

Original Article

## Non-invasive markers of atherosclerosis and their correlation with Framingham risk score in Indian patients with type 2 diabetes mellitus

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Received: 11.01.14; Accepted: 10.07.14; Published: 26.07.14

### ABSTRACT

**Background:** India has been referred as the "diabetes capital of the world". Diabetes mellitus (DM) is widely accepted as a vascular disease leading to substantive increase in cardiovascular disease (CVD). Recently, there has been much interest in the relationship between arterial stiffness and cardiovascular disease. So this study was conducted to assess the risk of atherosclerosis in patients with DM. **Aim:** To investigate the relationship between non-invasive oscillometric methods that assesses subclinical atherosclerosis, and Framingham Risk Score (FRS), an independent predictor of CVD, in patients with type 2 DM, and age-matched hypertensive and healthy controls. **Methods:** The four study groups consisted of group A I; patients with diabetes mellitus (>5 years) along with hypertension (n=55), group A II; newly diagnosed patients with DM without hypertension (n=28), group B I; patients with hypertension (n=31) and group B II; healthy controls (n=30). The participants were subjected to oscillometric measurements like arterial stiffness index (ASI), pulse wave velocity (PWV), and augmentation index (Alx). All these parameters were correlated with FRS. **Results:** The PWV, ASI, Alx as well as FRS of 30 yr risk of CVD were elevated in patients with DM compared to healthy controls. A significant correlation was observed between FRS, and PWV, ASI, and Alx. **Conclusion:** This study reveals that non-invasive oscillometric markers can be useful in early detection of early atherosclerosis in patients with type 2 DM.

**Key Words:** Diabetes, atherosclerosis, arterial stiffness index, pulse wave velocity, augmentation index, Framingham risk score

### INTRODUCTION

In India, prevalence of type 2 diabetes mellitus (DM) in urban and rural areas is 18.6% and 9.2%, respectively.<sup>[1]</sup> Cardiovascular diseases (CVD) are the

leading causes of morbidity and mortality in type 2 DM.<sup>[2-3]</sup> Hyperglycaemia has been postulated to accelerate atherosclerosis by induction of endothelial dysfunction and thus is an independent risk factor for the



development of cardiovascular diseases.<sup>[4-6]</sup>

Atherosclerosis is a progressive chronic inflammatory disease characterised by gradual thickening and hardening of arteries that ultimately leads to reduction in lumen diameter.<sup>[7]</sup> The stiffness of aorta and other arteries is a potential risk factor for increased cardiovascular morbidity and mortality.<sup>[8]</sup> Several pathogenic processes like hypertension, hyperlipidemia, obesity, insulin resistance and more significantly type 2 Diabetes Mellitus lead to early onset of atherosclerosis.<sup>[9]</sup>

Atherosclerosis can be detected by invasive and non- invasive tests. Invasive tests include cardiac catheterization and angiogram.<sup>[10]</sup> Non-invasive tests like computerized oscillometry and measurement of carotid intima media thickness- cIMT (using computed tomography, positron emission tomography, doppler ultrasound) can also identify sub clinical atherosclerosis.<sup>[11,12]</sup> Today, non-invasive methods are on the forefront for accurate assessment of atherosclerosis.

cIMT and markers of vascular dysfunction in peripheral circulation (measured by oscillometric methods) namely, pulse wave velocity (PWV), arterial stiffness index (ASI) and ankle brachial index (ABI) can independently predict risk of cardiovascular events including coronary artery disease (CAD) and stroke.<sup>[13-15]</sup> Identification of subclinical atherosclerosis and early treatment initiation has beneficial impact on cardiovascular morbidity and mortality.<sup>[16]</sup> The measurement of ABI has been recommended by the American Heart Association as a diagnostic criterion for the prevalence of peripheral arterial diseases.<sup>[17]</sup> The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and the Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines recommend using the Framingham risk scores to assess the absolute risk of type II diabetics developing CVD.<sup>[18]</sup>

Hence, the present study was conducted to assess arterial stiffness by oscillometric method and Framingham risk score (FRS) as well as correlation between them in patients with type 2 diabetes mellitus with

or without hypertension and compare with hypertensive and healthy controls. This will help in early detection of atherosclerosis in Type 2 Diabetes.

## METHODOLOGY

### Study design and participants

A total of 114 patients were enrolled for this cross-sectional study. A consecutive method of sampling was used to include all accessible participants according to our selection criteria and these were selected from Diabetes Clinic of Sir H.N. Hospital. All patients were selected from the same center to prevent heterogeneity of the subjects and investigators. Healthy controls were selected from the hospital staff. The study population consisted of patients with diabetes mellitus for > 5 years along with hypertension (group A-I), newly diagnosed patients with diabetes mellitus (of < 2 years duration) without hypertension (group A-II), patients with hypertension only (group B-I), and healthy controls (group B-II). All participants were selected using purposive sampling method.

All participants were above 40 years of age and of either gender. Participants who were on vasodilators, had history of physical injury to one or both limbs in the past fifteen days, varicose veins were excluded from the study. Details about DM, hypertension, smoking, and alcohol intake were documented for each participant. Five ml blood was collected for total cholesterol and HDL estimations from serum. Methods were based on enzymatic determination using the kits purchased from Randox Laboratories Ltd. (USA).

### Ethics consideration

The Scientific Advisory Committee, Institutional Review Committee and Institutional Ethics Committee approved the study. The study was carried out in accordance with the "Ethical Guidelines for Biomedical Research on Human Participants, 2006" by the Indian Council of Medical Research and the Declaration of Helsinki, 2008. Written informed consent was obtained from all the participants.

### Anthropometric measurements

Anthropometric rod was used to measure the subjects' height while standing in erect position with the head in the ear-eye plane. Reading was recorded to the nearest 0.1

cm. The body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ).<sup>[19]</sup> Waist circumference was measured at the level of the umbilicus with the subject in mid-expiratory position. Hip circumference was recorded at the widest point over the greater trochanters, and the waist-to-hip ratio was calculated.

#### Measurements of blood pressure

Readings were recorded in duplicates for systolic and diastolic blood pressure (SBP and DBP) in the brachial artery, and the average was used. The measurements were taken with the help of mercury sphygmomanometer in a sitting position with the right forearm placed horizontal on the desk as recommended by the American Society of Hypertension.<sup>[20]</sup>

#### Oscillometric measurements

Oscillometric measurements were performed using the "Periscope" (M/S Genesis Medical Systems, Hyderabad, India), which is a 8-channel real time Windows-based simultaneous acquisition and analysis system. It calculates parameters such as ASI, PWV, ABI and augmentation index (AI). Acquisition rate of instrument is 200 samples per second. System also has hard core module connected to 4 ECG electrodes and 4 Blood pressure measuring cuffs.<sup>[21]</sup> The report contains 8 second traces of lead I and II ECG.<sup>[21]</sup> All the reports can be stored in built-in data base present in the instrument. Electrodes for the electrocardiogram were placed on ventral surface of both the wrists and medial side of ankles, and BP cuffs were wrapped on both upper arm brachial artery and tibial artery above ankles.<sup>[21]</sup> The cuffs were connected to a plethysmographic sensor, which determines volume pulse form and an oscillometric pressure sensor, it measures blood pressure volume waveforms from the brachial and tibial arteries. All the data was stored in the computer for further analysis.<sup>[21]</sup> Participants were asked to abstain from smoking, aerated beverages, caffeine 12 hours before the test. They were advised to be on 12 hours fast and should not take morning dose of medicine on the day of the procedure. Test was always performed in the morning between 9 and 10am.

#### Cardiovascular risk calculation

The Framingham risk score (FRS) was used for calculating 30 year cardiovascular

risk of all the study participants. The predictors used by FRS were participant's age, systolic BP, use of antihypertensive treatment, smoking, diabetes mellitus, total cholesterol, and HDL.<sup>[15,16]</sup> This generates 2 outcomes namely, Hard CVD risk (coronary death, myocardial infarction, and stroke) and General CVD risk (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, haemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure).<sup>[22, 23]</sup>

#### Statistical analysis

Numerical data was tested for normality using Kolmogorov-Smirnov test, and between groups comparison was done using either one-way analysis of variance-ANOVA (if normally distributed) or Kruskal-Wallis test (if not normally distributed) with post-hoc tests. Categorical data was compared using Chi-square test. Correlation between 2 numerical variables was assessed using Spearman's rho correlation coefficient. Statistical analysis was considered significant at  $P < 0.05$ . All analyses were performed using SPSS software, version 21.0 (SPSS, Chicago, IL, USA).

## RESULTS

A total of 144 participants were recruited in this study, out of which 55 patients had diabetes mellitus for more than 5 years along with hypertension, 28 were newly diagnosed patients with diabetes mellitus of less than 2 years without hypertension, 31 patients with essential hypertension only (taken as hypertensive controls) and 30 age-matched healthy controls.

#### Baseline characteristics

All the groups were comparable with respect to the demographic details and anthropometric measurements except for age and blood pressure as shown in Table 1 Systolic blood pressure was significantly higher in patients with DM (>5 years) with hypertension compared to newly detected patients with DM, hypertensive controls, and healthy controls. Diastolic blood pressure was significantly increased in patients with DM (>5 years) with hypertension compared to newly detected patients with DM.

### Markers of atherosclerosis

Vascular age, aortic pulse pressure, ankle brachial index (ABI), brachial ankle pulse wave velocity (PWV), carotid femoral PWV, brachial arterial stiffness index (ASI), ankle ASI and augmentation index (AI) were significantly higher in patients with DM (>5 years) with hypertension compared to healthy controls, as shown in table 2. In addition, aortic pulse pressure, brachial ASI and AI were significantly elevated in hypertensive controls compared to healthy controls.

### Framingham risk score (FRS)

The risk of general CVD and hard CVD was significantly higher in patients with diabetes mellitus (with and without hypertension) and hypertensive controls compared to healthy controls (table 3).

### Correlation between markers of atherosclerosis and Framingham risk score (FRS)

Table 4 and figures 1 to 5 represent the Spearman's correlation between FRS and markers of atherosclerosis. A significant correlation was observed between FRS and selected markers of atherosclerosis viz. vascular age, brachial ankle PWV, ankle ASI, and augmentation index, in patients with DM (with or without hypertension), hypertensive controls.

### Correlation between PWV and augmentation index (Alx)

Figure 6 depicts very strong correlation observed between cfPWV and Alx (Spearman's correlation coefficient = 0.91,  $P < 0.001$ ). There was a strong correlation between brachial-ankle PWV and Alx (Spearman's correlation coefficient = 0.77,  $P < 0.001$ ).

## DISCUSSION

In the present study, markers of atherosclerosis mainly pulse wave velocity (PWV), arterial stiffness index (ASI), and augmentation index (Alx) were significantly elevated in patients with DM as compared to healthy controls. Thirty year cardiovascular risk of general CVD and hard CVD using Framingham risk score (FRS) was significantly higher in patients with long term DM with HT, and hypertensive controls than that of healthy controls. A moderate correlation was observed between the FRS and various markers of atherosclerosis like vascular

age, PWV, ASI, and Alx. However, there was a very strong correlation between cfPWV and Alx.

Oscillometric devices provide more accurate estimation of the prevalence of peripheral artery disease in elderly individuals than the conventional Doppler method.<sup>[24]</sup> A non-invasive device, Periscope, used in the present study to assess atherosclerosis has been validated and found to give reproducible results.<sup>[25]</sup> PWV is a well-established marker of early stage of atherosclerosis.<sup>[26]</sup> In this study, brachial-ankle PWV and carotid-femoral PWV were significantly increased in patients with T2DM (> 5 years) with hypertension than healthy controls. A few studies have reported significantly higher PWV in patients with diabetes, and hypertension as compared to healthy controls.<sup>[27-29]</sup> This suggests that arterial stiffness in diabetic patients was more severe than those of healthy individuals. Since diabetic patients in our study had no clinical evidence of atherosclerosis, high PWV may be a potential marker of sub-clinical atherosclerosis.

Our study showed increased Alx in patients with DM (> 5 years) with hypertension as compared to healthy controls. Studies have reported that Alx and PWV are associated with increased arterial stiffness, which marks beginning of atherosclerosis.<sup>[30, 31]</sup> In addition, results of the present study corroborate findings by Yasmin *et al.*<sup>[32]</sup> who showed a strong correlation between PWV and Alx. In contrast, a study failed to show correlation between PWV and Alx although they were individually associated with atherosclerosis.<sup>[33]</sup>

Another factor measured by periscope, which serves to measure the dynamic properties of vessels is "arterial stiffness index" (ASI). It can in fact provide information on a number of specific physical properties, including distensibility, elasticity, and resistance to deformation.<sup>[34]</sup> The findings by Hiramine *et al.*<sup>[35]</sup> are in concordance with the present study, which showed that brachial ASI in patients with DM and hypertension, and hypertensive controls was significantly higher than in healthy controls. This may result from the joint effect of elevated glucose, insulin, and triglycerides.<sup>[36]</sup>

Table 1: Demographics in the 4 study groups

Parameter	Group A-I (n= 55)	Group A-II (n=28)	Group B-I (n= 31)	Group B-II (n=30)	Overall P-value (Post-hoc P value after Bonferroni's correction)
Age in years	59.3 ± 9.6	52.1 ±10.4	55.1 ±10.7	51.7 ±9.5	0.002(a: 0.001 e: 0.007)
Male: Female	30:25	13:15	16:15	16:14	0.92
Height in cm	160.8 ± 9.6	159.3 ± 9.2	157.6 ± 6.5	158.9 ± 21	0.30
Weight in kg	69.2 ± 14.2	62.8 ± 15.8	66.0 ± 14.1	70.4 ± 22.2	0.4
BMI in kg/m <sup>2</sup>	26.69 ± 4.37	24.99 ± 4.1	26.5 ± 4.8	26.0 ± 6.0	0.41
Waist to hip ratio	0.89 ± 0.07	0.88 ± 0.06	0.87 ± 0.06	0.87 ± 0.05	0.10
Systolic blood pressure in mmHg	145.7 ± 18.8	134.8 ± 8.9	138.7 ±18.1	129.0 ± 13.3	0.001(a: 0.003 c: <
Diastolic blood pressure in mmHg	83.9 ± 7.0	78.6 ± 4.9	82.7 ± 8.0	80.0 ± 6.6	0.03(a: 0.003)

Data are expressed as Mean ± standard deviation

BMI- body mass index;

a: Patients with diabetes mellitus (>5 years) along with hypertension vs newly diagnosed patients with DM without hypertension

b: Patients with diabetes mellitus (>5 years) along with hypertension vs patients with hypertension

c: Patients with diabetes mellitus (>5 years) along with hypertension vs healthy controls

d: Newly diagnosed patients with DM without hypertension vs patients with hypertension

e: Newly diagnosed patients with DM without hypertension vs healthy controls

f: Patients with hypertension vs healthy controls

Table 2: Comparison of markers of atherosclerosis measured by oscillometric methods across 4 study groups (expressed as median, minimum and maximum)

Parameter	Group A-I (n= 55)	Group A-II (n=28)	Group B-I (n= 31)	Group B-II (n=30)	Overall P-value (Post-hoc Bonferroni's correction)
Vascular age years	71 (40, 90)	57.5 (36, 90)	61 (39, 90)	50 (30, 90)	0.005 (a: 0.01 c: 0.001)
Pulse pressure -mmHg	64 (43,113)	59 (42, 93)	66 (43,96)	55.5 (37, 76)	0.005 (c: 0.001 f: 0.001)
Right brachial-ankle PWV -cm/s	1505 (-18105, 55622)	1332 (-1400, 24145)	1387 (-1863, 2764)	1286 (950, 12479)	0.02 (a: 0.04 b: 0.03 c: 0.004)
Left brachial-ankle PWV -cm/s	1686 (-7378, 6617)	1335 (-44431, 55295)	1522 (1155, 4224)	1301 (-13792, 5683)	0.007 (a: 0.004 c: 0.01)
Carotid-femoral PWV -cm/s	1105 (113, 24567)	953 (660, 24868)	1019 (714, 2466)	857 (483, 10165)	0.03 (c: 0.006)
Right brachial-ankle ASI -mmHg	31.6 (14, 62.6)	28 (-52, 1052)	28 (13.6, 55.3)	25.3 (-14.8, 40.4)	0.01 (c: 0.001 f: 0.03)
Left brachial-ankle ASI -mmHg	30.8 (3.6, 73.8)	29.2 (-35.6, 47)	30.2 (15.6, 53.2)	27 (12, 42)	0.04 (c: 0.01 f: 0.05)
Right ankle ASI -mmHg	41.6 (19.8, 83.4)	33.2 (0, 74)	37.4 (27, 61.8)	36.9 (20.2, 56.2)	0.007 (a: 0.005 d: 0.03)
Left ankle ASI -mmHg	47.8 (20.8, 77.2)	32.7 (0, 70.6)	38.8 (24.4, 57.8)	36 (16.6, 50)	<0.001 (a: 0.001 b: 0.01 c: < 0.001) d: 0.01)
Right ABI	1.11 (0.84, 1.26)	1.1 (0.84, 23.8)	1.11 (0.88, 1.56)	1.11 (0.82, 1.2)	0.86
Left ABI	1.11 (0.98, 1.31)	1.09 (0.91, 1.27)	1.11 (0.9, 1.26)	1.1 (0.78, 1.22)	0.62
Aortic pulse pressure -mmHg	46 (26, 106)	41 (24, 110)	44 (25, 75)	36 (19, 63)	0.002 (c: 0.00 f: 0.005)
Aortic augmentation pressure -mmHg	12 (2, 63)	9 (0, 69)	10 (1, 39)	6 (-1, 53)	0.002 (c: 0.00 f: 0.01)
Augmentation index %	28 (7, 60)	22 (2, 60)	25 (7, 52)	17.5 (-6, 99)	0.003 (a: 0.01 c: 0.001 f: 0.03)

PWV- pulse wave velocity, ASI- arterial stiffness index, ABI- ankle brachial index

- a: Patients with diabetes mellitus (>5 years) along with hypertension vs newly diagnosed patients with DM without hypertension
- b: Patients with diabetes mellitus (>5 years) along with hypertension vs patients with hypertension
- c: Patients with diabetes mellitus (>5 years) along with hypertension vs healthy controls
- d: Newly diagnosed patients with DM without hypertension vs patients with hypertension
- e: Newly diagnosed patients with DM without hypertension vs healthy controls
- f: Patients with hypertension vs healthy controls

Table 3: Comparison of Framingham risk score across 4 study groups (values expressed as mean ± standard deviation)

Framingham risk	Group A-I (n= 55)	Group A-II (n=28)	Group B-I (n= 31)	Group B-II (n=30)	Overall P value (Post-hoc P value after Bonferroni's correction)
Risk of general CVD	68 ± 13.4	49 ± 17.5	45 ± 17.7	32 ± 12.6	p<0.001 (a: <0.001, b: <0.001, c: <0.001, e: 0.001, f: 0.006)
Risk of hard CVD	53 ± 16.9	38 ± 17.6	27 ± 14.4	19 ± 10.2	p<0.001, (a:<0.001, b: <0.0001, c: <0.001, d: 0.01, e: <0.001)

CVD- cardiovascular diseases;

- a: Patients with diabetes mellitus (>5 years) along with hypertension vs newly diagnosed patients with DM without hypertension
- b: Patients with diabetes mellitus (>5 years) along with hypertension vs patients with hypertension
- c: Patients with diabetes mellitus (>5 years) along with hypertension vs healthy controls
- d: Newly diagnosed patients with DM without hypertension vs patients with hypertension
- e: Newly diagnosed patients with DM without hypertension vs healthy controls
- f: Patients with hypertension vs healthy controls

Figure 1: Comparison of mean right and left brachial-ankle (PWV) and carotid-femoral (cfPWV) measurements in 4 study groups

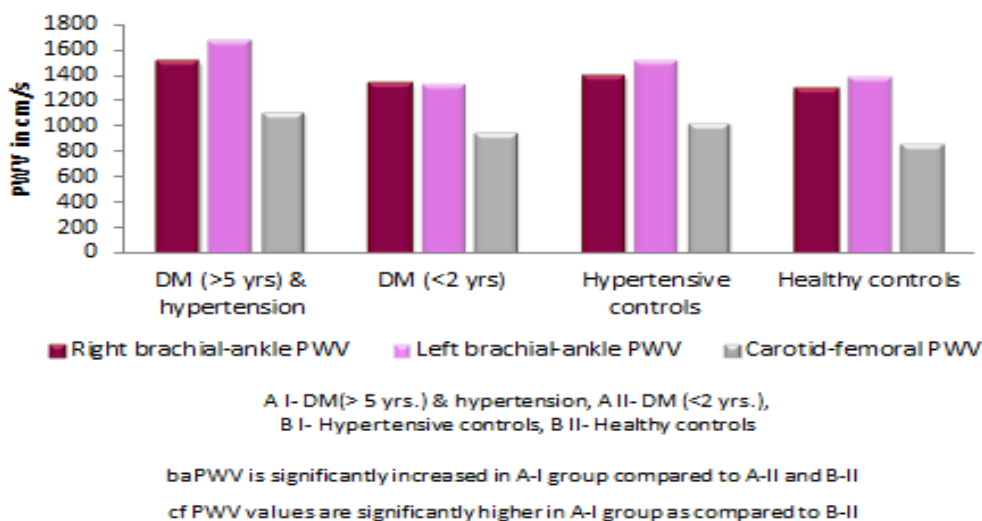


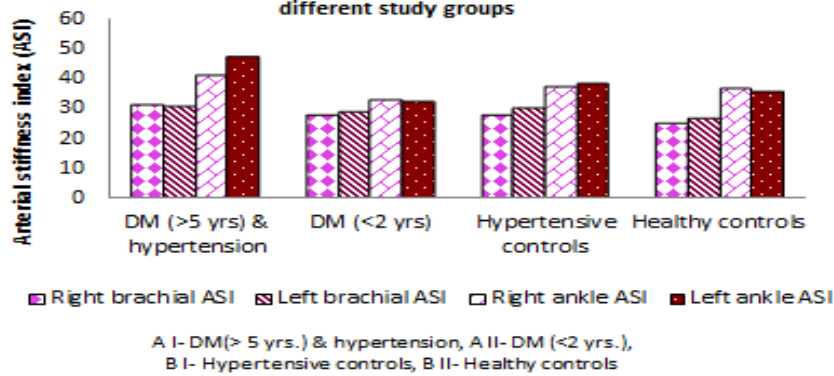
Table 4: Spearman’s correlation coefficient between various markers of atherosclerosis and Framingham risk score (Both Hard and General)

Markers of atherosclerosis	Patients with DM (group A-I and A-II)		Hypertensive controls (group B-I)	
	Correlation coefficient	P-value	Correlation coefficient	P-value
Vascular age (yrs)	0.35	<0.001	0.6	<0.001
Right brachial ankle PWV (cm/s)	0.29	<0.008	0.4	0.02
Left brachial ankle PWV (cm/s)	0.4	<0.001	0.51	0.003
Carotid femoral PWV (cm/s)	0.2	0.07	0.56	0.001
Right ankle ASI (mmHg)	0.55	<0.001	0.4	0.03
Left ankle ASI (mmHg)	0.5	<0.001	0.5	0.005
Aortic pulse pressure (mmHg)	0.38	<0.001	0.47	0.007
Augmentation Index (%)	0.6	<0.001	0.58	0.001

PWV- pulse wave velocity, ASI- arterial stiffness index



Figure 2: Mean right and left brachial and ankle arterial stiffness index (ASI) in different study groups



Brachial ASI values were significantly higher in A-I and B-I groups as compared to B-II. Ankle ASI is significantly higher in A-I and A-II groups compared to B-II group which shows that arterial stiffness is more in A-I, A-II and B-I

Figure 3: correlation between brachial ASI and Framingham risk score (GENERAL CVD) in patients with DM (group A-I and A-II)

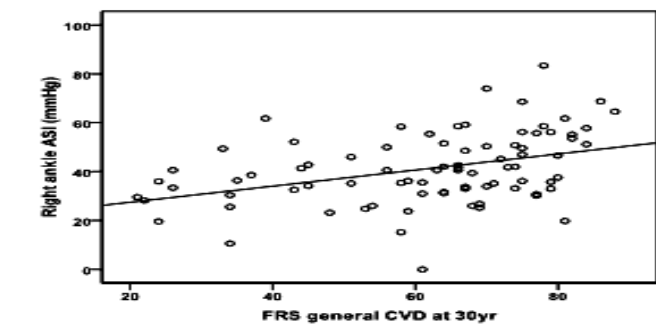


Figure 3 shows the moderate correlation observed between Right ankle ASI and FRS general CVD at 30 years in patients with diabetes. (Spearman's correlation coefficient = 0.42,  $p < 0.001$ )

Figure 4: Correlation between carotid-femoral PWV and Framingham risk score (general CVD) in patients with hypertension (group B-I)

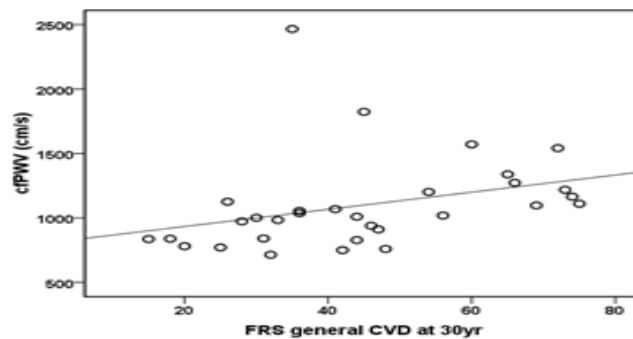


Figure 4 shows moderate correlation observed between cfPWV and FRS general CVD at 30 years in hypertension group. (Spearman's correlation coefficient = 0.56  $p < 0.001$ )

Figure 5: Correlation between augmentation index (Alx) and Framingham risk score (general CVD) in total study population

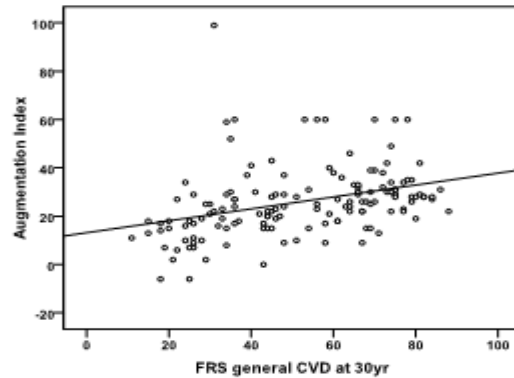


Figure 5 shows the moderate correlation was observed between Augmentation Index and FRS general CVD at 30 years in the whole study population. (Spearman's correlation coefficient = 0.48,  $p < 0.001$ )

Figure 6: Correlation between cfPWV and Alx in total study population

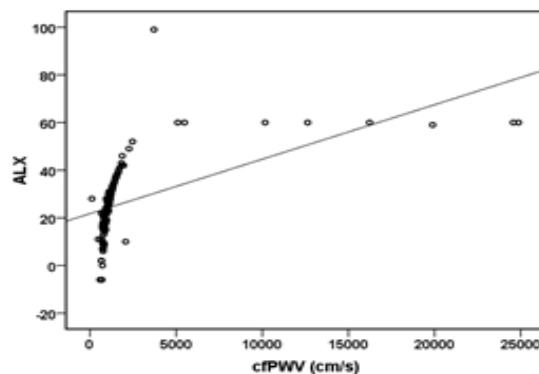


Figure 6 depicts very strong correlation observed between cfPWV and Alx (Spearman's correlation coefficient = 0.91,  $p < 0.001$ ). There was a strong correlation between brachial-ankle PWV and Alx (Spearman's correlation coefficient = 0.77,  $p < 0.001$ ).

Cardiovascular disease (CVD) is an important cause of mortality among individuals with type 2 DM.<sup>[37]</sup> Patients with DM are twice more likely to be affected by CVD than non-diabetics.<sup>[38]</sup> The Framingham equation for calculating 30-year cardiovascular risk of a patient is an independent predictor with a better odds ratio than metabolic syndrome alone.<sup>[39]</sup> In the present study, the risk of general CVD and hard CVD was significantly higher in patients with diabetes mellitus (with or without hypertension) and hypertensive controls compared to healthy controls. However, studies have documented that in people with newly diagnosed type 2 DM, the Framingham equation is moderately

effective at identifying those at high-risk (discrimination) and poor at quantifying risk (calibration).<sup>[40, 41]</sup>

Results of the present study showed a moderate but significant correlation between markers of atherosclerosis (i.e. baPWV, cfPWV, ASI, and Alx) and Framingham 30 year risk for CVD. This suggests that both Framingham risk score and oscillometric markers of atherosclerosis are independent but important markers of potential cardiovascular risk in patients with type 2 DM. Lau *et al.* demonstrated a modest but significant correlation between FRS

(recreated for Chinese) and baPWV in Chinese patients with type 2 DM.<sup>[42]</sup>

## CONCLUSION

Pulse wave velocity (PWV), arterial stiffness index (ASI), and augmentation index (AIx) are early non-invasive markers of atherosclerosis in Indian patients with type 2 diabetes mellitus. Though Framingham risk score (FRS) was significantly elevated in patients with DM and HT, only moderate correlation was observed between the FRS and the non-invasive markers of atherosclerosis.

## ACKNOWLEDGMENTS

Authors would like to express special thanks of gratitude to the Director of Sir H.N Medical Research Society and Management, for arranging necessary funds to carry out this project. We are also grateful to ethics review committee and scientific advisory committee for approving this project. We would like to thank other laboratory staff for their direct and indirect help. Last but not the least we would like to thank our participants for their valuable time and blood samples.

## PREVIOUS PUBLICATION

A part of this data was presented as a poster at the 41st Annual Conference of Research Society for the Study of Diabetes in India held at India Expo Centre, Greater Noida, National Capital Region Delhi, during 8th -10th November, 2013.

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**doi:** <http://dx.doi.org/10.14194/ijmbr.3.2.6>

**How to cite this article:** Namrata B.K, Meghana U.G, Sanjay G.G, Sudha S.D. Non-invasive markers of atherosclerosis and their correlation with Framingham risk score in Indian patients with type 2 diabetes mellitus. *Int J Med Biomed Res* 2014;3(2):101-113

**Conflict of Interest:** None declared

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