
ASSOCIATION OF BLOOD INFLAMMATORY MARKERS WITH ANKLE BRACHIAL PRESSURE INDEX IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: A significant positive correlation exists between the inflammatory markers, hs-CRP (C reactive protein) and ferritin and the parameters of dyslipidemia in patients with type 2 diabetes. Not much is known regarding diabetes, inflammation and vasculopathy especially in relation to ferritin from this region. **Aim:** To correlate serum CRP and ferritin levels with Ankle Brachial Pressure Index (ABPI) in type 2 diabetic patients. **Methodology:** Descriptive observational study of 50 diabetic patients done at K. S. Hegde Medical College Hospital, Mangalore, Karnataka, India. **Results:** ABPI correlated negatively with serum ferritin values; with a Pearson correlation value and p value of -0.187 and 0.194 respectively. Also, ABPI negatively correlated with CRP, and this correlation was statistically significant (-0.382, P=0.006). **Conclusion:** Measurement of ABPI is a simple and clinically useful tool in identifying peripheral arterial disease in patients at risk of accelerated atherosclerosis. ABPI negatively correlated with serum ferritin and CRP levels in this study, though the association with ferritin was statistically not significant. Further large scale studies are needed to elucidate the association of ferritin as a nonconventional risk factor of atherosclerosis and PAD in type 2 diabetes mellitus.

Keywords: Ankle Brachial Pressure Index (ABPI), hs-CRP (C reactive protein), Ferritin, Type 2 Diabetes mellitus, Cardio-Vascular Disease (CVD), Inflammation

1. Introduction

Atherosclerosis is a chronic low-grade inflammatory disease.¹ A significant positive correlation exists between the inflammatory markers, hs-CRP (C reactive protein) and ferritin and the parameters of dyslipidemia in patients with type 2 diabetes.² Serum C-reactive protein (CRP) has proven to be an independent marker of the extent of atherosclerosis in patients with coronary, cerebrovascular and peripheral arterial disease. Also, elevated circulating ferritin concentrations were associated with higher risk of type 2 diabetes and metabolic syndrome in middle-aged and elderly patients independent of obesity, inflammation and other risk factors.³

Comparison of BP measurements in the ankle and arm is a simple, low-cost diagnostic test for the detection of PVD.^{4,5} The ABI, a ratio of the ankle and arm pressures (also referred to as ankle/arm index [AAI] and ABPI) has been used widely in clinical and epidemiological studies to screen for PAD and is believed to be highly correlated with the PAD of lower extremity.⁵ An ABPI value less than 0.9 is an independent risk factor for an episode of CVD, for recurrent CVD and for mortality in elderly adults.⁶ Studies have shown the sensitivity of ABPI to be 90% with a

corresponding 98% specificity for detecting hemodynamically significant stenosis >50% in major leg arteries, defined by angiogram.⁷ Correlations between levels of ferritin, inflammatory biomarkers, and mortality in patients with peripheral arterial disease (PAD) is also described previously,⁸ but, not much is known regarding diabetes, inflammation and vasculopathy especially in relation to ferritin from this region. With this in the background, the study was done to correlate serum CRP and ferritin levels with ABPI in type 2 diabetic patients.

2. Materials and Methods

2.1 Study group: The study was done at K.S.Hegde Medical College Hospital, Deralakatte, Mangalore, Karnataka, India. This was an observational and analytical study of 50 patients with type 2 diabetes mellitus done during the period of June 2011 to August 2011. Study protocol was explained to the study population and consent was taken. The institutional ethical committee clearance was taken before the study. Study population was divided into group 1 with CVD and group 2 without CVD. All patients who fulfilled the

following inclusion criteria were considered for study.

Inclusion criteria:

1. Patients with Type 2 diabetes with the diagnosis of diabetes as per WHO criteria
2. No episode of ketoacidosis
3. Diagnosis of diabetes after the age of 30 years
4. Insulin therapy, if any, started after at least 5 years of known disease

Exclusion Criteria

1. Smoking
2. Renal failure with a serum creatinine concentration over 1.5 mg/dL
3. Age more than 60 years
4. Anemia with haemoglobin of ≤ 11 gms/dl.
5. Patients with liver disease (viral hepatitis or liver cirrhosis), known malignant disease, acute infections or chronic inflammatory disease (e.g., rheumatoid arthritis)

2.2 Definitions and diagnostic criteria:

Diabetes was diagnosed based on past medical history, drug treatment for diabetes (insulin or oral hypoglycemic agents) and/or criteria outlined by the World Health Organization. Diabetes was diagnosed if fasting plasma glucose (FPG) level was > 126 mg/dl and/or the 2-hr plasma glucose level was > 200 mg/dl. Hypertension was diagnosed based on the history of drug treatment for hypertension or if blood pressure was $> 140/90$ mmHg. Hypercholesterolemia and hypertriglyceridemia were defined as serum cholesterol or triglycerides were > 200 mg/dl and > 130 mg/dl, respectively, according to the National Cholesterol Education Program guidelines.

CVD was defined as coronary artery disease and/or stroke and/or PVD. Coronary artery disease is defined as a history of myocardial infarction, coronary artery bypass grafting or an abnormal coronary angiogram. Stroke is defined as a history of ischemic stroke confirmed by cerebral computed tomography or nuclear magnetic resonance imaging. PVD is defined as symptoms of intermittent claudication or a documented PVD by arterial doppler or peripheral angiogram. Patients with a history of peripheral artery reconstruction, amputation of a foot, or lower extremity vascular surgeries were excluded.

2.3 Study protocol: Height and weight of the patient is measured to estimate BMI. Waist circumference and hip circumference was measured with a measuring tape. Venous blood was obtained after an overnight fast for measurement of fasting plasma glucose levels

and fasting lipid levels. Serum concentration of CRP is estimated by slide test or latex agglutination test. Serum ferritin level is estimated by microplate immunoenzymometric assay.

2.4 Measurement of Ankle-brachial Pressure Index:

Blood pressure recordings were made of the brachial pulses in the both upper limb. Similar recordings were made of the dorsalis pedis and posterior tibial pulses in the both lower limb by inflating the cuff proximal to the ankle, and the mean of these 2 readings was taken as the ankle pressure. ABPI is calculated using the formula:

$$ABPI_{Leg} = P_{Leg} / P_{Arm}$$

Where P_{Leg} is the systolic blood pressure of dorsalis pedis or posterior tibial arteries and P_{Arm} is the highest of the left and right arm brachial systolic blood pressure.

Statistical analysis: Data was expressed as the mean \pm SD. Differences between groups will be analyzed by a Student's unpaired t test. Correlation was determined by Pearson correlate test. A p value of 0.05 was accepted as indicating statistical significance.

3. Results

In this study of 50 patients with type 2 diabetes mellitus in the age group of 30-60 years, 35(70%) were males and 15(30%) were females. The mean age was 52.36 years and majority of them (40, 80%) belonged to the age group of 51-60 years. 10 cases (20%) had past history of MI or CAD. 20 cases (40%) had PVD as defined above. Among them, 6 cases and 2 cases had documented PVD by arterial doppler or peripheral angiogram respectively. The mean diabetes duration was 7.38 ± 6.91 years. The mean BMI (kg/m^2) and waist-to-hip ratio were 21.91 ± 3.70 and $0.97 \pm .06$ respectively. The mean serum cholesterol and triglycerides were 173.68 ± 33.36 mg/ dl and 129.54 ± 41.24 mg / dl respectively. The mean LDL (mg/dl) and HDL (mg/dl) were 105.6 ± 31.74 and 42.12 ± 6.99 respectively. The mean ABPI was $0.99 \pm .22$ in the study group. The mean ferritin was 303.07 ± 175.22 mg/dl and the mean CRP (mg/dl) was 5.70 ± 1.82 in the study group. [Table 1

The study group was divided into two groups; 25 cases with CVD and 25 cases (50%) without CVD. Each group was subdivided into three age groups, 31-40 years (n=1), 41-50 years (n=9) and 51-60 years (n=40). Among 35 males, 18(51.43%) were in the group with CVD and 17(48.57%) were in the group without CVD.

Among 15 females, 7(46.67%) were in the group with CVD and 8(53.33%) were in the group without CVD. The cases were grouped into four groups depending on the ABPI values as 0.40–0.69, 0.70–0.90, 0.91–1.30 and >1.30. The numbers of cases in each group were 4, 17, 27 and 2 respectively.

The two groups with and without CVD were compared for the baseline characteristics. The mean age of diabetic patients with and without CVD was 54.44 ± 3.86 and 50.28 ± 9.59 years respectively ($p = 0.019$). The mean diabetes duration in the two groups was 7.80 ± 4.33 and 6.96 ± 8.86 years respectively. The BMI (Kg/m^2) and waist to hip ratio in the two groups were 22.58 ± 3.90 vs. 21.23 ± 3.44 and 0.97 ± 0.66 vs. 0.96 ± 0.05 respectively. The serum LDL (mg/dl) in the group with CVD was higher than the group without CVD (121.32 ± 35.97 vs. 89.88 ± 15.76) with a p value of 0.08. The serum triglyceride (mg/dl) in the group with CVD was higher than the group without CVD (156.16 ± 40.68 vs. 102.92 ± 17.93) and this difference was statistically significant ($p = 0.01$). The mean ABPI in the group with CVD and without CVD was 0.84 ± 0.14 and 1.15 ± 0.18 respectively. The serum ferritin (mg/dl) and CRP (mg/dl) in the group with CVD were higher than in the group without CVD (393.44 ± 179.11 vs. 212.70 ± 116.58 and 6.47 ± 1.79 vs. 4.93 ± 1.53). [Table 2]

ABPI correlated negatively with serum ferritin values, with a Pearson correlation value and p value of -0.187 and 0.194 respectively. Also, ABPI negatively correlated with CRP, and this correlation was statistically significant (-0.382 ; $P = .006$). [Table 3]

4. Discussion

The main observations of the present study are the following: 35 cases (70%) were males and majority of the cases (40, 80%) belonged to the age group of 51-60 years. CVD was also more common in the age group of 51-60 years (17 cases, 68%). Also, males contributed to more number of cases with low ABPI than females. Among the cases with ABPI of < 0.9 (21 cases), 15 were males and 6 were females. Both the groups with CVD and without CVD were matched with respect to diabetes duration, BMI, waist to hip ratio and serum cholesterol levels. The mean age of diabetic patients with and without CVD was 54.44 ± 3.86 and 50.28 ± 9.59 years and this difference between two groups was statistically significant ($p = 0.019$). The mean ABPI was much lower in the group with

CVD when compared with the group without CVD, though statistically not significant ($p = 0.701$). The mean ferritin values (mg/dl) in the two groups were 393.44 ± 179.11 and 212.70 ± 116.58 respectively with a p value of 0.106. Also, CRP values (mg/dl) were much higher in the group with CVD than the group without CVD (6.47 ± 1.79 vs. 4.93 ± 1.53).

The risk factors for PAD in the general population have been well characterized.⁹⁻¹³ The Framingham Study¹³ and other studies have identified a number of atherogenic risk factors, including increasing age, male gender, hypertension, diabetes mellitus, smoking, and elevated serum cholesterol levels. More recently, several emerging unconventional risk factors such as homocysteine, lipoprotein (a) and chronic inflammation have been identified as additional risk factors associated with PAD.¹⁴⁻¹⁵ Accumulating evidence suggest that chronic inflammation plays a role in atherogenesis and several studies have demonstrated that elevated levels of CRP predicts an increased incidence of PAD in the general population.¹⁴⁻¹⁵

The ABPI values were compared in the group with and without CVD after dividing the cases into four groups according to ABPI. The difference in the ABPI between these two groups was statistically significant with a p value of < 0.001 . This highlights the importance of ABPI measurement in individuals with potential risk factors for CVD as well as established CVD cases to prevent further complications by taking appropriate therapeutic measures. The ABPI offers a potentially important low-cost, noninvasive tool for the early assessment of generalized atherosclerotic disease as well as for PVD specifically. PAD as measured by the ankle/brachial blood pressure index (ABPI) is associated with the increased risk of mortality and morbidity in several patient populations.¹⁶⁻¹⁷ In this study, ABPI correlated negatively with serum ferritin values, with a Pearson correlation value and p value of -0.187 and 0.194 respectively. Also, ABPI negatively correlated with CRP, and this correlation was statistically significant (-0.382 $P = .006$).

Though the small sample size is a limitation in this study, measurement of ABPI as a simple tool may be clinically useful in identifying peripheral arterial disease in patients at risk of accelerated atherosclerosis. To conclude, ABPI negatively correlated with serum ferritin and CRP levels in this study, though the association with ferritin was statistically not significant. Further large scale studies are needed to

elucidate the association of ferritin as a nonconventional risk factor of atherosclerosis and PAD in type 2 diabetes mellitus.

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Table 1. Baseline characteristics of the study population (N=50)

	Mean
Male/Female	35 (70%)/15(30%)
Age (years)	52.36 ± 7.54
MI/CAD	10 (20%)
Stroke	4 (8%)
PAD	20 (40%)
Diabetes duration(years)	7.38 ± 6.91
BMI (kg/m ²)	21.91 ± 3.70
Waist-to-hip ratio	.97 ± .06
Serum cholesterol (mg/dl)	173.68 ± 33.36
LDL	105.6 ± 31.74
HDL	42.12 ± 6.99
Serum triglycerides (mg/dl)	129.54 ± 41.24
Serum creatinine (mg/dl)	.93 ± .26
FPG	183.82 ± 46.44
Glyco-Hb	8.32 ± 1.53
ABPI	.99 ± .22
Ferritin	303.07 ± 175.22
CRP	5.70 ± 1.82

Table 2. Comparison of base line characteristics in the group with CVD and without CVD

	With CVD(N=25)	Without CVD (N=25)	F value, P value
Male/Female	17/8	18/7	
Age (years)	54.44 ± 3.86	50.28 ± 9.59	5.846, 0.019*
MI/CAD		10 (20%)	
Stroke		4 (8%)	
PAD		20 (40%)	
Diabetes duration(years)	7.80 ± 4.33	6.96 ± 8.86	0.435
BMI (kg/m ²)	22.58 ± 3.90	21.23 ± 3.44	0.368
Waist-to-hip ratio	0.97 ± 0.66	0.96 ± 0.05	0.633
Serum cholesterol (mg/dl)	191.6 ± 30.8	155.76 ± 25.57	0.701
LDL	121.32 ± 35.97	89.88 ± 15.76	0.08
HDL	38.48 ± 5.51	45.76 ± 6.46	0.350
Serum triglycerides (mg/dl)	156.16 ± 40.68	102.92 ± 17.93	0.01*
Serum creatinine (mg/dl)	0.91 ± 0.29	0.95 ± 0.22	0.063
FPG	172.4 ± 46.51	195.24 ± 44.37	0.667
Glyco-Hb	8.18 ± 1.30	8.45 ± 1.74	0.572
ABPI	0.84 ± 0.14	1.15 ± 0.18	0.701
Ferritin	393.44 ± 179.11	212.70 ± 116.58	0.106
CRP	6.47 ± 1.79	4.93 ± 1.53	0.454

Table 3. Correlation of serum ferritin and CRP with ABPI (N=50)

ABPI (Mean ± SD)	Ferritin (Mean ± SD)	CRP (Mean ± SD)	Pearson correlation (ABPI vs. ferritin)(P value)	Pearson correlation (ABPI vs. CRP)
0.9943 ± .22194	303.07 ± 175.22	5.6985 ± 1.81773	-0.187 (0.194)	-0.382 (0.006)