RESEARCH ARTICLE

Relationship between symptomatic lower limb peripheral artery disease and calcified carotid artery plaque detected on panoramic images of neurologically asymptomatic males

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Objective: Males with peripheral arterial disease (PAD) are at high risk of ischaemic stroke given that atherogenic risk factors for both diseases are similar. We hypothesized that neurologically asymptomatic males diagnosed with PAD would demonstrate calcified carotid artery plaques (CCAP) on panoramic images (PI) significantly more often than similarly aged males not having PAD.

Methods: Investigators implemented a retrospective cross-sectional study. Subjects were male patients over age 50 diagnosed with PAD by ankle-brachial systolic pressure index results of ≤ 0.9 . Controls negative for PAD had an ankle-brachial systolic pressure index > 0.9 . Predictor variable was a diagnosis of PAD and outcome variable was presence of CCAP. Prevalence of CCAP amongst the PAD+ patients was compared to prevalence of CCAP among PAD- patients. Descriptive and bivariate statistics were computed and p -value was set at 0.05.

Results: Final sample size consisted of 234 males (mean age 72.68 ± 9.09); 116 subjects and 118 controls. Among the PAD+ cohort, CCAP+ prevalence rate (57.76%) was significantly ($p = 0.001$) greater than the CCAP+ rate (36.44%) of the PAD- (control). There was no significant difference in atherogenic “risk factors” in the PAD+ cohort between CCAP+ and CCAP- subjects.

Conclusion: We demonstrated that CCAP, a “risk factor” for future stroke and “risk indicator” of future myocardial infarction is seen significantly more often detected on the PIs of older male patients with PAD than among those without. Dentists treating patients with PAD must be uniquely vigilant for the presence of CCAPs on their patients’ PI.

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Introduction

Peripheral artery disease (PAD), a manifestation of a generalized atherosclerotic process evidences plaques

narrowing the arteries in the lower extremities. Ischaemic symptoms arising from a lack of blood flow (often heralded by weak or absent pulses) to the regional musculature, relative to its metabolic requirements, range from (1) pain in the lower limbs, buttocks, hips or thighs upon walking relieved by rest (intermittent

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claudication), (2) pain at rest (usually in soles of feet when elevated such as in bed), to (3) limb-threatening-gangrenous non-healing ulcers.¹ Risk factors most commonly associated with PAD include smoking, diabetes mellitus, hypertension, hyperlipidaemia, and age >70 years.² In healthy persons, blood pressure in the ankle is slightly higher than in the arm because of higher peripheral resistance at the ankle. However, in persons with partially occluded leg vessels, as in PAD, blood pressure readings in the ankle are lower than the arm.³ Specifically, the diagnosis of PAD is facilitated by the resting ankle-brachial systolic pressure index (ABI); formally described as the ratio of the systolic blood pressure in the ankle divided by the systolic blood pressure measured in the arm's brachial vessel.⁴ An ABI ≤ 0.9 is diagnostic for PAD⁴ but is also often substantiated by arterial duplex ultrasonography, CT angiography (CTA) angiogram (Figure 1), magnetic resonance angiography, and standard angiography which are capable of demonstrating the specific anatomic location and severity of the obstruction.⁵

Studies in the United States⁶ have identified more than 5 million Americans with PAD, and studies in Europe⁷ have denoted more than 40 million individuals afflicted with the disease. Specifically, in Germany⁸ and in Sweden,⁹ 18% of individuals over age 65 suffer from PAD. These numbers have markedly risen over the past two decades because of an ageing population and the increasing prevalence of obesity-related diabetes.² Various studies looking at the natural history of PAD have shown the bulk of patient morbidity and mortality results from coexisting atherosclerotic lesions in the cerebral and cardiac distributions.¹⁰ Specifically, 30% of patients with PAD have or will develop cerebrovascular disease and 60% have or will develop ischaemic heart disease.¹¹ Furthermore, within 5 years of PAD diagnosis, 10–15% of patients with intermittent claudication will die from cardiovascular disease.¹²

Given the similarity of aetiological factors between PAD and carotid artery atherosclerosis, radiologists utilizing carotid ultrasonography have demonstrated that more than 60% of neurologically asymptomatic patients with PAD harbour carotid plaques causing $\geq 50\%$ luminal reduction in the bifurcation region and that their presence signifies significant risk of future ischaemic cerebrovascular and cardiovascular events.^{13–15} These findings suggest that dentists and oral and maxillofacial radiologists may have an opportunity to participate in the identification of high risk individuals having PAD by assessing their panoramic image (PI) for the presence of calcified carotid artery plaques (CCAP) (Figure 2). Prior studies have convincingly demonstrated that panoramically imaged carotid lesions are significant “risk factors” for cerebrovascular ischaemic events and “risk indicators” for future myocardial infarction.^{16,17}

The only previously reported project documenting an association between CCAP on PI and PAD was conducted among a cohort of older, mixed gender South

Figure 1 CTA of an 87-year-old male with bilateral intermittent claudication after half block of walking confirmed as PAD with a resting brachial-ankle index study of 0.4 in the left leg and an inaudible doppler reading in the right leg. Arrow (A) denotes multiple “tandem” SFA stenoses in the right leg; arrow (B) identifies a site of occlusion in the SFA in the left leg; and, arrow (C) indicates severe atherosclerotic disease in the tibial artery leading to complete occlusion of all three tibial vessels by mid-calf of the right leg. CTA, CT angiogram; PAD, peripheral arterial disease; SFA, superficial femoral artery.

Figure 2 The panoramic image of the same 87-year-old male with peripheral arterial disease. The image, which has been digitally enhanced with the manufacturer's provided software, shows bilateral calcified carotid artery plaque (arrows) anterior to the fourth cervical vertebrae.

Koreans. That study limited its determinations to documenting the prevalence of PAD (5.5%) among those individuals having an atheroma on their panoramic image.¹⁸ However, there have never been any previously published studies documenting the prevalence of CCAP on PIs among individuals with PAD. Given the absence of this very cogent information for our profession, as well as the possibility that ethnicity influenced the Korean results where cerebrovascular disease is the second leading cause of death¹⁹ (whereas in the United States, it is fifth,²⁰ we sought to determine the prevalence of CCAP among a cohort of neurologically asymptomatic older American male veterans with a diagnosis of PAD.

Methods and materials/Patients

Study design & patient sample

To address this research question, the investigators designed and implemented a retrospective cross-sectional study. The study was conducted in accordance with the Declaration of Helsinki guidelines. The study protocol was granted exemption status by the Institutional Review Board of the Veterans Affairs Greater Los Angeles Healthcare System and the need for informed consent from each subject was waived given the retrospective nature of the project.

Our study evaluated the medical centre's electronic medical records of all male patients over age 50 who were treated between 1 January 2000 to 30 June 2018. Selected for further review were those records in which the patient offered a complaint of pain (exercise induced or at-rest) in their lower limbs.

To be included as a study subject (PAD+), the patient had to: (1) have an ABI ≤ 0.9 in either left or right lower limb, (2) a confirmatory doppler ultrasound study of their lower limbs, and (3) a PI (taken within the timeframe of 1 year before or 1 year after the ABI-measurement) which demonstrated, at a minimum, the area of interest: 2.5 cm inferior and 2.5 cm posterior to the cortical rim of the mid-point of the mandibular angle.^{21,22} All ABI and doppler limb ultrasound tests were conducted by a certified vascular laboratory technician utilizing a sphygmometer and Doppler ultrasound blood flow detector probes. The higher of the two systolic readings in the right and left arm (brachial artery) was used (to avoid bias owing to subclavian stenosis) in the assessment as was the higher of the four readings obtained from each foot's posterior tibial artery and dorsalis pedis arteries.^{3,4} A control group was constituted from the same pool of patients as the subjects. All individuals were enrolled in the control group if they were (1) over age 50, (2) had satisfactorily positioned PI utilizing the same criteria as above, (3) an ABI >0.9 in both limbs, and (4) doppler limb sonogram confirming absence of PAD.

Excluded from the study were: (1) females because of their paucity in the patient catchment, (2) patients with a history of prior transient ischaemic attack or stroke, (3) absence of either an ABI or doppler limb sonogram, (4) poorly positioned PI of non-diagnostic quality, and (5) cases in which the two clinicians differed as to the presence of CCAP.

Study variables and data source retrieval

The primary outcome measurement was the presence of CCAP on the PIs of subjects with and without PAD.

The panoramic images were captured using a Planmeca panorex unit and Romexis Pro 4.1.4 image transfer system (Planmeca OY, Helsinki, Finland). The images were viewed on Barco medical grade computer monitors (Barco Inc, Duluth, GA) in a darkened room. Images were enhanced using Romexis software to improve visibility of the area of interest by enlarging the area and/or increasing or decreasing the brightness and contrast. Evidence of CCAP was jointly determined by two oral and maxillofacial surgeons certified by the American Board of Oral and Maxillofacial Surgery using the American Academy of Oral and Maxillofacial Radiology-sponsored training packet.²² Of note, if these clinicians differed as to the diagnosis, rather than force consensus, the patient was dropped from the study in order to minimize discrepancies in data. These experienced clinicians, the senior author (AHF) having published more than 60 papers on the subject, and the research fellowship director (TIC) having published 15 papers on the subject, were masked as to the patient's medical history. Consistent with these guidelines, heterogeneous verticolinear radiopacities in close proximity to the hyoid bone, epiglottis, and in the vicinity of the intervertebral space C3-4 were diagnosed as CCAP. Special attention was given to rule out confounding radiopacities that lie in close proximity to the vessel such as the calcified elongated stylohyoid and stylomandibular ligaments, tonsilloliths, calcified triticeous cartilage and superior cornu of the calcified thyroid cartilage.²³

The secondary measurement assessed age, BMI, and the classical PAD “risk factors” for possible confounding influence on the outcome of CCAP. The “risk factors” included history of smoking, hypertension, hyperlipidaemia, and diabetes mellitus.

Data analysis

Population differences among the two groups based on PAD status (PAD+ vs PAD-) for diabetes mellitus, hypertension, smoking history, hyperlipidaemia, and prevalence of CCAP+ were investigated using χ^2 test and Fisher's Exact test, as appropriate. On the other hand, *t*-test was used for the comparison of means of age and BMI to determine if there was a significant difference between the PAD+ and PAD- groups.

Population differences between CCAP status (CCAP+ vs CCAP-) in the PAD+ cohort for diabetes mellitus, hypertension, smoking history, and hyperlipidaemia were tested using χ^2 test and Fisher's Exact test, as appropriate. On the other hand, *t*-test was used for the comparison of means of age and BMI to determine if there was a significant difference between the CCAP status groups. Multivariate analysis was carried out.

Logistic regression analysis was used to assess the odds of CCAP associated with PAD status accounting for probable confounders (*i.e.* “risk factors”). To quantify the degree of association, odds ratios (OR) with a 95% confidence interval (CI) was used. A univariate regression analysis was carried out to identify the

Table 1 Population characteristics

VARIABLE	Peripheral artery disease		<i>p</i> -value
	Present	Absent	
	<i>n</i> = 116	<i>n</i> = 118	
Age (years) (mean $\pm$ SD)	72.88 $\pm$ 8.66	72.49 $\pm$ 9.52	0.745
Range (years)	52–95	53–97	
BMI (mean $\pm$ SD)	28.63 $\pm$ 5.46	29.44 $\pm$ 6.23	0.2928
Range	17–46	19–53	
History of smoking, <i>n</i> (%)	90 (77.59)	68 (57.62)	0.001
Hypertension, <i>n</i> (%)	99 (85.34)	108 (91.52)	0.139
Hyperlipidaemia, <i>n</i> (%)	97 (83.62)	99 (83.90)	0.954
Diabetes mellitus, <i>n</i> (%)	55 (47.41)	61 (51.69)	0.513
CCAP prevalence	57.7%	36.44%	0.001

BMI, body mass index; CCAP, Calcified carotid artery plaque; SD, standard deviation.

probable confounders. All analyses were conducted using two-sided tests with α set at 0.05. Data were recorded in a deidentified fashion, and entered into a standardized electronic database. All statistical tests were performed using Stata/IC 15.1 for Mac (StataCorp LLC, College Station, TX).

Results

General population characteristics

Between 1 January 2000 and 30 June 2018, 42,876 male patients over age 50 were treated at the VA Medical Center. During this timeframe, 2071 male patients over age 50 were screened for PAD. Of these, 1757 patients were excluded because there were no PIs available. An additional 80 patients were excluded from the study due to history of prior transient ischemic attack or stroke (*n* = 11), absence of a lower limb doppler sonogram (*n* = 33), poorly positioned PI (*n* = 30), and cases in which the two clinicians differed as to the presence of CCAP (*n* = 6). The final sample of 234 male patients (mean age 72.68 $\pm$ 9.09) were enrolled in the project (Table 1). The study group consisted of 116 patients positive for PAD (PAD+) and the control group consisted of 118 patients negative for PAD (PAD-). The PAD+ group demonstrated a significantly (*p* = 0.001) higher population of patients with a history of smoking as opposed to the PAD- group (77.59 and 57.62% respectively). A total of 11 ABI values were missing from the study (*N* = 234) due to amputations of limbs, and therefore excluded from the mean analysis. No other atherogenic risk factors were significantly different between the PAD+ vs PAD- groups.

Primary outcome

The CCAP+ prevalence rate (57.76%) among the study (PAD+) group was significantly (*p* = 0.001) greater than the CCAP+ prevalence rate (36.44%) among the control (PAD-) group (Table 1). After conducting a

Table 2 Regression model: CCAP predicted by PAD

COVARIATE*	OR	SE	95% CI	p-value
Peripheral artery disease	2.230	0.61	1.30-3.81	0.003

CCAP, Calcified carotid artery plaque; CI, Confidence interval; OR, Odds ratio; SE, Standard error.

*Adjusted for smoking history

univariate regression analysis to identify the probable confounders, no covariates were found to modify the β coefficient greater than 10%. However, due to clinical suspicion, we adjusted our regression model for history of smoking. PAD+ patients showed significantly greater odds of having CCAP [OR: 2.230, 95% CI (1.30–3.81), $p = 0.003$] than those without PAD (Table 2).

Among PAD+ participants ($N = 116$), there was no statistically significant difference of atherogenic risk factors between CCAP+ and CCAP– patients (Table 3).

Discussion

The results of our study illustrated that older male veterans with PAD are significantly more likely to demonstrate CCAP on their PI than are a cohort of similarly aged male veterans free of the lower limb extremity artery disease. A positive history of smoking was the only classic atherogenic risk factor to significantly differentiate between the PAD+/subject cohort and the PAD-/control cohort. This results from cigarette smoking causing endothelial damage, arterial smooth muscle proliferation, inflammation, and increased sympathetic tone.²⁴

The study subjects in our project were all initially identified as having PAD because of a positive history of exercise induced or at rest lower limb pain, an ABI ≤ 0.9 , and a confirmatory Doppler lower limb ultrasound. The vascular surgery and imaging literature denotes that an ABI of ≤ 0.9 has a 95% sensitivity and 100% specificity for detecting haemodynamically significant stenosis ($>50\%$) in major leg vessels when compared

with angiography.² Such a value is also associated with having a plethora of atherosclerotic risk factors and for each decrement of 0.1 in ABI, mortality rates increase by approximately 13%, due to ischaemic cerebrovascular and cardiovascular events.^{25,26}

The results of our study, namely the positive association of carotid artery atheromas on dental PI's among patients previously diagnosed with PAD, may be explained through findings in the medical literature. A study conducted by the senior author (AHF) determined that 21% of those with atheromas on PIs had greater than 50% carotid artery stenosis.²⁷ Furthermore, Bez and Navarro²⁸ in Brazil conducted a prospective study among a mixed gender cohort ($N = 100$) of individuals having symptomatic (intermittent claudication, rest pain, or ulceration) PAD, and the prevalence of extracranial carotid artery atherosclerotic lesions in the bifurcation regions detected by echo-colour Doppler was 84% with significant stenosis ($\geq 50\%$ stenosis) noted in 40% of individuals, and severe in 17%. Similarly, Alexandrova *et al.*²⁹ in Canada, conducted a prospective study among a mixed gender cohort ($N = 373$) of individuals with peripheral vascular disease in which carotid artery duplex scanning identified 211 persons (57%) as having $\geq 30\%$ stenosis at the bifurcation with 67 of these patients having had a prior neurologic event (transient ischaemic attack or minor stroke). Most telling, however, was that in the neurologically asymptomatic group (114 of 211) 72 patients had haemodynamically significant (60%–90%) stenotic lesions placing them at risk of future stroke.

Ischaemic symptoms such as pain, aching, and fatigue or discomfort in the lower extremities brought about by exercise, and relieved by rest, is termed intermittent claudication. Stenotic atherosclerotic lesions are responsible for these symptoms because they result in an imbalance between supply and demand for oxygen-rich blood flow to the involved musculature. Ischaemic cramps and pain in the buttocks, hips and thighs arise because of stenotic lesions in the aorta and iliac artery. Similarly, pain in the thigh and upper two-thirds of the calf commence because of femoral arterial lesions, those in the lower third of the calf and ankle because of popliteal lesions and in the foot secondary to tibial lesions. Symptom severity ranges from mild pain to limb threatening gangrene.³⁰

Symptomatic treatment options for PAD include lifestyle modification such as smoking cessation, weight loss and exercise, administration of vasodilators (cilostazol, pentoxifylline), anti platelet medications (aspirin), and revascularization procedures (angioplasty, stenting, atherectomy, bypass grafting) or amputation for end-stage disease. Given the concomitant risk of stroke and myocardial infarction among patients with PAD, the integrity of the vascular distribution to brain and heart need also be evaluated. Management of atherosclerotic risk factors affecting the carotid and coronary vessels included metformin and insulin to control diabetes,

Table 3 Comparison of atherogenic risk factors between patients with peripheral artery disease

VARIABLE	Calcified carotid artery plaque		p-value
	Present <i>n</i> = 67	Absent <i>n</i> = 49	
Age (years) (mean $\pm$ SD)	73.40 $\pm$ 7.60	72.16 $\pm$ 9.97	
Range (years)	54–95	52–94	0.4487
BMI (mean $\pm$ SD)	28.41 $\pm$ 4.98	28.94 $\pm$ 6.09	
Range	17–40	17–46	0.6078
History of smoking, <i>n</i> (%)	56 (83.58)	34 (69.39)	0.070
Hypertension, <i>n</i> (%)	58 (86.57)	41 (83.67)	0.663
Hyperlipidaemia, <i>n</i> (%)	57 (85.07)	40 (81.63)	0.621
Diabetes mellitus, <i>n</i> (%)	30 (44.78)	25 (51.02)	0.506

BMI, body mass index; SD, standard deviation.

ACE inhibitors to control hypertension and statins to manage dyslipidaemia. These interventions also have positive effects on the PAD involved vessels.^{31,32}

Ascertainment of an ABI in all patients presenting with lower limb pain is critical as evidenced by all members of our project's control group who in fact had a negative test (ABI >0.9) for PAD. For it is not uncommon among older individuals to present with lower limb pain upon exertion which arises not because of vascular embarrassment, but rather because of lumbosacral radiculopathy such as degenerative joint disease, herniated discs, or spinal stenosis, as well as arthritis of the hip and knee.³³

The present study had limitations and strengths. The main limitations were that data derived were from a single centre, and the retrospective cross-sectional design which prevented us from proving a causal relationship between PAD and CCAP. Secondly, the sample population in our study may not be representative of the general population because the American military veteran population displays higher rates of cardiovascular disease because of aberrant behaviour associated with psychiatric and substance abuse disorders.^{33–36} Lastly, due to the retrospective nature of the study, the clinicians could not employ a duplex ultrasound to confirm the CCAP seen on PIs, which may have produced some bias. However, these biases were minimized due to masking of the clinicians. In terms of strengths, to the best of our knowledge, this is the first study to be

published in the dental literature that determined the prevalence of CCAP on the PIs of older males with PAD, thus, confirming the profession's responsibility to this vulnerable group of individuals. Follow-up consists of obtaining a consultation with the patient's physician and a carotid artery ultrasound study in order to determine appropriate secondary risk management treatment modalities directed towards control of cardiovascular risk factors and aberrant lifestyle, or on occasion, need for endarterectomy or carotid stent to manage critical stenosis.

In conclusion, we found that older neurologically asymptomatic males with PAD were significantly more likely to evidence calcified carotid artery atheromas on their panoramic image than a similarly aged population of male veterans without lower extremity artery disease. We further conclude that dentists must become familiar with PAD given that this vascular disorder is afflicting an ever-increasing number of individuals as societies age and the prevalence of obesity and related diabetes increases.⁶ Our profession has an opportunity when clinical findings indicate the need for dental imaging procedures to collaborate with primary care physicians in diagnosing vascular disease. If we diagnose vascular plaque and appropriately refer the patient, we enhance the likelihood of decreasing their cardiovascular risk. It must be emphasized, however that PIs should only be taken when dentally indicated and should not be taken to screen PAD+ patients for the presence of CCAP.

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