The Egyptian Journal of Hospital Medicine (April 2021) Vol. 83, Page 1575-1581

Ankle Brachial Index Screening for Peripheral Arterial Disease in Asymptomatic Diabetic Patients

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ABSTRACT

Background: Peripheral arterial disease (PAD) is a common macrovascular complication in diabetic patients related to atherosclerosis. Early diagnosis of PAD by ankle brachial index (ABI) is highly critical as this disease results in significant morbidity and mortality.

Objectives: To screen for PAD in asymptomatic diabetic patients by using ABI, determining its prevalence and associated risk factors.

Patients and Methods: This is a cross-sectional study conducted on 309 diabetic asymptomatic patients in Internal Medicine Department, Menoufia University Hospitals in the period between December 2018 and December 2020. Full history and biochemical profiles were obtained and ABI indices were measured to evaluate for PAD.

Results: The prevalence of PAD in this study was 36.2%. Advancing age, sedentary life, long duration of diabetes, smoking, poor glycemic control and dyslipidemia were identified as risk factors for PAD (p value <0.001) while, hypertension and body mass index were not significant among studied patients (p value 0.594 and 0.733 respectively).

Conclusion: PAD has a high prevalence in asymptomatic diabetic individuals. It is associated with multiple risk factors such as smoking, dyslipidemia, advancing age, atherosclerosis and prolonged uncontrolled hyperglycemia. Diabetic patients should be routinely examined by ABI to improve the outcome.

Keywords: Peripheral Arterial Disease, Diabetes, Ankle brachial index.

INTRODUCTION

In 2019, an estimated 463 million adults had diabetes all over the world and the number is predicted to be doubled by 2030 [(1)]. Diabetes mellitus (DM) is a major health problem, which leads to 2.2 million deaths worldwide related to high blood glucose and its associated complications (e.g. heart disease etc.), making it the 8th leading cause of death [(2)].

Peripheral arterial disease is the narrowing of the visceral arteries and the arteries of the lower limbs due to systemic atherosclerosis [(3, 4)] leading to limb amputation and death [(4)]. The commonest risk factors to PAD are increasing age, diabetes, obesity, dyslipidemia, hypertension and smoking [(5)]. The American Heart Association estimates that the worldwide prevalence of PAD is 202 million individuals. PAD is a common sequalae in diabetic individuals with 3-4 times higher prevalence than non-diabetic individuals [(6)] due to several mechanisms related to atherosclerosis as endothelial dysfunction, oxidative stress and production of advanced glycation end- products. Early detection of PAD is critically important for risk factor modification, enhancing of its outcome and minimizing its complications [(7)].

Ankle brachial index is a simple quick method, which is used for early diagnosis of PAD. The American Heart Association defines the ABI as the ratio of the ankle systolic pressure to the brachial systolic pressure, which is 1-1.4 in normal individuals. PAD is diagnosed when ABI is ≤ 0.9.

The aim of the work was to screen for PAD in asymptomatic diabetic patients by using ABI.

PATIENTS AND METHODS

This study was designed as a cross-sectional study and was conducted on 309 diabetic patients who did not have any symptoms for PAD and were selected from Outpatient Clinics and Inpatient Wards of Internal Medicine Department in Menoufia University Hospitals from December 2018 to December 2020. Then subjects were subdivided into two groups: **Group I** included **197** patients **without** PAD, and **Group II** included **112** patients **with** PAD.

Inclusion criteria: Diabetic patients (type 2 DM) without symptoms for PAD and older than 18 years old.

Exclusion criteria: Diabetic patients with symptoms for PAD, age less than 18 years old and type1 DM.

All patients were subjected to the following:

Full history: A full detailed history is taken including socio-demographic data and diabetic history (duration of DM and anti-diabetic medications), exclusion of symptoms of PAD (e.g., intermittent claudication) and history of risk factors as Smoking and hypertension.

Complete physical examination: Complete general examination, local examination, anthropometric measures (weight, height, BMI, waist circumference, hip circumference and waist-hip ratio), foot examination (peripheral pulsations, color, temperature, hair, nails and ulcers).

Received:18 /1 /2021
Accepted:15 /3 /2021

Measurement of ABI: By using a hand-held Doppler of 8 MHz and sphygmomanometer cuff. The ABI was performed by measuring the systolic blood pressure of both brachial arteries, both dorsalis pedis and posterior tibial arteries in the supine position. The ABI is calculated by dividing the highest systolic blood pressure at the ankle by the highest systolic blood pressures in the arm.

Interpretation of ABI: [8]

1. ABI value from 1.0 — 1.4 is normal.
2. The values above 1.4 suggest a non-compressible calcified vessel as in elderly patients.
3. The value between 0.91-1 is borderline and needs follow up.
4. ABI ≤ 0.9 is diagnostic of PAD.
   - The values from 0.8-0.9 are mild PAD.
   - The values from 0.4-0.79 are moderate PAD.
   - The values less than 0.4 suggest severe PAD.

Laboratory investigations including fasting blood glucose, 2hr post prandial blood glucose, HBA1c, lipid profile, complete blood count (CBC), serum urea, serum creatinine, albumin /creatinine ratio, AST, ALT and serum albumin tests.

Ethical approval and written informed consent:

An approval of the study was obtained from Menoufia University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation.

Statistics and Analysis

Statistics were done by using SPSS version 23 software for analysis. Numeric variables were represented as mean ± standard deviation, while non-numeric data were presented as frequency and percentage.

Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Chi-square test (χ^2) was used to study association between qualitative variables. Correlations between different parameters were determined by bivariate Pearson correlation test. P- value of ≤ 0.05 was considered statistically significant.

RESULTS

Table (1): Comparison between studied patients regarding demographic data (no=309)

	Group I No=197	Group II No=112	Test of significance	P value
Age (years)				
X ± SD	50.54 ± 16.03	56.78 ± 11.12	t	<0.001
Range	18-80	33-73	4.09	HS
Gender				
Male	94 (47.7%)	67 (59.8%)	X^2	0.041
Female	103 (52.3%)	45 (40.2%)	4.19	S
Occupation				
Jobs with physical activity	97 (49.2%)	35 (31.2%)	X^2	0.002
Sedentary jobs	100 (50.8%)	77 (68.8%)	9.44	S
Residence				
Urban	118 (59.9%)	31 (27.7%)	X^2	<0.001
Rural	79 (40.1%)	81 (72.3%)	29.9	HS
Duration of diabetes (years) X ± SD	7.85 ± 4.17	12.90 ± 7.01	U 6.41	<0.001 HS
Anti-DM medications				
Insulin	107 (54.3%)	33 (29.5%)		
Oral hypoglycemic drugs	67 (34%)	61 (54.5%)	X^2	<0.001
Both therapies	23 (11.7%)	18 (16.1%)	17.98	HS
Smoking				
No	169 (85.8%)	46 (41.1%)	X^2	<0.001
Yes	28 (14.2%)	66 (58.9%)	67.45	HS
Hypertension				
No	71 (36%)	37 (33%)	X^2	0.594
Yes	126 (64%)	75 (67%)	0.284	NS

Group I: Patients with no PAD, Group II: Patients with PAD, t=students t test, X^2 =chi-square test,
U=Mann-Whitney test p-value is significant if ≤0.05 x: mean SD: standard deviation

Table (1) showed that the mean age was significantly higher in PAD group than in non-PAD group (**p value<0.001**) and the male gender was more significant than female gender in PAD group (**p value=0.041).** Moreover**,** patients with sedentary jobs were more prevalent than patients with jobs requiring physical activity in PAD group and the sedentary occupation was more significant in PAD group than in non-PAD group. Patients who lived in rural areas were more prevalent and significantly higher than those who lived in urban areas in PAD group**.** The rural residence was significantly higher in PAD group than in non-PAD group. The mean duration of DM was significantly higher and longer in PAD group than in non-PAD group **(p value <0.001).** Patients who used oral hypoglycemic drugs were more prevalent and significantly higher than those who used insulin therapy in PAD group (**P value <0.001).** Subjects on oral hypoglycemic drugs and both therapies were significantly higher in PAD group than in non-PAD group**.** The number of smokers was significantly higher than that of non–smokers in PAD group**.** The number of smokers was significantly higher in PAD group than in non-PAD group (**p value <0.001).** There was no significant difference between the studied groups as regards hypertension **(p value= 0.594).**

In the current study, there was no significant difference between the studied groups as regards the anthropometric measurements and the vital signs (weight, height, BMI, waist circumference, hip circumference, waist-hip ratio, systolic blood pressure, diastolic blood pressure and heart rate) (**p value > 0.05).**

Table (2): Comparison between studied groups regarding the laboratory investigations (no=309)

	Group I No=197	**Group II No=112**	**Test of significance**	**P value**
FBS (mg/dl) X±SD	164.32±5.28	210.5±9.39	U 4.58	<0.001 HS
2Hour PPBs (mg/dl) X±SD	208.65±8.36	286.39±15.82	U 6.46	<0.001 HS
HbA1C (%) X±SD	7.73±1.66	8.79±2.10	t 3.88	<0.001 HS
Total Cholesterol (mg/dl) X±SD	156.5±8.67	203.94±4.39	t 8.83	<0.001 HS
Triglycerides (mg/dl) X±SD	150.39±6.75	194.62±17.06	U 3.75	<0.001 HS
LDL (mg/dl) X±SD	86.71±8.97	126.57±6.59	U 7.21	<0.001 HS
HDL (mg/dl) X±SD	41.13±2.01	40.93±1.06	t 0.148	0.889 NS
TLC (10^3/mm^3) X±SD	7.96±1.64	9.55±2.86	U 4.53	<0.001 HS
Albumin creatinine ratio (mg/gm) X±SD	0.408±0.02	0.528±0.031	U 1.64	1.00 NS

TLC: total leucocytic count FBS: fasting blood glucose PPBS: postprandial blood glucose HbA1c: glycated hemoglobin LDL: low density lipoprotein HDL: high-density lipoprotein

Table (2) showed that among studied groups, the mean fasting blood glucose level was significantly higher in PAD group than in non-PAD group **(p value <0.001).** The mean postprandial blood glucose level was significantly higher in PAD group than in non-PAD group **(p value <0.001).** The mean HbA1c level was significantly higher in PAD group than in non-PAD group **(p value <0.001).** The mean of serum total cholesterol level was significantly higher in PAD group than in non-PAD group **(p value <0.001).** The mean of serum triglycerides level was significantly higher in PAD group than in non-PAD group (**p value <0.001).** The mean LDL level was significantly higher in PAD group than in non-PAD group **(P value <0.001).** There was no significant difference between studied groups regarding HDL level **(p value 0.889).** The mean of serum total leucocytic count was significantly higher in PAD group than in non-PAD group **(p value <0.001).** There was no significant difference between studied groups regarding urinary albumin/creatinine ratio **(p value=1.00)**

Table (3): Pearson correlation between ABI value and demographic, clinical, and laboratory data in all studied patients (no=309)

	ABI value	
	r	**P value**
Age (years)	-0.114	0.045
Duration of diabetes (years)	-0.276	<0.001
Fasting blood sugar (FBS) (mg/dl)	-0.232	<0.001
2 Hour postprandial blood glucose (PPBS) (mg/dl)	-0.300	<0.001
HBA1C (%)	-0.259	<0.001
Total Cholesterol (mg/dl)	-0.350	<0.001
Triglycerides (mg/dl)	-0.208	<0.001
LDL (mg/dl)	-0.328	<0.001
Albumin-creatinine ratio (mg/gm)	-0.142	0.012

ABI value was correlated negatively with age, DM duration, fasting blood glucose, postprandial blood glucose, HbA1c, total cholesterol level, triglycerides, LDL and Albumin-creatinine ratio.

Table 4: predictors for peripheral arterial disease using Binary Logistic Regression

	Wald.	**significance**	**B (OR)**	**95% confidence interval**	
				Lower bound	**Upper bound**
Age	13.18	<0.001*	0.889	0.835	0.947
Sex	9.32	0.002*	32.23	3.46	229
Occupation	9.22	0.002*	4.84	1.78	13.15
Residence	0.220	0.630	0.986	0.980	1.04
Duration of DM	6.46	0.011*	1.005	1.001	1.009
Smoking	21.39	<0.001 *	251.9	24.19	262
TLC	10.7	0.001 *	1.23	1.09	1.40
FBS	2.68	0.101	1.01	0.997	1.01
2hr PPBS	0.955	0.328	1.01	0.997	1.01
HBA1C	3.99	0.046 *	0.734	0.543	0.994
Cholesterol	0.088	0.766	0.996	0.971	1.02
Triglycerides	2.66	0.103	1.01	0.999	1.01
LDL	2.01	0.155	1.02	0.992	1.05

OR: Odds ratio *=significant P value

This table revealed that residence**,** fasting blood glucose**,** 2hr post prandial blood glucose**,** cholesterol, triglycerides and LDL were not significantly related to the risk for developing peripheral arterial disease in asymptomatic diabetic patients **(P- value > 0.05):**.

The risk factors for developing peripheral arterial disease in asymptomatic diabetic patients were advancing age **(P value <0.001) (OR 0.889),** male sex (thirty-two times) **(P value= 0.002) (OR 32.23),** sedentary life style (four times) **(P value= 0.002) (OR 4.84),** long duration of diabetes mellitus > 12 years **(P value= 0.011) (OR1.005),** smoking **(P value <0.001) (OR 251.9)** and uncontrolled hyperglycemia (high HBA1C >8.5%) **(P value = 0.046) (OR 0.734).**

PAD was associated with elevated TLC **(P value = 0.001) (OR 1.23).**

DISCUSSION

The current study found a high prevalence of PAD in asymptomatic diabetic patients selected from Menoufia University hospitals **(36.2%).** This study is close to **Shaikh *et al.*** [9] who showed a high prevalence of PAD among diabetic patients without any symptoms for PAD **(34.8%).** In addition, this study was close to **Aljarid *et al.*** [10] who showed a high prevalence of PAD in diabetic patients with or without symptoms for PAD **(32.2%).**

Many studies showed the prevalence and the risk factors for developing PAD in diabetic patients without any symptoms for PAD such as **Shaikh *et al.*** [9] and **Ghosh *et al.*** [11]**.** However, other studies showed the prevalence and the risk factors for developing PAD in diabetic patients with or without symptoms for PAD.

This study showed that the mean age was significantly higher in PAD group than in non-PAD

group. This agrees with **Aljarid *et al.* [10], Ghosh *et al.* [11]** and **Weledji *et al.* [12]** who showed that increasing age was a significant risk factor for PAD in diabetic patients**.** Against this study, **Agboghoroma *et al.* [13]** showed that there was no significant difference between the two groups regarding age**.**

This study showed that the male sex was more predominant than female sex in diabetic patients with PAD may be because the majority of our participants were males and smokers. This agrees with **Shaikh *et al.* [9]** and **Ghosh *et al.* [11]** who showed that there was male predominance in asymptomatic diabetic patients with PAD**.** Against this study, **Agboghoroma *et al.* [13]** showed that there was female predominance due to associated high BMI and total cholesterol levels. Furthermore, **Weledji *et al.* [12]** showed that there was no significant difference between both groups regarding gender**.**

The current study showed that patients with sedentary jobs were more predominant in PAD group than in non-PAD group**.** This agrees with **Felício *et al.* [14]** who showed that sedentary lifestyle was an important risk factor for PAD**.** Against this study, **Weledji *et al.* [12]** showed that there was no significant difference between studied groups regarding occupation**.**

The current study showed that the prevalence of PAD in patients from rural residence was significantly higher than in those from urban residence due to the low socioeconomic and educational level. This study agrees with **Weledji *et al.* [12]** who showed that the prevalence of PAD was high in tropical forests. In contrary, **Weragoda *et al.* [15]** showed that no significant difference between both groups regarding the residence**.**

This study showed that the mean duration of DM was significantly higher in PAD group than in non-PAD group. This study agrees with **Ghosh *et al.* [11]** who showed that the long DM duration was a risk for PAD in diabetic patients without any symptoms for PAD. In addition, it agrees with **Felício *et al.* [14]** regarding that the duration of DM was a risk for PAD in diabetic patients with or without symptoms for PAD. In contrary, **Shaikh *et al.* [9]** and **Agboghoroma *et al.* [13]** showed that no significant difference between both groups regarding DM duration**.**

This study showed that patients on oral hypoglycemic drugs and those on both therapies were more predominant in PAD group than non-PAD group. In addition, the prevalence of PAD was significantly higher in patients on oral hypoglycemic drugs than in insulin users due to the majority of participants used 2 or 3 oral hypoglycemic drugs or mixed therapy and were not compliant. This study agrees with **Yang *et al.* [16]** who showed that PAD was significantly higher in patients on oral hypoglycemic drugs than in insulin users**.** In contrary, **Yeboah *et al.* [17]** showed that PAD was more frequent in insulin users due to the effect of insulin resistance on atherosclerosis progression. Besides, **Aljarid *et al.* [10]** showed that no significant difference between both groups regarding anti-DM medications.

The current study showed that the number of smokers was significantly higher in PAD group than in non-PAD group. So, smoking was a risk factor for PAD. Smoking led to atherosclerosis, which is the main cause for PAD by damaging the blood vessels through raising the blood pressure and unhealthy cholesterol levels. Furthermore, nicotine in tobacco also tightens the blood vessels and reduces the blood flow in the arteries. This study agrees with **Shaikh *et al.* [9]** and **Shou *et al.* [18]** who showed that smoking was a risk for PAD in diabetic patients**.** In contrary, **Aljarid *et al.* [10]** showed that no significant difference between both groups regarding smoking**.**

This study showed that there was no significant difference between both groups regarding hypertension may be because the majority were well-controlled by anti-hypertensive drugs. This study agrees with **Agboghoroma *et al.* [13]** who showed that there was no significant difference between studied groups regarding hypertension**.** Against this study, **Ghosh *et al.* [11]** and **Shou *et al.* [18]** showed that hypertension was a significant risk factor for PAD in diabetics because elevated blood pressure leads to hardening of the blood vessels, which is known as atherosclerosis that results in development of PAD.

This study showed that there was no significant difference between both groups regarding all-anthropometric measurements and this might be due to the effect of obesity paradox phenomenon demonstrated by variable studies. **Ludhwani *et al.* [19]** showed that in spite of the strong association between elevated BMI, cardiovascular outcomes and PAD, there were favorable cardiovascular outcomes in obese patients as compared to those with normal BMI, which was known as the obesity paradox**.** This had been explained by different theories such as body composition of large muscle bulk, improved cardiorespiratory fitness, greater mobilization of endothelial progenitor cells, decreased thromboxane production, increased ghrelin sensitivity and excess adipose tissue produced of soluble tumor necrosis factor receptor, which plays a protective role by neutralizing the toxic effects of tumor necrosis factor alpha. Similar paradoxical results were observed in patients with peripheral arterial disease (PAD). PAD was noted in the underweight patients. However, this was attributed to excess mortality in the underweight who had a history of smoking and obstructive lung disease. the current study agrees with **Ana Tereza do Nascimento *et al.* [20]** regarding all-anthropometric measurements, with **Shaikh *et al.* [9] and Shou *et al.* [18]** regarding BMI and with **Weragoda *et al.* [15]** regarding waist circumference

and waist hip ratio. In contrary, **Agboghoroma *et al.*** [13] showed that the higher BMI and the higher waist circumference were risk factors for PAD.

The current study showed that poor glycemic control was a risk for PAD because of progression of atherosclerosis process by abnormal platelets activation, enhanced production of advanced glycation end- products and the oxidative stress. The means of FBS, 2 hrPPBS and HBA1c were significantly higher in PAD group than in non-PAD group**.** This study agrees with **Shaikh *et al.*** [9] and **Yang *et al.*** [16] regarding that FBS and HBA1c levels were higher in patients with PAD. In contrast, **Cornejo Del Río *et al.*** [21] showed no significant difference between studied groups regarding FBS and 2 hrPPBS. Moreover, **Shou *et al.*** [18] reported that there was no significant difference regarding HBA1c%.

The current study showed that dyslipidemia was a risk for PAD in diabetic patients because of increasing atherosclerosis and its related oxidative stress. The means of total cholesterol, triglycerides and LDL levels were significantly higher in PAD group than in non-PAD group and this agrees with **Soyoye *et al.*** [5] who demonstrated that dyslipidemia was a risk factor for PAD. In contrast, **Cornejo Del Río *et al.*** [21] showed no significant difference between studied groups regarding dyslipidemia. However, our study showed no significant difference between both groups regarding HDL level and this agrees with **Cornejo Del Río *et al.*** [21] but against **Agboghoroma *et al.*** [13] who showed that low serum HDL level was a risk factor for PAD. **Ghosh *et al.*** [11] agrees with our study considering that serum HDL was of non-significant difference between both groups. In contrast to the current study, **Ghosh *et al.*** [11] showed non-significant difference between both groups as regards serum total cholesterol and LDL.

This study showed high total leucocytic count in PAD group as a sequalae to PAD due to the association between atherosclerosis and rising of inflammatory markers. This agrees with **Soyoye *et al.*** [5] regarding leucocytic count.

Our study showed that there was no significant difference between both groups regarding albuminuria. This agrees with **Yang *et al.*** [16] but in contrary to **Weledji *et al.*** [12] who showed that proteinuria was a significant association with PAD.

CONCLUSION AND RECOMMENDATIONS

Prevalence of PAD in asymptomatic diabetic patients was 36.2%. Advancing age, sedentary life style, smoking, dyslipidemia, long duration of DM and poor glycemic control were the risk factors for PAD. However, hypertension and obesity were not significant in our study. ABI screening must be mandatory in all diabetic patients even if not symptomatic for early diagnosis of PAD and enhancing its outcome.

Financial support and sponsorship: Nil. **Conflicts of interest**: Nil.

Declaration: This manuscript has not been published or submitted for publication elsewhere.

Acknowledgment: All authors have contributed significantly and agreed with the content of the manuscript.

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