient's fitness.

Table 1 Rutherford classification of peripheral arterial disease

Grades	Categories	Clinical findings
Stage 0	RC0	Asymptomatic
Stage 1	RC1	Mild claudication
Stage 2	RC2	Moderate claudication
Stage 3	RC3	Severe claudication
Stage 4	RC4	Ischemic rest pain
Stage 5	RC5	Minor tissue loss
Stage 6	RC6	Severe ulceration or gangrene

RC, Rutherford category.

Statistical analysis

All statistical calculations were carried out using computer program statistical package for the social sciences (SPSS, version 15 for Microsoft Windows; SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean±SD, or frequencies (number of cases), and percentages according to type of data. Comparison of numerical variables between the study groups was done using Student's '*t*' test for independent samples. χ^2-Test was performed for comparing categorical data. Exact test was used instead when the expected frequency was less than 5. Correlation between various variables was determined using Spearman's rank correlation equation. *P* values less than 0.05 were considered statistically significant.

Results

The study included 29 (78.4%) male and eight (21.6) female PAD patients with a mean age of 60.41±8.72 years. Table 2 shows patients' demographic data and risk factors. Rest pain was the most frequent presentation

(RC4) occurring in 19 (51.4%) patients, as shown in Fig. 1, and infrapopliteal block was the most frequent site of arterial occlusion (n = 21, 57.76%) followed by femoropopliteal (n = 15, 40.5%), and then iliofemoral (n = 1, 2.7%), as shown in Fig. 2.

CAD was found in 20 (54.1%) patients. This proportion included a spectrum of pathologies ranging from increased IMT to high-grade stenosis. Eight (21.6%) patients had a significant degree of extracranial ICA stenosis (group 2+group 3). They included six (16.2%) patients in group 2 and two (5.4%) patients in group 3 with significantly more patients above the age of 60 years (n = 7, P = 0.017) and no sex difference (P > 0.05). There was no association between smoking, hypertension, diabetes, history of TIA/stroke, ischemic heart disease, obesity nor hyperlipidemia, and extracranial ICA stenosis (P > 0.05). Hyperlipidemia (n = 27) was the nearest to significance (P = 0.057).

All patients with moderate to severe grades of extracranial carotid stenosis in group 2 and group 3 had critical limb ischemia (RC4, RC5, and RC6). There was significant association between extracranial ICA stenosis and higher RCs (RC4, RC5, RC6, collectively; P = 0.044), but when comparing individual categories, only association to RC6 was significant (n = 4, P = 0.013).

Extracranial ICA stenosis showed no statistically significant association with lower ABI categories (P > 0.05) although ABI was significantly lower in patients with RC4–RC6 (P = 0.041) and significantly correlated to RCs (r = 0.515, P = 0.001) and grade of carotid disease (r = 0.356, P = 0.03).

Critical lower limb ischemia RC6 was significantly associated with prior history of ischemic cerebrovascular events (P = 0.009; Table 3).

Out of 37 patients, 13 (35.1%) had intracranial stenosis. Intracranial stenosis was significantly more frequent in patients aged 60 years or more (n = 10, P = 0.014) and all patients were males (P = 0.019). Intracranial stenosis was significantly associated to history of prior ischemic cerebrovascular events (n = 7, P = 0.048), critical limb ischemia RC6 (P = 0.001) (Table 4), and the presence of high grades of carotid artery stenosis in group 2 and group 3 (P < 0.0001; Table 5).

Presence of diabetes mellitus was significantly associated with intracranial stenosis (P = 0.024), history of ischemic cerebrovascular events (P = 0.043),

Table 2 Patients' demographic data and risk factors

Demographic data and risk factor	*N* (%)
Sex	
Male	29 (78.4)
Female	8 (21.6)
Smoking	
Never smoker	10 (27)
Light smoker (<1 packet/day)	3 (8.1)
Heavy smoker	24 (64.9)
Hypertension	10 (27)
Diabetes mellitus	22 (59.5)
Obesity	7 (18.9)
History of stroke or TIA	12 (32.4)
Ischemic heart disease	16 (43.3)
Family history of PAD	14 (37.7)

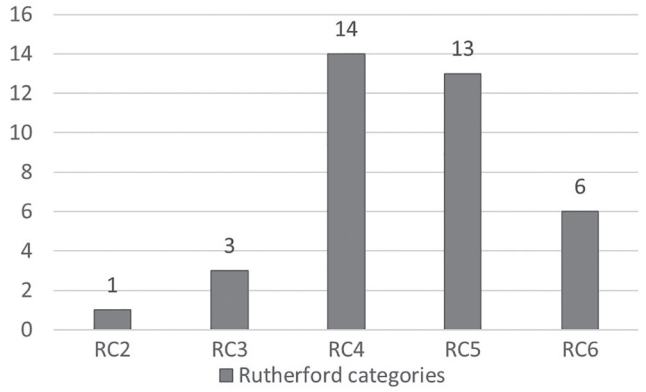
PAD, peripheral arterial disease; TIA, transient ischemic attack.

Table 3 Relationship of different grades of critical lower limb ischemia to occurrence of ischemic cerebrovascular event (transient ischemic attack/stroke)

Occurrence of ischemic cerebrovascular event	RC4	RC5	RC6	*P*
TIAs/stroke	3	3	5	0.009*
No TIAs/stroke	11	10	1	
Total	14	13	6	

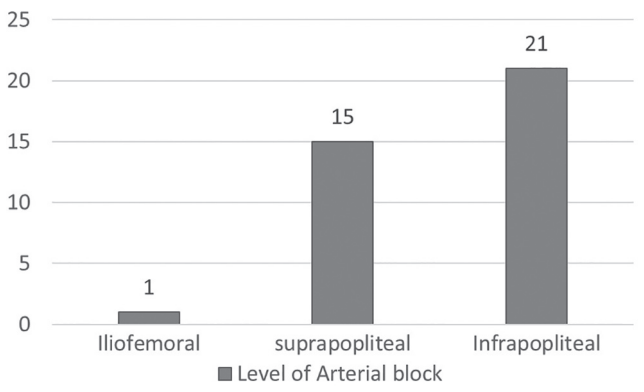
RC, Rutherford category; TIA, transient ischemic attack,
*Significant at P < 0.01

Figure 1



Distribution of the presentation according to Rutherford categories.

Figure 2



Level of arterial occlusion.

Table 4 Relation of intracranial stenosis to critical limb ischemia

Presence of intracranial stenosis	Rutherford category					Total	*P*-value
	RC2	RC3	RC4	RC5	RC6		
No intracranial stenosis	0	1	11	12	0	24	0.001*
Intracranial stenosis	1	2	3	1	6	13	
Total	1	3	14	13	6	37	

RC, Rutherford category, *Significant at $P < 0.01$.

low ABI (P = 0.037), and critical limb ischemia RC6 (P = 0.032). There was no association between smoking, hypertension, ischemic heart disease, obesity, and hyperlipidemia, and intracranial stenosis (P > 0.05).

Table 5 Relation of intracranial stenosis to different grades of extracranial artery disease

Presence of intracranial stenosis	EC carotid artery disease			Total	*P*-value
	Group 1	Group 2	Group 3		
No intracranial stenosis	24	0	0	24	<0.0001*
Intracranial stenosis	5	6	2	13	
Total	29	6	2	37	

EC, extracranial, *Significant at $P < 0.01$.

Discussion

A total of 37 Egyptian patients presenting with PAD were evaluated using carotid duplex ultrasonography for the presence of CADs. Results showed that extracranial CAD was related to severity of PAD. All patients with CAD in group 2 and group 3 (n = 8) had critical limb ischemia (RC4, RC5, RC6). A relatively high proportion of patients with intracranial stenosis (n = 10) had critical limb ischemia.

Atherosclerotic ischemic diseases such as cerebrovascular disease, coronary artery, disease and PAD often exist together. Carotid duplex ultrasonography is an accuracy-proven noninvasive diagnostic examination used to detect asymptomatic carotid artery stenosis, which is relatively high in PAD, and thus it can be helpful for screening population at risk [12].

The risk of stroke is substantially increased in PAD patients, and PAD is a strong independent predictor for stroke [13]. In our study, there was a significant association between PAD and prior history of ischemic cerebrovascular events (stroke/TIA).

Distribution of PAD in our patients was as follows: arterial block was mainly at infrapopliteal level (n = 21, 57.76%), followed by femoropopliteal (n = 15, 40.5%), and then iliofemoral (n = 1, 2.7%). Most of the patients presented with a RC4 (n = 14, 37.8%) and RC5 (n = 13, 35.1%). This pattern of presentation with mostly critical ischemia can be explained by the fact that most patients were referred for peripheral revascularization.

In our study, majority of the included patients were males (75.5%). A Korean study [12] showed similar male predominance (92.4%), yet it had a more or less different PAD presentation with 44.1% infrainguinal arterial disease, 34.1% aortoiliac disease, and 21.8% had combined lesions. This difference in presentation may be attributed to genetic and environmental factors.

Risk factors were distributed as follows: 64.9% of the patients were heavy smokers, 59.5% had diabetes mellitus, 43.3% had a history of coronary artery disease, 32.4% had a past history of stroke or TIA, 27% were hypertensive, and 18.9% were obese. In a meta-analysis of 19 studies by Ahmed and Al-Khaffaf [14], the most common atherosclerotic risk factor prevalent among patients in those studies was smoking (60%), followed by hypertension (47%), ischemic heart disease (34%), and diabetes mellitus (25.5%).

Duplex ultrasound scanning is considered a valuable imaging modality to evaluate carotid arteries, with high sensitivity and specificity and virtually nonexistent hazards, and is capable of differentiating between different phenotypes of carotid artery atherosclerosis, including increased intima–media thickness, plaque morphology, and carotid stenosis. These phenotypes will not necessarily have the same determinants or risk factors [15]. Duplex ultrasound remains an important tool to identify significant carotid artery stenosis, which may benefit from carotid revascularization irrespective of the ongoing debate and controversy on optimal management of asymptomatic carotid artery stenosis [16] with carotid endarterectomy as the present 'gold standard' treatment for suitable carotid stenosis, and carotid artery stenting procedures performed according to the specific characteristics of the patient and lesion [17]. Both procedures are better considered complementary rather than competing modes of therapy [18], each of which can be optimized with careful patient selection.

B-mode ultrasound examination of our patients who primary presented with PAD revealed CAD prevalence

in 54.1% of them, ranging from a simple increase in IMT to more severe pathologies like high-grade stenosis. Eight (21.6%) patients had significant carotid stenosis (≥50), yet severe carotid artery stenosis (≥70%) was found only in two (5.4%) patients. In a study of a series of 4733 Egyptians, extracranial carotid stenosis ≥50% represented 2.5% [19] and severe stenosis (≥70%) represented less than 1% of the study population, and we concluded that extracranial carotid stenosis is relatively rare among Egyptians, and yet higher percentage of patients with carotid stenosis (50–69%) in our study may be due to different selection criteria as our aim was to relate CAD to PAD. Yun *et al.* [12] in their study found the prevalence of asymptomatic CAD (≥70% stenosis or occlusion) in 13.8% of the Korean patients presenting with chronic atherosclerotic lower extremity ischemia. This later study included a larger sample size (340 patients) and represented a different population with possible influence of racial and environmental factors.

Previous studies disclosing a prevalence of carotid stenosis in PAD patients ranged from 5 to 24% [12,20–22]. Bavil *et al.* [23] reported that the prevalence of significant ICA stenosis (³70% ICA stenosis but less than near occlusion) in Iranian patients with PAD is low (4.2%). These results are more or less close to ours. Close geographic distribution and racial similarities may have contributed to this similarity.

Patients with asymptomatic PAD have a significantly increased risk compared with patients without PAD. PAD is an indicator for generalized atherosclerosis, and has a high prognostic value in primary care. Early form of PAD has been underestimated, underdiagnosed, and undertreated [24]. A study conducted by Miura *et al.* [25] found that ~70% of the patients with polyvascular disease had been underdiagnosed and were asymptomatic or had atypical symptoms, despite being at an increased risk for morbidity and mortality, justifying the use of systematic screening with duplex ultrasound and ABI for identifying patients at a high risk for cardiovascular events.

In contrast, a study to detect asymptomatic PAD with vascular events in patients with stroke or TIA showed that 'an abnormal ABI is prevalent in approximately one-fourth of the patients with cerebrovascular disease and identifies population at high risk of cardiovascular events over a median of 2 years'. Thus, ABI measurement can be an appropriate measure for screening patients with stroke/TIA at a high risk for peripheral vascular events [26].

In the present study, there were no significant difference in distribution of patients with and without significant extracranial carotid stenosis among ABI categories. Yet, there was a statistically significant correlation between the grade of carotid stenosis and lower ABI (P = 0.3). In addition, all patients with moderate to severe grades of carotid stenosis in group 2 and group 3 had critical limb ischemia (RC4, RC5, and RC6). This finding indicates that CAD, if present in PAD patients, would tend to be a critical pathology that will probably need intervention or may carry a higher risk and morbidity with poor prognosis.

Extracranial CAD was not significantly associated with hyperlipidemia. This contradicts previous studies that confirm the strong relation between this risk factor and CAD [27,28]. However, Yun *et al.* [12] failed to demonstrate such an association, although they included only asymptomatic CAD as inclusion criterion.

Despite its wide distribution in patients (59.5%), diabetes was not associated with extracranial CAD. This is in agreement with the results of previous studies [12,23] and might be explained on genetic or environmental basis. Yet this disagrees with the results of a study by Cina *et al.* [28]. Larger numbers of patients included in the latter study may explain this difference.

In our study, no statistically significant association was found between CAD and coronary artery disease. However, Yun *et al.* [12] found that critical ICA stenosis was more common in patients with coronary artery disease [6]. In addition, Shirani *et al.* [29] found carotid artery stenosis greater than 60% in 7% of the coronary artery bypass graft candidates. This difference may be attributed to the fact that Egyptians may have different cerebrovascular pathology with a predominance of intracranial stenosis [30].

Ischemic cerebrovascular events showed a statistically significant association with critical lower limb ischemia RC6 (P = 0.009) and intracranial stenosis (P = 0.048) but not to CAD greater than or equal to 50%. Cina *et al.* [28] found that carotid stenosis greater than or equal to 50% was associated with a history of stroke (P = 0.01). Patients with severe lower limb ischemia must be closely monitored to avoid cerebrovascular stroke (CVS) whether CAD was found or not and in presence or absence of carotid bruit [31].

Intracranial stenosis was positive in 35.1% of our PAD patients. A study conducted by Tawfik *et al.* [30] showed that Egyptians had more intracranial stenosis. Extracranial vessels might be distinct from intracranial ones by their response to atherosclerotic risk factors. This finding was in contrast to that of a study by

Watanabe *et al.* [32], in which they showed that subclinical atherosclerosis of the femoral artery was strongly related to the presence of extracranial disease but not intracranial disease. In addition, racial and environmental factors may have played a role.

Intracranial stenosis showed a statistically significant association to critical limb ischemia, mainly RC6 (P = 0.001) and extracranial carotid stenosis group 2 and group 3 (P = 0.048). Ratanakorn *et al.* [33] showed that patients with PAD had an increased frequency of concomitant cerebrovascular events because of intracranial stenosis and that concomitant vascular disease (in general) commonly coexists. In their study, Li *et al.* [34] reported that patients with intracranial stenosis are strongly associated with a history of previous ischemic stroke.

In our study, both extracranial and intracranial stenosis occurred more frequently in patients aged more than 60 years. Su *et al.* [35] in their study found that asymptomatic intracranial stenosis was more frequent in patients aged more than 70 years, suggesting a significant impact of age on vascular pathology.

In our study, all patients with intracranial stenosis were males. The relationship between intracranial stenosis and sex is still controversial. Some studies reported female predominance, whereas other studies showed more prevalence in men, especially at younger ages [36,37].

Conclusion

Intracranial and extracranial carotid stenoses are commonly encountered in patients with PAD and may be related to PAD severity. This highlights the importance of duplex ultrasound screening for CAD presence and severity, especially in the elderly and patients with critical limb ischemia. The findings of this study and relationship between PAD and CAD with respect to vascular risk factors need to be further confirmed in a study of larger sample of Egyptians.

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Conflicts of interest

There are no conflicts of interest.

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