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Dobutamine stress echocardiography in patients with chronic peripheral artery disease

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Abstract---Background: peripheral artery disease (PAD) whether symptomatic or asymptomatic, is a risk factor for non-fatal and fatal coronary disease and cerebrovascular events, screening tests for early diagnosis of coronary artery disease (CAD) may lead to early treatment and therefore improved outcomes. AIM OF THE STUDY: is to study the relation between severity of peripheral artery disease by ankle-brachial index and myocardial ischemia by dobutamine stress echocardiography in patients free from cardiac symptoms Patients and Methods: fifty patients diagnosed with peripheral arterial disease (case group) and another fifty individuals without PAD (control group). Full history taking, complete physical examination, ECG, Echocardiography, ankle brachial index and dobutamine stress echocardiography were done to all patients. Results: Our study showed that there was a statistically significant higher percentage of distal lesion in patients with DM and higher percentage of proximal lesion among cases with hypertension with p-value <0.05. There was a statistically significant lower ABI level with p-value <0.05 among diabetic patients treated by insulin and ex-

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smokers and there was statistically significant invers correlation with p-value <0.05 between ABI level and smoking index. There was a positive correlation between ABI and APSV level on both sides with p-value <0.05.There was statistically significant invers correlation between ABI level and WMSI with p-value <0.05 and there was a statistically significant with p-value <0.05 in ABI degree of severity in different WMSI levels among cases with 80% of negative cases had moderate degree of ischemia by ABI and 90% of positive WMSI had sever degree of ischemia by ABI. Conclusion: Our findings showed that decrease ABI was significantly related to the presence of myocardial ischemia by DSE, it is reasonable to recommend doing DSE and ABI to patients with PAD to identify asymptomatic patients with peripheral artery disease at higher risk for CAD and as indirect predictor for CV events.

***Keywords*---**peripheral artery disease, ankle brachial index, cardiovascular disease coexisting with peripheral artery disease, dobutamine stress echocardiography.

Introduction

Individuals with peripheral artery disease (PAD) have an exceptionally elevated risk for cardiovascular events and the majority will eventually die of a cardiac or cerebrovascular etiology.

As PAD represents a local manifestation of systemic atherosclerosis and portends a 2-6 fold increase in both cardiovascular and cerebrovascular events. The diagnosis is also associated with an annual mortality rate of 4-6%. In addition to causing lifestyle limiting claudication symptoms, uncontrolled disease can progress on to critical limb ischemia the end stage of PAD. [1]

The coexistence of coronary artery disease (CAD) and PAD was described since 1960. PAD whether symptomatic or asymptomatic, is a risk factor for non-fatal and fatal coronary disease and cerebrovascular events. [2]

Such coexistence may carry important prognostic and therapeutic implications and often needs a multidisciplinary approach. [3]

Screening tests for early diagnosis of CAD may lead to early detection and therefore improved outcomes. So, many clinical trials were conducted searching for a valid and reliable screening method. However, no sufficient evidence could be concluded from these trials which make an open field for more research.

Several ways for screening CAD were tried to predict abnormal myocardial perfusion such as exercise or pharmacological stress tests, ankle brachial index, carotid intima media thickness, coronary artery calcium, Radionuclide Imaging and CT coronary angiography.

The ankle-brachial index (ABI) is an effective, simple, and noninvasive method to screen and diagnose PAD and has a high sensitivity, specificity and small variability and dobutamine stress echocardiography (DSE) is a non-invasive method with established diagnostic accuracy.

Patients and Methods

This study was conducted with fifty patients diagnosed with peripheral arterial disease recruited from vascular department at El-Fayoum University Hospital (case group) and another fifty individuals without PAD (control group).

Case group (group A) fifty individuals;

Case selection

a. Inclusion criteria: Patients with documented peripheral arterial disease attending vascular surgery clinic diagnosed by ABI ≤ 0.9.

b. Exclusion criteria: Documented IHD, patient with history of cardiac intervention (PCI or CABG), patients with moderate or severe valvular disease, patients with conduction abnormalities, pacemaker, ongoing arrhythmia, patients with congenital heart disease, patients with reduced EF ≤ 50% or cardiomyopathy, atrial fibrillation, poor echocardiographic window and patient's refusal.

c. Classification: Patient group was classified according to limb affection into one limb affection and both limb affection. Also, was classified according to ABI into mild arterial disease (ABI 0.8 – 0.89), moderate arterial disease (ABI 0.4 – 0.79) and severe arterial disease (ABI < 0.4). [4]

Control group (group B):

Fifty healthy individuals, age and sex matched, used as a control group.
Methods:

(1) Clinical evaluation: including full history taking, general and local examination.

(2) Resting 12 lead ECG leads: for analysis for any of exclusion criteria.

(3) Transthoracic echocardiogram (TTE):

a) Standard trans-thoracic echocardiographic study (TTE):

TTE was performed using S 5-1 transducer 5-1 MHz with a commercially available ultrasound system Philips Epic7c. Left ventricular ejection fraction (LVEF), diastolic dysfunction and mitral regurgitation if found.

b) Dobutamine stress test:

All participants had 4-6 hours fasting duration and stopped beta blocking medications before the test.

Dobutamine was injected initially intravenously at a dose of 10μg/kg/min then increased by 10μg/kg/min every 3 minutes until a dose of 40μg/kg/min will be reached. If the patient didn't reach 85% of the age-predicted heart rate after dobutamine infusion, atropine was administered (up to a maximum of 2 mg) while dobutamine infusion continues at a dose of 40 μ g/kg/min. Digital images will be acquired in the parasternal short axis, apical 4-chambers, 2-chambers and 3-chambers views. Regional wall motion was analyzed by determining the regional wall motion score (RWMS) with a model that divided the left ventricular myocardium into 16 segments and assigned a wall motion score of 1 to 4 to each segment (1 = normal or hyperkanetic, 2=hypokensia, 3=akensia and 4 = dyskinetic).

The test was ended in the following cases:

- Achievement of the target heart rate.
- Detection of moderate wall motion abnormalities in at least two territories.
- Angina or chest discomfort.
- Marked dyspnea or fatigue.
- Ataxia, dizziness, or near syncope.
- Signs of poor perfusion (cyanosis and pallor)
- Excessive ST segment depression (>2mm)
- ST segment elevation (>1mm) in leads without diagnostic Q waves (except for leads V1 or aVR).
- Sustained supraventricular or ventricular tachycardia.
- Development of bundle branch block (LBBB) or interventricular conduction delay (IVCD) that cannot be distinguished from ventricular tachycardia.
- Drop in systolic blood pressure of >10mm Hg from baseline, despite an increase in workload, when accompanied by other evidence of ischemia.
- Hypertensive response (systolic blood pressure >250 mm Hg and/or diastolic pressure > 115 mmHg.
- Patient's request to stop.

Heart rate, blood pressure, and ECG were continuously monitored for 10 to 15 minutes or until they return to the baseline state. [5]

(4) Ankle brachial index (ABI):

The blood pressure cuff was inflated proximal to the artery in question until the pulse in the artery ceases then, the pressure cuff was slowly deflated. When the artery's pulse was re-detected through the handheld doppler probe the pressure in the cuff at that moment indicated the systolic pressure of that artery. The pressures in each foot's posterior tibial artery and dorsalis pedis artery were measured in the same way then; ABI was calculated for each leg.

The ABI value was determined by taking the higher pressure of the two arteries at the ankle, divided by the brachial arterial systolic pressure. In calculating the ABI, the higher of the two brachial systolic pressure measurements was used.

Interpreting the Ankle Brachial Index:

1. Values below 0.9 are considered diagnostic of PAD.

2. Values less than 0.4 suggests severe PAD.

Results

The mean age of participants included was 57.6 ± 5.9 and the majority of the patients were males (N= 31; 62%). In addition a similar number of participants for the control group the mean age of subjects included was 59.3 ± 6.1 and the majority of the patients were males (N= 40 ; 80 %). Table1.

There was no statistically significant difference with p-value >0.05 between study groups as regards medical history. Figure1.

This study revealed that 50% of cases and had proximal arterial occlusion on right side versus 38% had distal arterial occlusion, and 40 had a proximal lesion on left side versus 44% of cases had distal arterial occlusion. Finally 72% of cases show bilateral lesion. Table2.

This study revealed that there was a statistically significant lower mean of ABI on right, and left side, among cases with p-value <0.05. Table3.

This study revealed that 54% of cases had a moderate level of arterial occlusion on right side, and 60% on left side. Figure2.

This study revealed that there was a statistically significant higher mean of WMSI among cases with p-value <0.05. Table4.

This study illustrated that there was a statistically significant with p-value <0.05 in ABI degree in different WMSI levels among cases with 80% of negative cases had moderate degree of ABI and 90% of positive WMSI had sever degree of ABI. Figure3.

This study revealed that there was a statistically significant lower ABI level on right side with p-value <0.05 among diabetic patients who treated by insulin. Finally, there was a statistically significant lower ABI level on left side with p-value <0.05 among diabetic patients treated by insulin, ex-smokers and patients used atropine.

On the other hand, there was no statistically significant difference with p-value >0.05 as regards other variables. Table5.

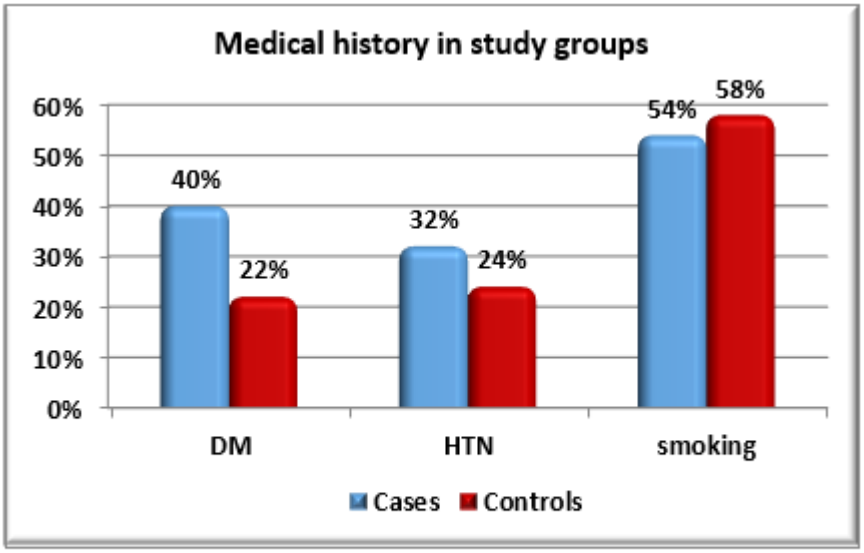
This study revealed that there is statistically significant negative correlation with p-value <0.05 between, ABI level on right side and both smoking index, and WMSI, and a positive correlation with EF % and APSV level on both sides. In addition, there is statistically significant negative correlation with p-value <0.05 between, ABI level on left side and WMSI level, and a positive correlation with both EF % and APSV level on both sides. On the other hand, there is no statistically significant correlation with p-value >0.05 between other variables. Table6.

This study revealed that there was a statistically significant higher percentage of distal lesion in patients with DM, but higher percentage of proximal lesion among cases with hypertension with p-value <0.05. On the other hand, there was no statistically significant difference with p-value >0.05 as regards smoking. Table7.

Table1: Comparisons of demographic characters in different study groups.

Variables	Cases (N=50)		Control (N=50)		P-value	Sig.
Age (years)						
Mean /SD	57.6	5.9	59.3	6.1	0.2	NS
Sex						
Male	31	62%	40	80%	0.08	NS
Female	19	38%	10	20%		

Abbreviations: N, Number; NS, non-significant; SD, standard deviation; Sig, significance.



Abbreviations: DM, Diabetes Mellitus; HTN, hypertension.

Figure1: Medical history in study groups

Table2: Frequency of lesion site among cases.

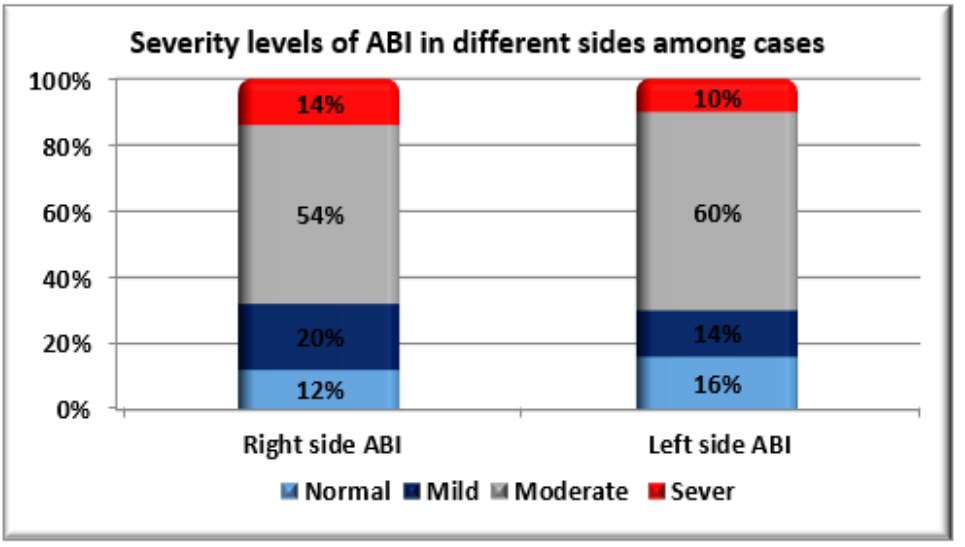
Variables	Frequency (N=50)	
	N.	%
Right side		
No	6	12%
Proximal	25	50%
Distal	19	38%
Left side		
No	8	16%
Proximal	20	40%
Distal	22	44%
Lesion side		
Unilateral	14	28%
Bilateral	36	72%

Abbreviations: N, number

Table3: Comparisons of Ankle brachial index (ABI) value in different study groups.

Variables	Cases (N=50)		Control (N=50)		P-value	Sig.
	Mean	SD	Mean	SD		
ABI						
Right side	0.74	0.25	1.23	0.08	<0.001	HS
Left side	0.73	0.21	1.20	0.07	<0.001	HS

Abbreviations: ABI, Ankle Brachial Index; HS, highly significant; SD, standard deviation; Sig, significance.



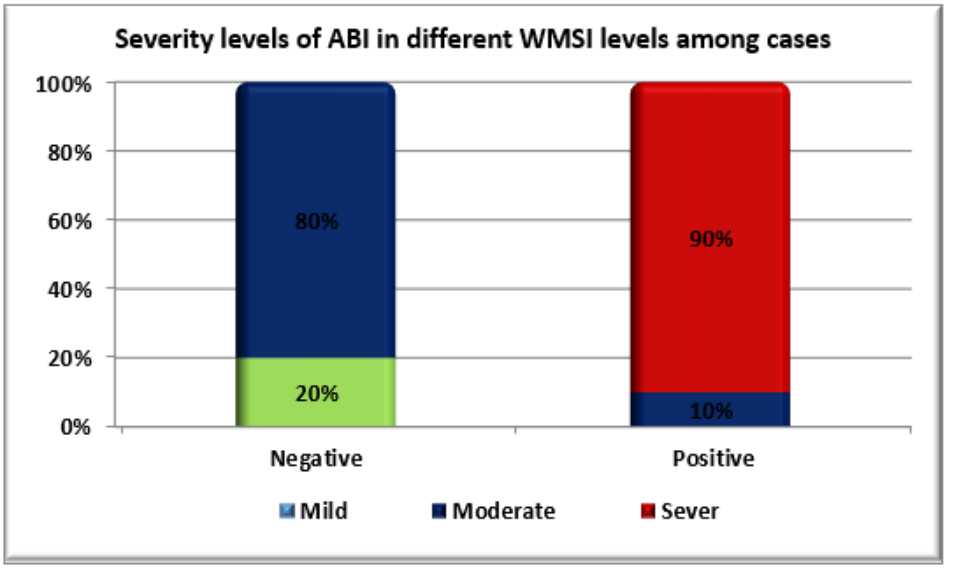
Abbreviations: ABI, Ankle Brachial Index

Figure2: Severity levels of ABI in different sides among cases

Table4: Comparisons of WMSI in different study groups.

Variables	WMSI level		P-value	Sig.
	Mean	SD		
Cases	1.07	0.14	<0.001	HS
Control	1	0		

Abbreviations: HS, highly significant; SD, standard deviation; Sig, significance; WMSI, Wall Motion Score Index.



Abbreviations: ABI, Ankle Brachial Index; WMSI, Wall Motion Score Index.

Figure3: Severity levels of ABI in different WMSI levels among cases

Table5: Comparisons of ABI level in different demographic and medical characters among cases.

Variables	ABI					
	Right		p-value	Left		P-value
	Mean	SD		Mean	SD	
Sex						
Male	0.71	0.28	0.4	0.69	0.21	0.1
Female	0.78	0.19		0.79	0.21	
Diabetes mellitus						
No	0.75	0.25	0.5	0.75	0.20	0.5
Yes	0.71	0.25		0.70	0.24	
Treatment of DM						
Oral	0.81	0.19	0.01	0.80	0.17	0.004*
Insulin	0.53	0.26		0.51	0.22	
Hypertension						

Table6: Correlation between ABI level on right and left side with study variables among cases.

Variables	ABI			
	Right		Left	
	r	P-value	r	P-value
Age	-0.05	0.7	0.03	0.8
Duration of DM	-0.004	0.9	-0.11	0.6
Duration of HTN	0.31	0.2	0.45	0.08
Smoking index	-0.57	0.001*	-0.08	0.7
APSV right	0.91	<0.001*	0.34	0.02*
APSV left	0.46	0.002*	0.85	<0.001*
At rest (Vital signs- EF %)				
Systolic BP	-0.02	0.9	-0.20	0.2
Diastolic BP	-0.11	0.5	-0.17	0.2
HR	0.12	0.4	0.17	0.2
EF%	-0.18	0.2	-0.14	0.3
At peak stress (Vital signs- EF %)				
Systolic BP	-0.22	0.1	-0.21	0.1
Diastolic BP	0.14	0.3	0.09	0.5
HR	0.15	0.3	-0.09	0.6
EF%	0.61	<0.001*	0.56	<0.001*
WMSI	-0.63	<0.001*	-0.53	<0.001*

Abbreviations: ABI, Ankle Brachial Index; APSV, Ankle Peak Systolic Velocity; BP, blood pressure; DM, Diabetes Mellitus; EF, Ejection Fraction; HR, Heart Rate; HTN, Hypertension; r, correlation coefficient; WMSI, Wall Motion Score Index.

Table7: Comparisons of medical history in different lesion site among cases.

Variables	Lesion site					
	Right		P-value	Left		P-value
	Proximal	Distal		Proximal	Distal	
	N (%)	N (%)		N (%)	N (%)	
Diabetes mellitus						
No	23(92%)	3(15.8%)	<0.001*	18(90%)	7(31.8%)	<0.001*
Yes	2(8%)	16(84.2%)		2(10%)	15(68.2%)	
Hypertension						
No	12(48%)	17(89.5%)	0.005*	10(50%)	18(81.8%)	0.04*
Yes	13(52%)	2(10.5%)		10(50%)	4(18.2%)	
Smoking						
No	8(32%)	10(52.6%)	0.2	5(25%)	11(50%)	0.2
Yes	14(56%)	9(47.4%)		13(65%)	10(45.5%)	
Ex-smoker	3(12%)	0(0%)		2(10%)	1(4.5%)	

Abbreviations: N, number.

Discussion

Peripheral and Coronary Artery Disease are two sides of the same coin they represent local manifestation of systemic atherosclerosis. The coexistence of CAD and PAD was described since 1960. PAD whether symptomatic or asymptomatic, is a risk factor for non-fatal and fatal coronary disease and cerebrovascular events. [2] CAD can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. However, the disease is chronic, most often progressive, and hence serious, even in clinically apparently silent periods. The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS). [6]

In an effort to lower the high burden of coronary deaths in asymptomatic adults, numerous measurements of risk factors and risk markers, as well as stress tests, are often performed as screening investigations.

Regarding disease distribution and risk factors:

In our study, we found that 50% of cases and had proximal arterial occlusion on right side versus 38% had distal arterial occlusion, and 40 had a proximal lesion on left side versus 44% of cases had distal arterial occlusion. Finally 72% of cases

show bilateral lesion. There was a statistically significant higher percentage of distal lesion in patients with DM, but higher percentage of proximal lesion among cases with hypertension with p-value <0.05. On the other hand, there was no statistically significant difference with p-value >0.05 as regards age, sex and smoking.

N. Diehm et al. 2006 conducted a cohort study on 2659 patients with chronic PAD undergoing primary endovascular treatment highlighted a statistically significant association between cardiovascular risk factors and pattern of atherosclerotic lesions of the lower limbs. Similar to our study they found that Infra-geniculate disease was associated with diabetes mellitus (p<0.001) and they also found that iliac disease was associated with younger age (p<0.001), male gender (p=0.004) and cigarette smoking (p<0.001). Infra-geniculate disease was associated with higher age (p<0.001), male gender (p=0.005). Whereas no distinct pattern was apparent related to arterial hypertension. [7]

Victor Aboyans et al. 2010 studied 400 PAD patients (age 68.3 ± 12.3 years, 77.5% men). Aortoiliac disease (proximal PAD) and infrailiac disease (distal PAD) were noted in 211 (52.8%) and 344 (86.0%) cases, respectively. Similarly to our study they found that diabetes was more prevalent in distal PAD and in contrary to our study they found that age, hypertension and renal failure were more prevalent in distal PAD and men and smoking were prevalent in proximal PAD (p <0.05). [8]

Qian Chen et al. 2013 conducted a cohort study on 8930 patients with PAD and found that disease location differs with risk factors. In the line with our findings diabetes was more strongly associated with distal disease than with proximal disease (interaction P<0.001) and history of hypertension was more strongly associated with proximal disease. In contrast to our study they found that men had distal disease more than women and smoking was associated with proximal disease. [9]

Similarly Aboleineen et al. 2014 studied 200 patients with PAD and concluded that there was difference between diabetic and non-diabetic patients regarding the distribution of arterial tree affection in the lower limbs. In agreement with our study diabetic patients had more severe arterial affection in the below knee arteries (popliteal, anterior tibial, peroneal, posterior tibial) than non-diabetic patients with high statistical significance, (p < 0.001). [10]

Correlation between CAD and PAD:

Many studies used different modalities to detect myocardial ischemia in patients suffering from peripheral artery disease.

In our study we used dobutamine stress echocardiography to assess myocardial ischemia and we found that there was statistically significant invers correlation between ABI level and WMSI with p-value <0.05 and there was a statistically significant with p-value <0.05 in ABI degree of severity in different WMSI levels among cases with 80% of negative cases had moderate degree of ischemia by ABI and 90% of positive WMSI had sever degree of ischemia by ABI.

Likewise, Langan EM 3rd et al., 1993 used dobutamine stress echocardiography to evaluate 81 patients before infrarenal aortic surgery. Patients were placed into three groups. Group I (n = 31) had normal DSEs. Group II (n = 25) had resting wall motion abnormalities without dobutamine-induced changes of ischemia. Group III (n = 25) had evidence of dobutamine-induced ischemia and found that using DSE for preoperative assessment of cardiac risk allowed them to operate on 74 of 81 patients being considered for elective aortic reconstruction, with no operative deaths and a 4.1% rate of perioperative MI. and concluded that dobutamine stress echocardiography has the ability to identify patients with asymptomatic stress-induced ischemic myocardium and its increased risk for perioperative MI ($p < 0.001$). [11]

Similarly Feringa HH et al., 2007 studied 852 patients with suspected or known peripheral arterial disease (mean age 63 years, 70% male), the ankle-brachial index was measured, left ventricular ejection fraction was assessed, and all patients underwent additional stress testing. Stress-induced ischemia was observed in 352 patients (41%). In multivariate analysis with adjustment for clinical risk factors and ankle-brachial index, each 5% decrease in left ventricular ejection fraction was associated with increased all-cause mortality and hard. Stress-induced ischemia also independently predicted all-cause mortality and hard events. Left ventricular ejection fraction and stress-induced ischemia provided incremental prognostic information over clinical data and ankle-brachial index values ($P <.001$). [12]

In the line with our study Thatipelli MR et al., 2007 among 395 patients (mean age, 69.7 ±9.6 years; 40% women) found that 341 had abnormal ABI and 268 had abnormal DSE (95 fixed and 173 stress-induced wall motion abnormalities). During a mean follow-up of 4.7 years, 27.3% of patients experienced a cardiovascular event, and 39.4% died. By multivariate analysis, ABI provided the strongest prediction of all-cause mortality ($P = .002$). Conversely, DSE with inducible or fixed wall motion abnormalities showed no association with cardiovascular events or increased mortality in multivariate analysis. The only DSE variable independently predictive of mortality was decreased left ventricular ejection fraction (<50%) at peak stress ($P = .002$). [13]

In contrary to our study Joakim Nordanstig et al., 2019 studied 111 patients with intermittent claudication and didn't observe any pathological wall motion abnormalities during pharmacological stress. This striking difference compared with previous reports is most likely related to differences due to retrospective versus prospective study design and differences in disease severity. In previous reports patients has been studied prospectively prior to vascular surgery, or retrospectively identified among patients with PAD that also had performed dobutamine echocardiography. It is therefore conceivable that these earlier results partly are due to selection bias, i.e. the patients included in these previous studies had both more advanced peripheral arterial disease and coronary artery disease. [14]

In agreement with our study Cho SW et al., 2015 Investigated 107 patients with PAD who underwent peripheral and simultaneous coronary angiography for the

prevalence and predictors of CAD found that 62% (67/107) of patients had concomitant CAD, although most (87%, 58/67) had no cardiac symptoms. [15]

In concordance to our study Nandi S et al., 2020 studied the association of severity of coronary artery disease by SYNTAX score (SS) and lower extremity arterial disease by duplex ultrasound (DUS) among 637 subjects above 45 years of age and found that high SS was significantly more common in subjects with LEAD (p = 0.04). [16]

Correlation between ABI and Ankle Peak Systolic Velocity (APSV):

In agreement with our study that found a positive correlation between ABI and APSV level on both sides with (p-value <0.05) Bishara RA et al. 2004 calculated APSV as the mean value of the distal anterior and posterior tibial arteries peak systolic velocities (PSV). Ankle brachial index (ABI) was calculated for the anterior tibial and posterior tibial arteries. A mean ABI for both tibial arteries was also calculated. APSV was correlated with the mean ABI and concluded that APSV can be used as an alternative to ABI for the assessment of degree of peripheral ischemia. [17]

Correlation between ABI and diabetes mellitus patients:

In our study we found that there was a statistically significant lower ABI level with p-value <0.05 among diabetic patients treated by insulin.

In the line with Ugwu E et al., 2021 put ABI in comparison with DUS in patients with T2DM. 163 patients comprising of 156 subjects with intact legs and 7 patients who had undergone unilateral lower limb amputations were studied. The mean age of the participants was 56.1±17.3 years. 195 legs (61.1%) had sonographically confirmed PAD which was mild, moderate and severe in 40%, 41.5% and 18.5% respectively. The accuracy of ABI in detecting PAD was 76.7% for mild stenosis, 91.7% for moderate stenosis and 93.1% for severe stenosis. The sensitivity of ABI improved with increasing severity of arterial stenosis, reaching 100% in severe cases. ABI demonstrated good agreement with DUS (P < 0.001). ABI demonstrated good reliability for diagnosis of PAD in high risk T2DM patients. The utility of this simple and non-invasive procedure should therefore be maximized in clinical practice. [18]

Correlation between smoking and ABI:

In our study there was a statistically significant lower ABI level with p-value <0.05 among ex-smokers and there was statistically significant invers correlation with p-value <0.05 between ABI level and smoking index.

In agreement with Kianoush S et al., 2017 who found in total, 13 268 (99.4%) participants were included in the analysis. Prevalence of ABI ≤1.0 among current smokers (9.8%) was higher compared with former smokers (5.8%) and never smokers (P<0.001). After full multivariable adjustment, compared with never smokers, former and current smokers had higher odds of ABI ≤1.0 (P<0.001).

Among ever smokers, each 5-pack-year increase was associated with higher odds of ABI ≤1.0 (P=0.02). Each 5-year lapsed since quitting was associated with lower odds of ABI ≤1.0 (; P=0.003). Smoking intensity was also associated with ABI ≤1.0 (P=0.002). [19]

Similarly He Y et al., 2008 among 1209 women who never smoked, 39.5% were exposed to second hand somking (SHS) at home or in workplaces. Those individuals who were exposed to SHS had a significantly higher risk of coronary heart disease and ischemic stroke than those never exposed to SHS. Dose-response relationships were found between SHS exposure amount (cigarettes per day) and duration (minutes per day) and increasing prevalence of coronary heart disease, ischemic stroke, and PAD. [20]

Conclusion

The coexistence of CAD and PAD was described since 1960. PAD whether symptomatic or asymptomatic, is a risk factor for non-fatal and fatal coronary disease and cerebrovascular events. Screening tests for early diagnosis of CAD may lead to early detection and therefore improved outcomes. The ankle-brachial index (ABI) is an effective, simple, and noninvasive method to screen and diagnose PAD and has a high sensitivity and specificity and small variability and Dobutamine stress echocardiography (DSE) is a non-invasive method with established diagnostic accuracy.

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