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A Correlational Study of Ankle-Brachial Index with Estimated Glomerular Filtration Rate and Urine Albumin-Creatinine Ratio to Assess Renal Function in Diabetes

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Abstract

Background: Diabetes mellitus related complications are a major burden in public health and with the onset of complication; there has been a significant reduction in the overall quality of life. It is the most important risk factor for atherosclerotic vascular disease and the most frequent cause of end-stage renal disease. Aims and Objectives: This study was conducted to diagnose early microvascular complications like renal dysfunction in early stage by using the Ankle Brachial Index (ABI) which is a non-invasive marker for diagnosing macrovascular complications of diabetes. **Design:** 100 cases of diabetes were taken for study and their data were correlated with the same number of age sex-matched controls.

Materials and Methods: The study included 100 male and female patients aged 20-60 years diagnosed with Diabetes mellitus both Type 1 and Type 2; on insulin and/ or oral agents for at least 5 or more years. ABI was correlated with Estimated Glomerular Filtration rate (e-GFR) and urine Albumin Creatinine Ratio (UACR) in combination.

Results: Bivariate correlation between ABI and e-GFR; ABI and UACR showed strong positive and negative linear correlations respectively with significant (p-value < 0.001) coefficient values (r) of 0.697 and - 0.652. It was also found that increasing age, increasing duration of diabetes and sedentary lifestyle was associated with low ABI.

Conclusions: It can be taken that ABI is a non-invasive diagnostic tool for peripheral arterial diseases, which also can also be used in the detection of microvascular complications of diabetes like renal dysfunction in early stage.

Keywords: Diabetic vasculopathy; Ankle-Brachial Index; Estimated Glomerular Function Rate; Urine Albumin-Creatinine Ratio

Introduction

Diabetic vasculopathy broadly comprises of micro-vascular and macro-vascular complications. The micro-vascular complications of diabetes include diabetic nephropathy, neuropathy and retinopathy and macro-vascular complications are cardio-vascular, cerebro-vascular and peripheral vascular diseases (1). Diabetic nephropathy is major micro-vascular complication of diabetes, a leading cause of end-stage renal disease and is associated with increased cardiovascular mortality (2). According to various epidemiology studies that about 20-40% of diabetic people will develop proteinuria and progressive renal failure within 15-20 years of onset of diabetes (3). After clinical proteinuria mean survival is only 5 years without renal replacement therapy (4).

Ankle-brachial index (ABI) is simple useful method used in clinical practice for assessment of the peripheral vascular diseases (PAD) and in epidemiological studies (5). Ankle-brachial index (ABI) is the ratio of the resting ankle to brachial systolic blood pressure. A low ABI (< 0.90) was considered to be a predictor for risk of cardiovascular diseases (6). The measurement of ABI is also recommended by American Heart Association as a diagnostic criterion for the prevalence of peripheral arterial diseases (7).

Micro-albuminuria is a potent risk factor for progressive renal disease. It may be an early sign of endothelial dysfunction, inflammation with intra-renal vascular dysfunction (8). Low ABI which is associated with PAD may be related to micro-albuminuria which is due to endothelial damage and also declining Glomerular Filtration Rate (GFR) (9).

So, we conducted a hospital based study in diabetic population with appropriate matched control, to determine correlation between ABI and diabetic renal dysfunction measured by e-GFR calculation with MDRD formula and Urine Albumin Creatinine Ratio (UACR).

Materials and Method

Patients: This study was conducted at Departments of Medicine and Departments of Endocrinology and Cardio-Diabetes clinic in IPGMER & SSKM Hospital with 100 male and female patients aged 20-60 years diagnosed with Diabetes mellitus both Type 1 and Type 2 (according to ADA 2018 guidelines); on insulin and/ or oral agents for at least 5 or more years. Proper informed consent was taken from all of them before history evaluation and investigations.

Patients with deep vein thrombosis, excruciating lower limb pain, history of smoking and end stage renal disease or on renal replacement therapy, were excluded from the study.

Control group: 100 age and sex matched non diabetic control were taken in the study for better comparison in analysis.

Ankle Brachial Index: ABI was measured in patients, at rest for 5 – 10 minutes in the supine position, relaxed, head and heels supported, in a room with comfortable temperature (19°C–22°C/66°F–72°F) . The width of the sphygmomanometer cuff covered at least 40% of the limb circumference and 80% of arm circumference. The lower edge of the cuff was 2 cm above the superior aspect of the medial malleolus. An 8- to 10-MHz Doppler probe was placed in the area of the pulse at a

45° to 60° angle to the surface of the skin. The cuff was inflated progressively up to 20 mm Hg above the level of flow signal disappearance and then deflated slowly to detect the pressure level of flow signal reappearance. The maximum inflation was 300 mm Hg. The higher of the two ankle pressures was divided by the brachial artery pressure. Values were interpreted as follow:

ABI	Interpretations
0.91 – 1.30	Normal
0.70 – 0.90	Mild obstruction
0.40 – 0.69	Moderate obstruction
< 0.40	Severe obstruction
> 1.30	Poorly compressible

Blood parameters

Serum glucose, fasting (F) and post prandial (PP) were measured by Spectrophotometry with 2 mL (1 mL min.) each of Ship refrigerated or frozen plasma from Grey Top (Sodium Fluoride) tube, collected at minimum 12 hours overnight fasting and after 2 hours after finishing a normal meal. HbA1c was measured by High Performance Liquid Chromatography with 3mL (2mL min.) of Ship refrigerated whole blood in EDTA tube. Serum Creatinine was estimated by Compensated Jaffe's Reaction with 2 mL (0.5 mL min.) of Ship refrigerated or frozen serum from serum-separating tubes. Serum LDL, HDL, Total cholesterol and Triglyceride were quantified by Spectrophotometry with 2 mL (0.5 mL min.) of Ship refrigerated or frozen serum from 1 serum-separating tubes, collected at minimum 12 hours overnight fasting. Urine albumin creatinine ratio (UACR) was measured by Immunoturbidimetry, Spectrophotometry with 15 mL (10 mL min.) aliquot of random urine in a sterile screw capped container which was Ship refrigerated.

e-GFR:

Renal function was be assessed by serum creatinine and e-GFR and calculated using the abbreviated MDRD formula as follows:

e-GFR = 186 × (SCR × 0.011)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female) × (1.210 if African American) (SCR was serum creatinine expressed as µmol/L).

Study design

Study approval: This study was approved by the IPGME&R Research Oversight Committee (Institutional Ethics Committee), Institution of Post graduate Medical Education & Research, 244, A.J.C. Bose road, Kolkata 700020.

Data analysis: Data was analysed with appropriate statistical tests and methods to determine the significance and power of study with the help of standard statistical software (SPSS) version 16.

Results and Analysis

Data generated from this study, conducted to analyze the correlation between Ankle-brachial Index (ABI) and renal function in diabetic population of 100 cases with 100 age and sex matched controls, are as follow.

In case population, the mean age (mean ± S.D.) of patients was 49.23 ± 9.06 years with range 23-60 years and the median age was 51 years. In controls, the mean age (mean ± S.D.) of patients was 45.12 ± 10.18 years with range 23-59 years and the median age was 47 years. Total numbers of females in case and control population are 29 and 37 respectively and total numbers of males in case and control population are 71 and 63 respectively.

Among 39 out of 100 cases with history of hypertension had ABI < 0.9 with p value of < 0.001. There were 23 cases without any family history of diabetes, dyslipidemia, hypertension having ABI < 0.9 with p value of 0.8641. Respectively 22 and 21 cases had ABI < 0.9 in those who were treated with oral hypoglycemics and those were not. 20 and 23 cases had ABI < 0.9 in insulin treated and non-insulin group respectively [Table 1].

Among all study population 42 patients aged more than 40 years had ABI < 0.9 with Odds ratio (OR) 5.37 and *p* value 0.003. Diabetes more than 10 years and cases who did not do regular exercise were significantly correlate with low ABI (< 0.9) having OR 2.78 and 5.39 respectively and *p* value < 0.001 in both group [Table 2]. The coefficients of Pearson correlation analysis between ABI and other variables like blood pressure, body mass index (BMI) and lipid profile are shown [Table 3]. ABI has significant negative correlation with systolic blood pressure, BMI, triglyceride and total cholesterol levels and weak and no correlation with LDL and HDL levels respectively.

Diabetic people with ABI < 0.9 had minimum e-GFR of 38.70 ml/min/1.73m^2 and maximum e-GFR of 115.10 ml/min/1.73m^2 with mean ± SD e-GFR value of (63.69 ± 16.30) ml/min/1.73m^2 and statistically significant *p* value against their non-diabetic controls [Table 4]. Also, cases with ABI < 0.9 had minimum, maximum and mean ± SD UACR levels of 124.70 mg/g, 2413.10 mg/g and (946.47 ± 719.50) mg/g respectively with *p* value of < 0.001 [Table 5]. Bivariate correlation between ABI and eGFR ; ABI and UACR showed strong positive and negative linear correlations respectively with significant (*p* value < 0.001) coefficient values (r) of 0.697 and -0.652 [Figure 2,3].

Discussion

In this study, we have found that increasing age, increasing duration of diabetes and sedentary life style without any exercise has been associated with low ABI, which is further associated with peripheral arterial disease (PAD) and other cardiovascular complication both in diabetic and non-diabetic population as described by various study. The crude risks of all-cause and CVD mortality among the low compared with normal-ABI groups were 2.05 (1.98 to 3.04) and 3.76 (2.57 to 5.49), respectively (10).

Poor glycaemic control is associated with low ABI which further increases chances of cardiovascular mortality and PAD. Helaine ER et al in their study showed that, high fasting plasma glucose was associated with low ABI with crude OR of 17 and 95% CI was 7-27 (10). It was also stated in the study that high BMI, total cholesterol, triglyceride, LDL cholesterol was also associated with low ABI of < 0.9. One important finding is that low ABI has no correlation with HDL cholesterol level suggested by r = 0.2364 and *p* value of 0.0178 and had weak correlation with LDL cholesterol level suggested by r = -0.3054 and *p* value of 0.0020. Doza et al in their study showed that all subjects with type 2 diabetes ABI was negatively correlated with SBP ($r = -0.247$, $P = 0.001$; $r = -0.145$, $P = 0.002$) and DBP ($r = -0.171$, $P = 0.001$; $r = -0.102$, $P = 0.029$) for men and women, respectively (11).

Sheen YJ et al. group found significant correlation between low estimated Glomerular filtration rate with ankle-brachial and toe-brachial index (TBI) in 1461 Taiwanese type 2 diabetic outpatients. Ankle-brachial index values < 0.9 were found in 2.8% of the patients. Estimated glomerular filtration rate (e-GFR; 90 ± 33 mL/min/1.73 m^2) obtained from 473 patients correlated significantly with both ABI and TBI. Progressive e-GFR decline was observed in 419 participants with normal ABI and TBI, 35 with normal ABI but low TBI, and 19 with low ABI and normal or low TBI (*p* for trend < 0.001) (12). According to Jin X et al a study which was done on 2057 hospitalized patients with T2 DM, low ABI (< 0.9) was positively correlated with e-GFR (*p* <

0.01) by logistic regression. In addition to the association of the ABI with cardiovascular events, stroke, and PAD, ABI may also predict the change in renal function in patients with T2DM (13). In the Atherosclerosis Risk in Communities study, ABI < 0.90 was associated with increased risk of having an e-GFR < 90 mL/min/1.73 m^2 (OR: 1.80; 95% CI: 1.40-2.32) (14).

Chin-Hsiao Tseng et al in their study on elderly Taiwanese patients with type 2 diabetes mellitus showed that ACR was inversely correlated with ABI in all patients ($\gamma = -0.198$, $p < 0.01$) and in separate sexes ($\gamma = -0.211$ for men and $\gamma = -0.181$ for women) (15). Population with T2 DM aged ≥ 65 years (71.6 ± 4.9) was included in the study. Compared to this study we included patient with age < 60 years, because increased age itself can be associated with vascular atherosclerosis and stiffening which may decrease or increase ABI respectively.

Even after extensive literature review there was no article regarding correlation between ABI with e-GFR and UACR in combination. Both e-GFR and UACR are used to detect renal function in diabetes. ABI is commonly used as a non-invasive diagnostic tool for diagnosis of PAD which may be one of the macrovascular complications in diabetes causing significant cardiovascular morbidity. Diabetic renal dysfunction is a major microvascular complication in diabetes causing immense health cost burden because diabetes is one of the major cause of ESRD. The renal dysfunction in diabetes is attributed due to endothelial dysfunction. Thus UACR has been considered as a marker of endothelial dysfunction, which has been associated with increased insulin resistance, arterial stiffness, vascular inflammation, cardiovascular events, vascular atherosclerosis. Thus ABI can also be used as a non-invasive marker of endothelial dysfunction, which is the corner stone to both macrovascular and microvascular complications of diabetes (16).

The results of our study suggested that early CKD also may be associated with significant PAD risk. Atherosclerosis of the lower extremities has been associated with whole-body atherosclerosis, specifically in the large and medium-sized renal arteries (17).

Conclusion and Limitations

From our study, it can be stated that

1. ABI can be used as a non-invasive diagnostic tool for diagnosis of microvascular complications like nephropathy, retinopathy and neuropathy.
2. It can also be concluded that ABI is negatively correlated with blood pressure, BMI, serum Triglyceride and cholesterol level, so therapeutic intervention in the form of ACE-I, ARBs and statin therapy can be options to prevent micro vascular complications of diabetes and would benefit from the early implementation of appropriate therapeutic strategies.

1. This study was limited to only 100 cases and controls with majority from the older population. So, result may not be applicable to younger group and a larger sample size would have been better for stronger correlation.
2. Inter-observer variation while measuring Ankle Brachial Index (ABI) and technical difficulties contributed to some limitations.
3. Our study is a cross-sectional retrospective study which measured only associations rather than direct cause and effect relationship and follow ups are essential to establish the therapeutic efficacy of various drugs on renal function of diabetes population compared with follow up ABI.

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Legends Tables and Figures

Table 1: Correlation of ABI with history of hypertension; family history of hypertension, diabetes, dyslipidemia; oral hypoglycemic and insulin use

ABI	History of hypertension		Family history of hypertension, diabetes and dyslipidemia		On oral hypoglycemic agents		On insulin	
	Positive	Negative	Positive	Negative	Yes	No	Yes	No
< 0.9	39	4	20	23	22	21	23	20
≥ 0.9	32	25	24	33	48	9	10	47

Table 2: Overall correlation of ABI with age; sex; duration of diabetes and exercise with Odd ratios and *p* values

		ABI < 0.9 N (%)	ABI ≥ 0.9 N (%)	Odds ratio with 95% confidence limit	*p* value
Age	≥ 40 years	42 (27.3)	112 (72.7)	5.37 (1.58 , 18.26)	0.003
	< 40 years	3 (6.5)	43 (93.5)		
Sex	Female	13 (19.7)	53 (80.3)	0.78 (0.37 , 1.61)	0.506
	Male	32 (23.9)	102 (76.1)		
Duration of diabetes	> 10 years	11 (100.0)	0 (0.0)	2.78 (2.10 , 3.67)	< 0.001
	≤ 10 years	32 (36.0)	57 (64.0)		
Exercise	No	35 (36.5)	61 (63.5)	5.39 (2.45 , 11.68)	< 0.001
	Yes	10 (9.6)	94 (90.4)		

Table 3: Correlation coefficients of ABI with blood pressures, BMI and serum lipid profile

Variables	Correlation coefficient (r)	*p* value
Systolic blood pressure	- 0.5056	< 0.00001
Diastolic blood pressure	- 0.3164	0.001361
Body mass index	- 0.4259	< 0.0001

Low density lipoprotein	- 0.3054	0.0020
High density lipoprotein	0.2364	0.0178
Triglyceride	- 0.542	< 0.00001
Total cholesterol	- 0.6034	< 0.00001

Table 4: Correlation between ABI and e-GFR in cases and controls

ABI	e-GFR* (ml / min./ 1.73 m^2)		
		Case	Control
< 0.9	Min.	38.70	87.30
	Max.	115. 10	114.00
	Mean	63.69	100.65
	SD	16.30	18.88
	p value	< 0.001	0.509
0.9 – 1.3	Min.	62.60	90.40
	Max.	132.50	128.40
	Mean	97.68	105.42
	SD	14.84	9.95

*e-GFR Estimated Glomerular filtration rate

Table 5: Correlation between ABI and UACR in cases and controls

ABI	UACR* (mg / g)		
		Case	Control
< 0.9	Min.	124.70	22.00
	Max.	2413.10	26.87
	Mean	946.47	24.44
	SD	719.50	3.44
	p value	< 0.001	0.087
0.9 – 1.3	Min.	3.56	3.76
	Max.	221.70	29.00
	Mean	35.42	17.05
	SD	39.48	6.01

*UACR Urine Albumin-Creatinine Ratio

Figure 1: Study design flow chart

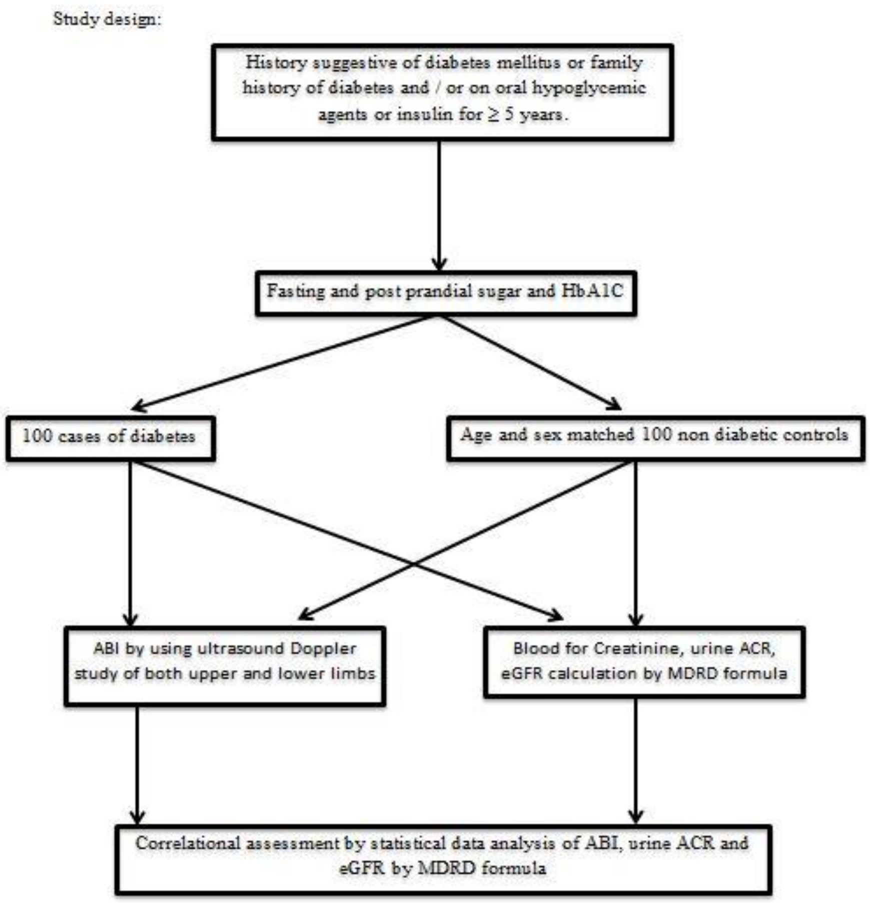

Figure 2: Scatter dot plot showing linear strong positive correlation between ABI and e-GFR.