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Original Research Article

Study of association between urine albumin creatinine ratio and ankle brachial index or peripheral arterial disease in type 2 diabetes mellitus patients

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ABSTRACT

Background: To establish association between urine albumin creatinine ratio and ankle brachial index or peripheral arterial disease in type 2 diabetes patients.
Methods: Total 74 patients of type 2 diabetes mellitus of >50 years of age subjected to calculation of urine albumin creatinine ratio and ankle brachial index was calculated using doppler sonography and estimation of peripheral arterial diseases was done. The data obtained subjected to analysis.
Results: In group with ABI <0.9 suggestive of PAD, mean age of the patient was 62.32±5.8 years, mean BMI was 26.11±2.48kg/m2, mean duration of diabetes was 11.19±41 years, 7 (18.92%) were smokers, 15 (40.54%) were insulin users, 27 (72.97%) were hypertensive, mean SBP was 142.49±13.46mmHg, mean DBP was 84±6.42mmHg, mean serum cholesterol was 221.35±17.10mg/dl, mean serum triglyceride was 242.81 ± 17.10mg/dl, mean serum HDL was 44.03±5.77mg/dl, mean serum LDL was 116.89±28.77mg/dl, mean urine ACR was 294.62±314.90mg/gm, prevalence of normoalbuminuria, microlbuminuria and macroalbuminuria was 12 (32.43%), 21 (56.76%) and 4 (10.81%) respectively. The statistical significant difference was found in age, duration of diabetes, number of patients on insulin therapy, systolic BP, serum cholesterol, triglyceride, LDL, HDL, urine ACR and distribution of albuminuria.
Conclusions: we conclude that statistical significant relationship exist between urine ACR and PAD. Hence urinary ACR can be considered as surrogate marker for early prediction of PAD in elderly patients with type 2diabetes mellitus eventually leading to aggressive intervention for prevention and management.

Keywords: Urine albumin creatinine ratio, Ankle brachial index, Peripheral arterial disease, Type 2 diabetes mellitus

INTRODUCTION

Albuminuria is not only the marker of renal damage in diabetics but denotes generalized endothelial dysfunction thereby predisposing the patient to multitude of vascular complications like onset of early atherosclerotic disease.[1,2] This finding establish the potential pathophysiologic relationship between albuminuria and various microvascular and macrovascular complications of diabetes thereby corroborating that kidney act as a window to the vasculature in other organs.[3-7] Thus markers of kidney dysfunction like albuminuria provides additional prognostic information about outcomes of health in diabetic patients.[8,9] For example, In the Heart Outcomes Prevention Evaluation Study (HOPE) trial, patients with microalbuminuria had almost three fold increase risk of major cardiovascular disease event in comparison to those without microalbuminuria.[10] The albuminuria can be broadly applied in the routine care of diabetic patients because is easily measurable and regarded as early predictor of end organ damage both in terms of micro and macroalbuminuria.

The relationship between albuminuria and one of the macrovascular complications namely peripheral arterial diseases (PAD) is not extensively evaluated. Though many epidemiological studies showed increase risk of PAD in patients with chronic kidney disease.[11,12] However establishing albuminuria as a surrogate marker for early prediction of PAD needs more further studies.[13,14] The Peripheral arterial disease is around twenty times more prevalent in diabetic patients and accounts for more than thirty fold higher risk of lower limb amputation in diabetes.[15,16] The onset of peripheral arterial diseases in diabetics heralds the development of all foot problems including infections, ulceration, gangrene, arthropathy and finally amputation.[17] The clinical detection of PAD in elderly diabetic patients is important to prevent occurrence of diabetic foot problems that otherwise take a huge toll over morbidity and mortality.[18,19] In this study we aim to evaluate the association between urinary albumin creatinine ratio (marker of albuminuria) and the Ankle Brachial Index (ABI) marker of peripheral arterial disease in patients with type 2 diabetes mellitus.

METHODS

Study subjects

It is a hospital base cross sectional study conducted in department of medicine at S.M.S medical college and hospital, Jaipur over a period of one and a half year. After taking clearance from ethical committee of our tertiary care hospital, patients / relatives were explained about the study and given complete information about the procedures undertaken and written consent was taken in their local language. The study population comprises of 74 patients diagnosed as type 2 diabetes mellitus after application of inclusion and exclusion criteria.

Inclusion criteria were; type 2 diabetic patients, age >50 years and informed consent to participate in the study. Exclusion criteria were; age <50 years, fever, urinary tract infection, nephritic syndrome, unwillingness to participate in the study and known case of vaso occlusive disease.

Methodology

All 74 diabetic patients comprising the study group were subjected to the following parameters: estimation of patient's risk factors; the basic determination of risk factors like age, sex, smoking habits, duration of diabetes, treatment history of oral hypoglycemic agents or insulin therapy and whether history of hypertension is present or not. The body mass index of the patient calculated by dividing body weight in kilogram with the square of the height in meters. Obtaining blood samples; The venous blood samples of all the study subjects were collected early in the morning to ensure at least 8 h period of fasting and samples obtained were subjected to determination of fasting plasma glucose and lipid profile including serum triglyceride and total cholesterol measurement including estimation of HDL and LDL levels. Measurement of urinary albumin-creatinine Ratio (ACR); also urinary samples also collected early in the morning, mainly first void and mid stream urine collected. The concentration of albumin and creatinine were measured in the urine using nephelometry and Jaffe method, respectively and the values so obtained were subjected to measurement of urinary ACR. The study population was further dividing on the basis of ACR into 3 categories as: normoalbuminuria <30 mg/g, microalbuminuria 30-300mg/g and macroalbuminuria >300 mg/g.

Ankle brachial index measurement

All study population were subjected to measurement of ABI for detection of PAD. In this technique, systolic blood pressure is measured in bilateral brachial arteries and in bilateral dorsal pedis and posterior tibial arteries after 20 min of rest by placing the patient in supine position. The ankle pressure was measured by placement of occluding cuffs just above the malleoli and flow further sensed by placing the Doppler probe. The higher pressures obtained in both the post tibial or dorsal pedis artery divided by the bilateral brachial artery pressures. The data so obtained is further used for classification of PAD. The ABI <0.9 in either of lower extremity is diagnostic of PAD.

Statistical analysis

Data thus collected were entered in the excel sheet and were subjected to the statistical analysis. The continuous variables were expressed as mean and standard deviation (SD) while quantitative data as percentages. Unpaired t test was used for the comparison of continuous variables while chi square test was used for qualitative data. The correlation analysis was done by using Pearson's correlation coefficient and linear regression analysis was done to find out significant predictors of the PAD. The value of significance of p value was taken to be <0.05.

RESULTS

Among the 74 subjects taken for the study 34 subjects had PAD and 34 subjects were not having PAD. Baseline Parameters compared in subjects with PAD and without PAD are mentioned in the (Table 1). The comparison among the mean values of the parameters in subjects with and without PAD is mentioned in (Table 2).

In this study, 74 type 2 diabetic subjects were taken after application of inclusion and exclusion criteria. Out of 74 subjects taken, 40 (54.05) were male and 34 (45.95) were female. Among those with PAD, 22 (59.46) were male and 15 (40.54) were female and in those without PAD, 18

(48.65) were male and 15 (40.54) were female. There was no significant difference in the sex distribution of two groups in context of with and without PAD.

Table 1: Baseline parameters.

Parameters
Age
Sex
Body mass index
Smoking habits
Duration of diabetes
Insulin therapy
History of hypertension
Systolic BP
Diastolic BP
S. Triglyceride level
S. Cholesterol level
S. HDL level
S. LDL level
Urine ACR

The mean age group of patient with PAD was 62.32± 5.8 years, while those without PAD were 56.97±4.48 years. There was significant difference in the mean age of two groups with p<0.001 thereby indicating that PAD was more prevalent in older age groups as indicated in (Figure 1). A study done by Farah Amir Ali et al conducted in Karachi found that subjects with ABI>0.9 were comparatively younger than subjects with ABI<0.9.

In our study mean BMI in group with PAD was 27.08±2.43 while those without PAD had mean BMI 26.11±2.43. There was no statistical significant difference seen in BMI between two groups (p=0.094). the study conducted by Basawaraj Belli et al at Karnataka, India also did not found any statistical significance in BMI between groups with and without PAD (p=0.875).

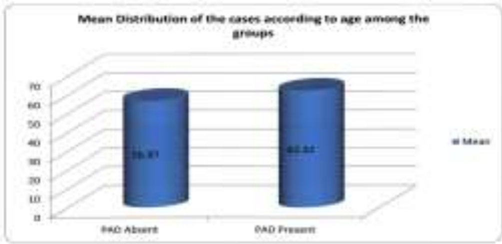

Figure 1: Mean distribution of cases according to age among the groups.

Out of 37 patients with PAD, 7 were smokers and out of 37 patients without PAD, 6 were non smokers. There was no statistical significant difference obtained BMI between two groups (p=1.00).

The mean duration of diabetes in patients with PAD was about 11.19±4.1 yrs and those without PAD were about 8.22±3.33 yrs. The mean duration of diabetes was significantly higher in group with PAD with p<0.001 as shown in the (Figure 2). The study done by Chin-Hsiao Tseng et al also found significant higher duration of diabetes in group with PAD in comparison to group without PAD. Similarly study conducted in Iran by Khadijeh Makhdoomi et al also concluded that the same point.

The number of patients on insulin therapy in patients with PAD was 15 (40.54) in comparison to only 5 (13.51) in patients without PAD. The higher number of patients on insulin therapy in patients with PAD showed statistical significance with p<0.001 as shown in the (Figure 3).

Table 2: Comparison of parameters in subjects with and without PAD.

Parameters	PAD Present	PAD Absent	P value
Age (years)	62.32±5.803	56.97±4.481	<0.001
Sex male (%)	22 (59.46)	18 (48.65)	0.484
Sex female (%)	15 (40.54)	19 (51.35)	0.555
Body mass index (kg/m^2)	26.11±2.48	27.08±2.43	0.094
Smoking status (%)	7 (18.92)	6 (16.22)	1.00
Diabetes duration (years)	11.19 ± 4.1	8.22 ± 3.33	0.001
Insulin therapy (%)	15 (40.54%)	5 (13.15)	0.018
History of hypertension (%)	27 (72.97%)	21 (56.76)	0.223
Systolic BP (mmHg)	142.49±13.46	133.19±15.7	0.008
Diastolic BP (mmHg)	84±6.42	81.62±6.87	0.129
S. Cholesterol (mg/dl)	221.35±17.10	206.81±24.33	0.004
S. triglyceride (mg/dl/)	242.81±40.66	199.76±35.06	<0.001
S. LDL (mg/dl)	116.89±28.77	103.59±25.74	0.04
S.HDL (mg/dl)	44.03±6.49	40.30±6.49	0.011
Mean ACR	294±314.90	143±214.6	0.018
Normoalbuminuria	4 (10.81%)	16 (43.24%)	
Microalbuminuria	21 (56.76%)	17 (45.95%)	<0.004
Macroalbuminuria	12 (32.43%)	4 (10.81%)	

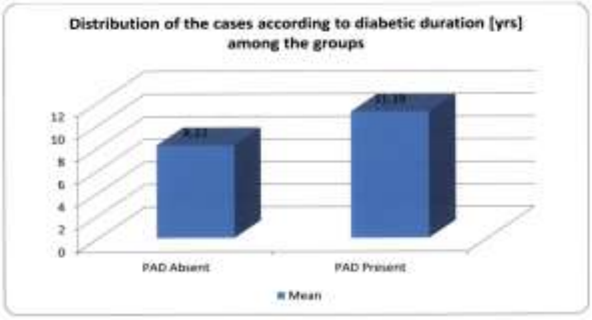

Figure 2: Distribution of cases according to diabetic duration among the groups.

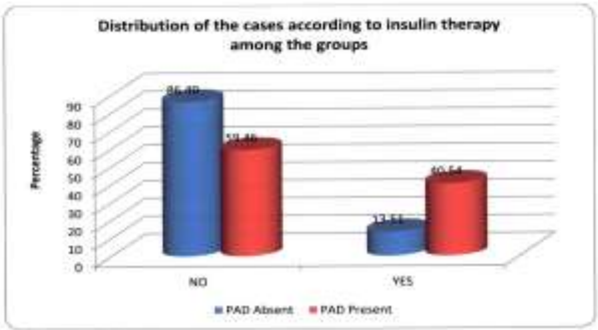

Figure 3: Distribution of cases according insulin therapy among the groups.

There was no statistical significant difference obtained in the prevalence of hypertension in two groups with p value 0.104 that further corroborated with findings of study done by Khadijeh Makhdoomi et al and Basawaraj Belli et al.

The mean systolic BP was significantly higher in group with PAD 142.49±13 mm Hg in comparison to 133.19± 15.7mmHg in group without PAD. The comparison showed statistical significance with p<0.008 as shown in the (Figure 4), however no significant difference was obtained in the diastolic BP (p=0.129).

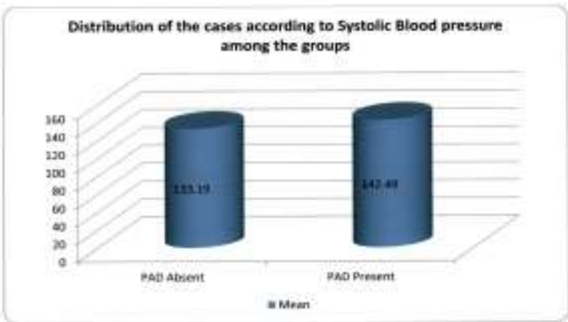

Figure 4: Distribution of cases according to systolic blood pressure among the groups.

The mean serum cholesterol in group with PAD was 221.35±17.10mg/dl while in group without PAD was 206.81±24.33mg/dl. The serum cholesterol level was significantly higher in group with PAD with p=0.004. The serum triglyceride level also showed statistical significance in group with PAD (p<0.001) with mean value 242.81±40.66mg/dl in group with PAD and mean value of 199.76±35.06mg/dl in group without PAD. The above findings of achieving statistical significance in serum cholesterol and serum triglyceride levels in group with PAD were also corroborated in the study done by Chin-Hsiao Tseng et al.

The mean serum LDL levels in group without PAD were 103.59±25.74mg/dl while those with PAD were around 116.89±28.77mg/dl. The serum LDL levels in group with PAD was significantly higher in comparison to group without PAD with p<0.004.

In contrast the mean serum HDL level in group without PAD was 40.30±5.77mg/dl while in group with PAD was about 44.03±5.77mg/dl, thereby showing no statistical significance between two groups(p=0.011). The observation of getting statistical significance in mean values of serum cholesterol, triglycerides and LDL in our study (Figure 5) is evident by the fact that there is higher prevalence of metabolic syndrome in PAD thereby establishing dyslipidemia as a risk factor for PAD.

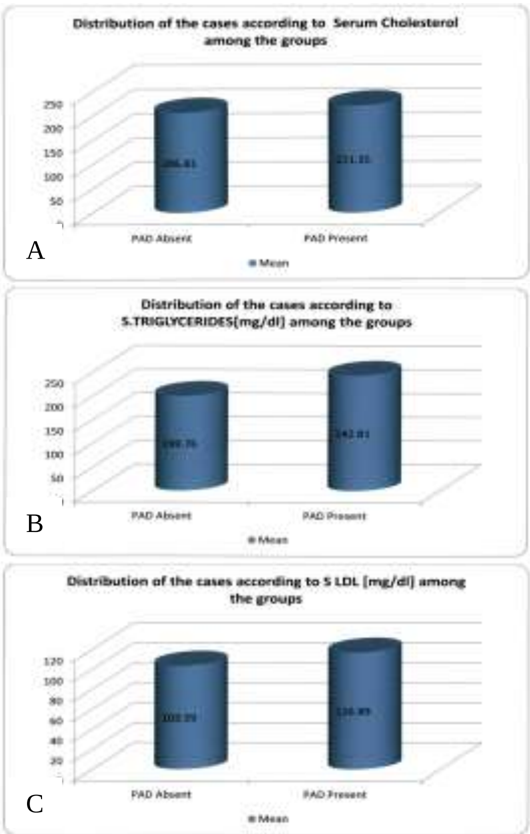

Figure 5: Distribution of cases according to serum (A) cholesterol, (B) triglycerides and (C) LDL among the groups.

In our study the prevalence of normoalbuminuria, microalbuminuria and macroalbuminuria in group without PAD was 4 (10.81%), 17 (45.95%) and 16 (43.24%), while in group with PAD, the prevalence was 12(32.43%), 21 (56.76%) and 4 (10.81%). The prevalence of normoalbuminuria, microalbuminuria and macroalbuminuria in group with PAD was statistically significant in comparison to group without PAD (p=0.004) as shown in the (Figure 6). The study done by Chin-Hsiao Tseng et al also showed similar result with the proportion of normoalbuminuria, microalbuminuria and macroalbuminuria in patients with PAD was 20.0, 57.8 and 22.2% and was 42.0, 51.4 and 6.5% in patients without PAD. The prevalence of micro and macroalbuminuria was significantly higher in patients with PAD (p<0.001).

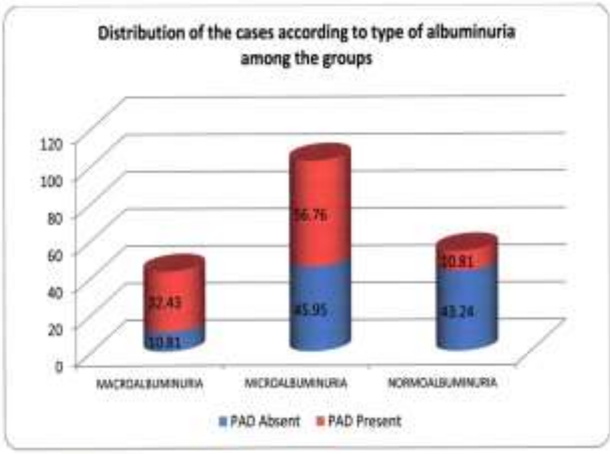

Figure 6: Distribution of cases according to albuminuria among the groups.

The mean ACR in our study in group with PAD was 294.62±314.90 mg/g while mean ACR was 143.32± 214.6mg/g in patients without PAD, thereby showing significantly higher value in group with PAD as shown in the (Figure 7).

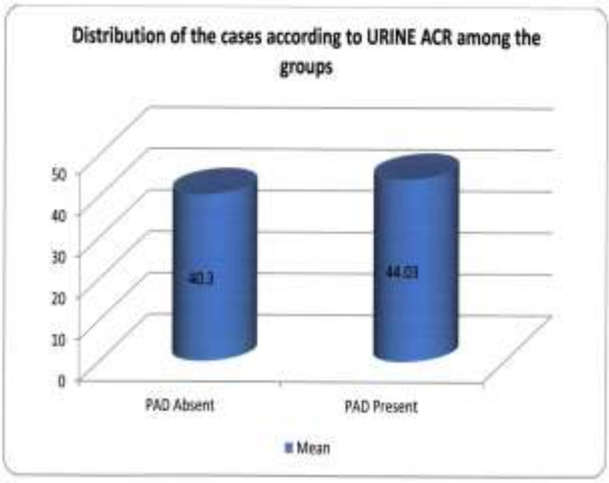

Figure 7: Distribution of cases according to urine ACR among the groups.

Correlation between urine ACR and ABI

The Pearson's correlation coefficient is applied between urine ACR and ABI levels showed significant negative correlation (r = -0.415, p<0.001) in our study. The value of r^2 is 0.172 meaning 17.2% of total variation in urine ACR was explained by linear relation with ABI as evident in (Table 3 and Figure 8).

Table 3: Correlation between urine ACR and ABI.

	n	Mean± SD	R	R^2	F Change
ABI	74	0.93±0.21	-0.415	0.172	<0.001
Urine ACR	74	244.59± 330.63			

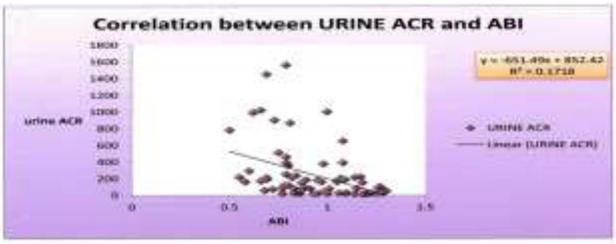

Figure 8: Correlation between urine ACR and ABI by Pearson correlation coefficient.

Correlation between urine ACR and ABI among males

A significant negative correlation existed between urine ACR and ABI levels in males (r = -0.441, p=0.004) by using pearson coefficient. The r2=0.194, it means 19.4% of the total variation in urine ACR was explained by the linear relation with ABI level as shown in (Table 4 and Figure 9)

Table 4: Correlation between urine ACR and ABI among males.

	n	Mean± SD	R	R^2	F Change
ABI	40	0.912±0.21	-0.441	0.194	<0.004
Urine ACR	40	265.87± 354.43			

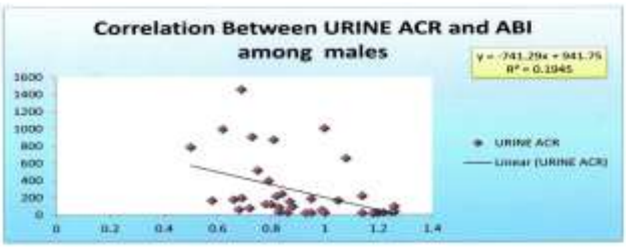

Figure 9: Correlation between urine ACR and ABI among males by Pearson correlation coefficient.

Correlation between urine ACR and ABI among females

A significant negative correlation existed between urine ACR And ABI levels in females (r= -0.137, p=0.031) by using pearson coefficient. The r^2=0.137, it means 13.7 % of the total variation in urine ACR was explained by the linear relation with ABI level as shown in (Table 5 and Figure 10).

Table 5: Correlation between urine ACR and ABI among females.

	n	Mean± SD	R	R^2	F Change
ABI	34	0.957±0.21	-0.317	0.137	<0.031
Urine ACR	34	219.87± 303.58			

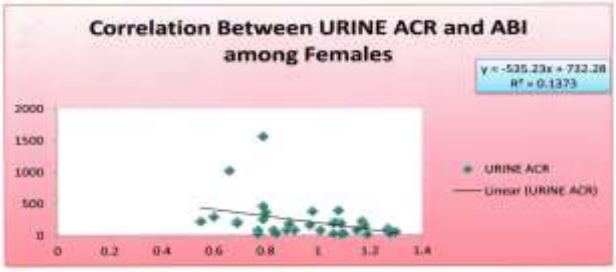

Figure 10: Correlation between urine ACR and ABI among females by Pearson correlation coefficient.

Correlation between urine ACR and various variables

Linear regression analysis showed that urine ACR had a significant positive correlation with FBS (r= -0.486, p=0.000). Rest of the parameters like age, sex, duration of diabetes, SBP, DBP, cholesterol, triglyceride levels, HDL and LDL did not show any significant correlation with urine ACR as evident in (Table 6).

Table 6: Correlation between urine ACR and other variables.

	n=74	Age	Sex	Duration of diabetes	SBP	DBP	Choles -terol	TG	HDL	LDL	FBS
Urine ACR	Pearson coefficent	0.173	-0.089	-0.130	0.101	0.064	0.043	0.035	0.106	-0.098	0.486
	Significance (2-tailored)	0.142	0.451	0.269	0.394	0.588	0.715	0.770	0.369	0.408	0.000

Predictors for PAD status by using logistic regression

A logistic regression analysis was done to predict the PAD among 74 patients using variables like age, sex, BMI, duration of diabetes, smoking habit, history of hypertension, serum cholesterol, serum triglyceride level, HDL, LDL, Urine ACR and albuminuria as predictors. A test of full model considered to be statistically significant indicating that predictors reliably distinguish between PAD present and PAD absent status. The good relationship between predictors and grouping is evident by chi square test 63.35, df 11, p<0.001 S and $r^{2\ of}$ 0.78. The Hosmer and Lemeshow test show significant model as chi square value 1.62 at df 8 and p=0.991. The overall predictive value accuracy was 87.8% with specificity 83.8% and sensitivity of prediction 91.9%. The Wald statistics showed that age, duration of diabetes, triglycerides and albuminuria significantly predicted the status of PAD. These variables were considered to be independent associated with PAD status with odd ratio of 1.420, 0.674, 1.039 and 45.245 respectively. The conclusion of our observation reached was that age, duration of diabetes, triglycerides and albuminuria were significant and independent predictors of PAD (Table 7).

DISCUSSION

The present study was conducted in department of medicine at SMS medical college and hospital, Jaipur. Our study establish negative correlation between urinary ACR and ABI levels and also established independent predictors of PAD in patients with diabetics like age, duration of diabetes and serum triglycerides in addition to albuminuria.

Following parameters were having statistically significant difference in the mean values among type 2 diabetic patients with and without PAD like age, duration of diabetes, number of patients on insulin therapy, systolic BP, serum cholesterol, serum triglycerides, serum HDL and LDL levels, urinary ACR, and distribution of albuminuria. In contrast no significant difference was noted in mean values of BMI, smoking habits, history of hypertension and diastolic BP.

The level of significance achieved by obtaining the p value for each parameters leads to important observation as illustrated in (Table 8).

It has been suggested that albuminuria is a marker of endothelial dysfunction, and is associated with many disease states like hypertension, hyperlipidemia, diabetes and many inflammation associated systemic diseases. Further albuminuria also reflects increased risk of kidney damage and cardiovascular diseases including PAD. In diabetes the hyperglycemia induces endothelial cells to increase the production of reactive oxygen species, free radicals and many advanced glycation end products (age), that in turn damage the vascular endothelial cells and establish a pro thrombotic state, thereby predisposing development and progression of atherosclerosis in the vascular beds of lower extremities causing PAD.[21-23] This endothelial dysfunction can even damage the glomerular basement membrane, causing damage to the podocytes that directly alter the permeability of glomerular barrier causing albuminuria.[23] Even in the absence of albuminuria, other features of kidney damage like low estimated glomerular filtration rate also denotes increase risk of PAD as shown by previous studies.[24]

Table 7: Predictors for PAD by using logistic regression.

Variables in the equation						
	B	**S.E**	**Wald**	**Df**	**Sig**	**Exp (B)**
Age	0.351	0.114	9.476	1	0.002.	1.420
BMI	-0.018	0.227	0.006	1	0.938	0.982
Diabetes duration	-0.394	0.153	6.683	1	0.010	0.674
Smoking	-1.107	1.224	0.819	1	0.366	0.331
HTN	0.272	0.992	0.075	1	0.784	1.313
Triglyceride	0.038	0.015	6.757	1	0.009	1039
HDL	-0.064	0.095	0.447	1	0.504	0.938
LDL	0.017	0.019	0.776	1	0.379	1.017
Urine ACR	0.002	0.002	0.928	1	0.335	1.002
Albuminuria	-	-	5.327	2	0.070	-
Albuminuria(1)	2.134	2.405	0.788	1	0.375	8.448
Albuminuria (2)	3.812	1.700	5.026	1	0.025	45.245
constant	-26.720	12.277	4.737	1	0.030	0.000

Table 8: Significant and non significant parameters in subjects with PAD.

Parameters with high level of significance	Parameters with no significance
Older age group	No differences in sex
Prolonged duration of diabetes	No differences in BMI
High insulin users	No differences by smoking habits
Higher systolic BP	No differences in terms of hypertension
Higher serum cholesterol leveL	No differences in diastolic BP
Higher serum triglyceride level	No difference in S. HDL level
Higher serum LDL level	
Urine ACR value significantly higher in patients with PAD	
The prevalence of normoalbuminuria, microalbuminuria and macroalbuminuria was significantly higher in PAD group	

There are many cross sectional studies that establish positive association between albuminuria and cardiovascular diseases and also between PAD and renal diseases but very few studies establish a correlation between albuminuria and PAD. There are few studies done previously like Chin-Hsiao Tseng et al on Taiwanese population, Yudkin et al and the cardiovascular heart study also showed increased prevalence of PAD in subjects with albuminuria, the findings of our study also matches with these previous studies and also further establish the fact that albuminuria is a major risk factor for generalized vasculopathy.

Establishing urinary ACR as surrogate marker for early prediction of PAD in elderly patients with type 2 diabetes mellitus has major potential implications. The main symptom of PAD is intermittent claudication.[25] Many of the diabetic patients are asymptomatic in regards to this symptom and also the clinical course of PAD is insidious in onset with low incidence rate, thus making PAD as underrecognized and undiagnosed for a long period of time until it commences in the form of major diabetic foot problems like infection, ulceration and arthropathy that significantly alter the quality of life. ABI is commonly used to measure PAD and value <0.9 is considered to be diagnostic of PAD whereas value between 1 and 1.40 is considered to be normal.[26-28] But ABI determination suffers from some serious limitations because diabetes renders arteries non compressible because of calcification leading to unusually high ABI values if lower limb arteries are affected. Hence sometimes ABI also cannot differentiate patients who have arterial occlusion from those who do not. The prevalence of albuminuria (whether micro or macro) is much higher than PAD in diabetics and also albuminuria is broadly applied in care of diabetics because of its easy measurability. Therefore establishing urinary ACR as marker of predictability of PAD can lead to timely detection and management of PAD causing serious reversibility of serious consequences.

CONCLUSION

The conclusion drawn from our study is that urinary ACR can be considered as early important marker for determination of PAD in patients of type 2 diabetes thereby necessitating the need of more prospective studies to corroborate this finding, as hospital based cross sectional design of our study confounds the emergence of casuality and directionality of cause effect association established in this study. Also timely institution of intervention on grounds of prevention and management can be properly launched.

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Ethical approval: Not required

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