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Urinary Albumin to Creatinine Ratio and the Risk for Asymptomatic Peripheral Arterial Disease among Elderly with Type 2 Diabetes Mellitus

KEYWORDS: Peripheral arterial disease urinary albumin to Creatinine ratio diabetes mellitus Ankle brachial index

Moatasem S. Amer	Mohamed S. Khater	Wessam H. El-Kawaly
Professor, the Geriatrics and Gerontology Department; Faculty of Medicine, Ain shams university, Cairo, Egypt.	Associate Professor, the Geriatrics and Gerontology Department; Faculty of Medicine, Ain shams university, Cairo, Egypt.	Lecture, Geriatrics and Gerontology Department; Faculty of Medicine, Ain shams university, Cairo, Egypt.

Omar H. Omar	Randa A. Reda
Professor, Radiodiagnosis Department; Faculty of Medicine, Ain shams university, Cairo, Egypt.	Professor, Clinical Pathology Department; Faculty of Medicine, Ain shams university, Cairo, Egypt.

ABSTRACT *Peripheral arterial disease (PAD) is more prevalent in patients with diabetes mellitus resulting in increased risk of lower extremity amputation and mortality 2. Microalbuminuria is also highly prevalent among diabetic patients and is an indicator for overt nephropathy and early cardiovascular disease but whether urinary albumin excretion rate is a risk factor for PAD or not, this question needs to be answered 10.*

Methods: 90 elderly subjects were subdivided into 3 groups; first group included 30 elderly diabetic patients without PAD, second group included 30 elderly diabetic patients asymptomatic for PAD but with arterial duplex showing PAD and third group included 30 controls without any health problems.

The relationships between urinary albumin to creatinine ratio, high sensitivity C - reactive protein (hs-CRP) and ankle-brachial index were examined.

Conclusion: Higher urinary albumin to creatinine ratio and higher CRP levels were risk factors for PAD in elderly diabetic patients asymptomatic for PAD.

Introduction:

Although diabetes mellitus is strictly defined by plasma glucose levels, it is also considered a vascular disease, in which the vasculature representing the "target organ" for atherosclerosis. Since this process diffusely affects the arterial system, a patient with diabetes and coronary artery disease may be expected to have coexistent PAD, cerebrovascular disease, and/or an abdominal aortic aneurysm 23.

One of the major health concerns for older diabetic persons is their potential risk for serious cardiovascular events; this risk rises dramatically with increasing age 3, 8.

The prevalence of PAD in diabetic patient`s population increases with advancing age, duration of diabetes, and the presence of peripheral neuropathy 20. Furthermore, cardiovascular and cerebrovascular events rates are higher in diabetic individuals with PAD than in comparable non-diabetic populations 24.

Microalbuminuria is considered a risk factor for cardiovascular disease as it is associated with several other factors that are highly correlated to cardiovascular diseases as hypertension, hyperglycemia, renal dysfunction, dyslipidemia, hyperhomocysteinemia, obesity, smoking and markers of acute phase response. Albuminuria also reveals increased renal endothelial permeability and may be easily measured marker of diffuse endothelial dysfunction 15.

Vascular inflammation, as measured by CRP, may be a common contributor to cardiac and renal affection in diabetic patients, therefore elevated CRP levels may be associated with microalbuminuria. Moreover microalbuminuria, an established risk marker for progressive kidney disease, can be used as a strong predictor of cardiovascular outcomes in diabetic patients 16.

The detection of the relationship between urinary albumin to creatinine ratio and the risk for asymptomatic PAD among elderly diabetic patients is the aim of this study.

Methods:

Study population

90 elderly (≥ 60 years) subjects were recruited from the inpatient wards and outpatient clinics at Ain Shams University Hospital. They were subdivided into 3 groups; the first group (Group I) included 30 elderly diabetic patients without PAD. The second group (Group II) included 30 elderly diabetic patients asymptomatic for PAD but with arterial duplex showing signs of PAD and the third group (Group III) included 30 controls without any health problems.

Diabetes mellitus was defined according to the American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dl (minimum of 8 h fasting), a random or post load serum glucose level glucose ≥200 mg/dl after an oral glucose tolerance test, or use of hypoglycemic medication. Subjects with hypertension, history or symptoms suggestive of PAD, ischemic heart disease, renal or hepatic diseases, medical conditions affecting urinary albumin to creatinine ratio as congestive heart failure or urinary tract infection, medical conditions affecting CRP level as rheumatoid arthritis, osteoarthritis, infections, systemic malignancies, autoimmune diseases, trauma or tissue necrosis were all excluded from the study. Also those taking aspirin or statins were excluded for their effect on CRP level.

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The body mass index (BMI) was calculated as body weight (kg)/height2 (m2).

Laboratory assessment:
Morning sample of urine for measurement of albumin to creatinine ratio (ACR) was subjected to centrifugation for exclusion of any sediment then frozen at -20 ° C until assayed by enzyme immunoassay for the quantitative determination of albumin in urine using Orgentec Diagnostika GmbH kit (Germany).

Serum level total cholesterol, HDL, LDL and TG were measured by enzymatic hydrolysis and oxidation of a fasting sample using Stanbio cholesterol colorimetric detection kit (USA), CRP was measured using enzyme linked immunosorbant assay (ELISA) using DiaMed EuroGen diagnostic Kit (Belgium).

Measurement of fasting plasma glucose levels is done using the glucose oxidase-peroxidase method.

Radiological assessment:
A diagnosis of PAD was made based on an ankle–brachial index (ABI) of less than 0.90 on either leg by using Hitachi, EUB-565A, B mode-Doppler associated with color imaging.

Ethical considerations
Informed consent was taken from all elderly participating in this study. The study methodology was reviewed and approved by the Research Review Board of the Department of Geriatrics and Gerontology, Faculty of medicine, Ain Shams University.

Statistical methods:
Analysis of data was performed by using version 13 of the Statistical Package for Social Science (SPSS). Comparison between quantitative variables was done using ANOVA (analysis of variance) to compare the 3 groups. Comparison of qualitative variables was carried out using the Chi-square test. Correlation between variables was carried out using the Spearman correlation co-efficient. A $P < 0.05$ (two sided) was considered significant.

Results:
The mean age was 70.867± 9.457 years for cases and 69.433 ± 7.205 years for controls with 41 male and 49 female patients (Table 1).

Diabetic patients with PAD had a mean (± SD) urinary albumin to creatinine ratio (ACR) of (137.887 ± 116.93) mg/g and in those without PAD it was (72.877 ± 55.125) mg/g while the mean urinary albumin to creatinine ratio in the control group was (34.712 ± 16.469) mg/g ($p < 0.001$) (Table 1).

Diabetic patients with PAD showed a mean (± SD) hs CRP level of (18.700 ± 4.858) mg/l and in those without PAD it was (7.067 ± 2.420) mg/l while controls showed a mean (± SD) CRP level of (2.157 ± 1.533) mg/l ($p < 0.001$) (Table 1).

Microalbuminuria was present in 70% (n=21) of diabetic patients with PAD, in 66.6% (n=20) of diabetic patients without PAD and in 30 % (n=9) of the controls. All the patients with macroalbuminuria (n=7) had PAD. However, most of the normoalbuminuric subjects (70%) are among the control group (Table 2).

Among diabetic patients the urinary albumin to creatinine ratio was negatively correlated to ABI measured by Doppler method (r=-0.219, p 0.032) and positively correlated to hs CRP (r=0.255, p= 0.049) and the ABI was negatively correlated to total cholesterol (r=-0.490, p= <0.001), low-density lipoprotein cholesterol (r=-0.297, p= 0.021), and hs CRP (r=-0.664, p<0.001) (Table 3).

Diabetic patients with PAD had higher BMI, higher and longer diabetic duration than diabetic patients without PAD (Table 1).

Diabetic patients with PAD had higher FBS, 2hPP, total cholesterol, triglycerides, low-density lipoprotein cholesterol and lower levels of high-density lipoprotein cholesterol compared to those without PAD (P<0.05) (Table 1).

Table 1 Characteristics of the studied sample

	Group I	Group II	Group III	ANOVA	
	Mean± SD	Mean± SD	Mean± SD	F	p-value
Age	70.067±7.084	70.867±9.457	69.433±7.205	0.24242	0.785
BMI	31.553±7.794	40.847±5.684	25.090±3.635	53.131	<0.001
T.CHO	180.800 ±54.085	254.800 ±36.226	130.500±51.545	28.924	<0.001
TG	153.767 ± 66.372	203.433±65.778	96.000 ±69.399	8.581	<0.001
LDL	129.800 ±36.964	152.233 ± 39.605	87.000 ±38.338	12.174	<0.001
HDL	34.23 ± 13.216	33.767 ±8.106	50.133 ± 13.733	16.028	<0.001
Hs CRP	7.067±2.420	18.700±4.858	2.157±1.533	184.984	<0.001
ACR	72.877±55.125	137.887±116.93	34.712±16.469	14.420	<0.001
ABI	1.087±0.107	0.690±0.192	1.067±0.099	77.198	<0.001

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Table 2 Urinary albumin excretion (UAE) in the studied groups

UAE		Group I	GroupII	GroupIII	Total
Normoalbuminuria	N	10	2	21	33
	%	33.33	6.67	70.00	36.67
Microalbuminuria	N	20	21	9	50
	%	66.67	70.00	30.00	55.56
Macroalbuminuria	N	0	7	0	7
	%	0.00	23.33	0.00	7.78
Total	N	30	30	30	90
	%	100.00	100.00	100.00	100.00
Chi-square	X^2	35.865			
	P-value	<0.001			

Table 3 The correlation between ABI and studied variables

	ABI	
	r	P-value
ACR	-0.219	0.032
hs-CRP	-0.664	<0.001
T.Cholesterol	-0.490	<0.001
TG	-0.204	0.118
HDL	0.123	0.350
LDL	-0.297	0.021

Discussion:

Older patients with diabetes are particularly clinically challenging, as they are considered as a heterogeneous population with differences in functional status, duration, severity, and complications of diabetes. Added to the challenge of how to prioritize care for those individuals is the recognition that atherosclerotic vascular disease in older adults is often clinically silent and lacking symptoms 32.

Because vascular changes inflicted by multiple environmental and genetic factors develop years before an event, detection of vascular damage can serve as a predictor of future cardiovascular complications 30.

In the current study BMI is higher among diabetic patients and highest among diabetic patients with PAD. In the Framingham Heart Study each 5-point increase in BMI made a person 40% more likely to develop PAD 21. Other studies as 5, 6, 7, and 14 agreed with the same results.

However, unlike our results Tseng et al. 28 found that diabetic patients with PAD had lower BMI than those without PAD. This controversy may be related to ethnic differences as this study was conducted among Japanese patients.

Duration of diabetes in our study was longer in diabetic patients with PAD than in those without PAD (19 years vs. 4.6 years). The same results were reported by Li et al. 17 who suggested that patients with low ABI had a longer duration of diabetes compared with those with a normal ABI. Also, Asakawa et al. 5 and Tseng et al. 28 agreed with our results.

The results of the current study revealed a highly statistically significant difference between the studied groups as regards total cholesterol, LDL, HDL cholesterol, and TG levels. In which the mean values of total cholesterol, LDL cholesterol and TG are higher in diabetic patients than controls and highest among diabetics with PAD. Also, the mean value of HDL cholesterol was lower in diabetic patients than controls and lowest among diabetics with PAD. These results agreed with 1, 14, and 18.

Regarding albumin to creatinine ratio, most studies 10, 26, and 32 had shown that microalbuminuria is highly predictive not only for the development of diabetic nephropathy but also for subsequent atherosclerotic vascular disease.

Dysfunction of the vascular endothelium and chronic low-grade inflammation are key features of the initiation of atherosclerosis. Many biochemical parameters can detect endothelial dysfunction and chronic inflammation (e.g., CRP, von Willebrand factor, sialic acid, soluble vascular cell adhesion molecule 1, and fibrinogen) have been shown to be significantly associated with microalbuminuria. These findings support a hypothesis that microalbuminuria reflects generalized vascular damage which may promote atherosclerosis 34.

The current study demonstrated that microalbuminuria was high among diabetic patients and higher among diabetic patients with PAD. Moreover, macroalbuminuria was also presented among diabetic patients with PAD by 23.3%. 4, 12, 27, 28, 31 all agreed with these results.

As regards the correlation between ACR and ABI, the current study revealed significant negative correlation of ACR with ABI. Similar results were reported by the study of Tseng et al. 28, in which ABI was correlated significantly with ACR in all subjects.

Furthermore, the study of Escobedo et al. 11, that was conducted to evaluate the effect of diabetes duration and microalbuminuria or macroalbuminuria on the presence and severity of CAD and PAD, revealed that the presence of albuminuria is a potential surrogate marker for the severity of vascular disease in diabetes.

The current study also found a significant positive correlation between hs-CRP level and ACR. CRP is significantly higher with microalbuminuria. The results elicit the hypotheses that vascular inflammation may be a determinant of microalbuminuria. These findings add evidence to the relation between early renal and cardiovascular diseases. Furthermore, CRP and ACR are minimally invasive, inexpensive, and quantitative in nature, and so can be used not only in clinical research but also, in routine patient care 9. Similar results were obtained by Kshirsagar et al. 16 and Nakamura et al. 22.

Also, Mojahedi et al. 19 revealed in their study that microalbuminuria is positively correlated to elevated hs-CRP suggesting the measurement of serum hs-CRP as a screening method in future studies, to help in diagnosing early stages of diabetic nephropathy sooner and easier.

Regarding the levels of inflammatory markers among diabetic patients, most studies 2, 18, 25, had shown that diabetic patients had higher concentration of inflammatory markers than normal persons. The same results were supported by the current study which found that diabetic patients (mean hs-CRP 7 mg\L) had higher levels of high sensitivity C-reactive protein than the control group (mean hs-CRP 2.1 mg\L). Moreover, diabetic patients with PAD had the highest levels of hs- CRP (mean hs-CRP 18.7 mg\L).

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As regards the correlation between hs-CRP levels and ABI, the current study revealed significant negative correlation of hs-CRP levels with ABI. Wildman et al. 33 also concluded that inflammation is independently associated with PAD. In this study, ABI was highly negatively correlated to hs- CRP. 13, 29, 35 agreed with this.

The current study revealed that the markers of vascular endothelial Dysfunction (ACR), chronic low-grade inflammation (hs-CRP) and lipid abnormalities are associated with PAD in diabetic patients and are considered as key features of the initiation of atherosclerosis in these patients.

Conclusions:

Our study shows that elderly diabetic patients with asymptomatic peripheral arterial disease had increased cardiovascular risk factors, including CRP, albumin to creatinine ratio, dyslipidemia and obesity than diabetic patients without peripheral arterial disease.

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