Original Article

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Physiology Section

Effect of Age and Blood Pressure on Surrogate Markers of Atherosclerosis in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Increased arterial stiffness may be an important pathway linking diabetes mellitus to increased cardiovascular risk.

Aim: The study was conducted to assess the surrogate markers of arterial stiffness in patients with Type 2 diabetes mellitus (T2DM), and compare with age-matched hypertensive and healthy controls. Also the effect of age and blood pressure on these markers was evaluated.

Settings and Design: This cross-sectional study was carried out at a tertiary care hospital in West India.

Methods: After a detailed medical history and anthropometric evaluation, all the participants were subjected to measurements of Arterial Stiffness Index (ASI), Pulse Wave Velocity (PWV), and Augmentation Index (AIx) using a non-invasive oscillometric method. The four study groups consisted of patients with T2DM (>5 years) along with hypertension, newly diagnosed patients with T2DM (<2years) without hypertension, hypertensive controls, and healthy controls.

Results: PWV, ASI, AIx were elevated in patients with T2DM compared to healthy controls ($p<0.05$). Patients with T2DM above 60 years had higher carotid-femoral PWV, ASI and AIx than those below 60 years ($p<0.05$). ASI and AIx were significantly increased in patients with T2DM with hypertension having systolic BP > 140 mmHg compared to those with systolic BP < 140 mmHg. A very strong correlation between PWV and AIx in patients with T2DM and hypertensive controls was observed.

Conclusion: This study reveals that markers of arterial stiffness (PWV, ASI, AIx) were increased significantly in patients with T2DM compared to healthy controls. Age and systolic blood pressure had significant influence on these markers. Thus, oscillometric markers have potential utility in identifying subclinical atherosclerosis in patients with T2DM.

Keywords: Arterial stiffness, Augmentation index, Pulse wave velocity

INTRODUCTION

Atherosclerosis (or arteriosclerotic vascular disease) is a condition where the arteries become narrowed and hardened (stiff) due to an excessive build-up of plaque around the artery wall. In recent years, great emphasis has been placed on the role of arterial stiffness in the development of cardiovascular (CV) diseases. Indeed, arterial stiffness is increasingly used in the clinical assessment of patients [1]. Arterial stiffness increases with age and other concomitant cardiovascular risk factors like coronary artery disease (CAD), diabetes mellitus (DM) and end stage renal disease [2, 3]. In contrast to systemic arterial stiffness, which can be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and noninvasively, at various sites along the arterial tree [4, 5]. Non-invasive markers involve the measurement of augmentation index (AIx), pulse wave velocity (PWV), arterial stiffness index (ASI) which can predict the early onset of atherosclerosis. Abnormalities in rigidity markers have been reported in patients with Type 2 DM [6]. Thus, increased arterial stiffness may be an important pathway linking diabetes to increased cardiovascular risk.

Hence, the present study was conducted to assess the surrogate markers of arterial stiffness using non-invasive oscillometric technique in patients with Type 2 diabetes mellitus (T2DM), and compare with age-matched hypertensive and healthy controls. Also the effect of age and blood pressure on these markers was evaluated.

METHODS

The Scientific Advisory Committee and Institutional Ethics Committee approved the study. A written, informed consent was obtained from all the participants. 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.

The study cohort consisted of 144 participants divided in to four groups, viz. patients with T2DM for more than five years along with hypertension (Group A-I, n=55), newly diagnosed patients with Type 2 DM without hypertension (Group A-II, n=28), patients with essential hypertension only (hypertensive controls; group B-I, n=31) and healthy controls (Group B-II, n=30). All the cases were recruited from the same private diabetes clinic to elude the diverseness of the patients and investigators. Healthy controls were recruited from the hospital and clinic staff. Patients with T2DM aged less than 40 years, taking vasodilators, having history of physical injury to one or both limbs in past 15 days, suffering from varicose veins were excluded from the study.

Demographic details, personal as well as family medical history were recorded on the case report forms. Anthropometric measurements like height (in cm), weight (in kg), body mass index (BMI) were measured. BMI was calculated as weight divided by height squared (kg/m^2), and waist-to-hip ratio was calculated. Blood pressure was measured using a mercury sphygmomanometer on the right arm with subjects in seated position. Pressure was measured two times with a 5-min interval, and the average was used in the statistical analysis. The measurements were taken as recommended by the American Society of Hypertension.

Markers of arterial stiffness such as, ASI, PWV, ankle brachial index (ABI), pulse pressure (PP), vascular age (VA) and AIx were measured using an instrument, "Periscope" (M/S Genesis Medical Systems, Hyderabad, India), which is a eight channel real time Windows-based simultaneous acquisition and analysis system based on oscillometric method. 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. The report contains eight second traces of Lead I and II ECG. All the data was stored in the computer for further analysis [7]. Participants were asked to abstain from smoking, aerated beverages, caffeine 12 hours before the test. They were advised to be 12 hours fasting and should not take morning dose of medicine on the day of the procedure. Test was always performed in the morning hours between 9 and 10.

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 and unpaired t-test (if normally distributed), or Kruskal-Wallis test and Mann-Whitney U-test (if not normally distributed). Categorical data was compared using chi square test. Correlation between two 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

Clinical Profiles/outcomes

All the groups were comparable with respect to the demographic details and anthropometric measurements as shown in [Table/Fig-1]. However, systolic and diastolic blood pressure were significantly increased in patients with DM (>5 years) with hypertension, and hypertensive controls compared to healthy controls.

Non-invasive Markers of Atherosclerosis

[Table/Fig-2] shows that non- invasive markers of atherosclerosis across the four study groups. In patients with T2DM (>5 years) with hypertension, there was a significant increase in vascular age, ankle brachial index (ABI), brachial-ankle pulse wave velocity (PWV), carotid-femoral PWV, brachial arterial stiffness index (ASI), ankle ASI, aortic augmentation pressure and augmentation index (AIx) compared to healthy controls. Similarly, pulse pressure, brachial ASI, aortic augmentation pressure and AIx were significantly elevated in hypertensive controls compared to healthy controls, as shown in [Table/Fig-2].

Effect of Age on Oscillometric Makers

The Brachial ASI, ankle ASI and AIx were significantly elevated in patients above 60 years of age compared to those below 60 years of age with T2DM and hypertension, as shown in [Table/Fig-3].

Effect of Systolic Blood Pressure on Oscillometric Markers

Brachial as well as ankle ASI, and AIx were significantly higher in patients with systolic BP $\geq$ 140 mmHg compared to those with systolic BP < 140 mmHg in Group A-I and B-I, as shown in [Table/Fig-4].

Correlation between Oscillometric Markers, Systolic Blood Pressure and Waist to Hip Ratio

Vascular age ($\rho = 0.4$), brachial ASI ($\rho = 0.53$), and AIx ($\rho = 0.5$) showed moderate correlation while ankle ASI ($\rho = 0.7$), had strong correlation with systolic blood pressure in patients with T2DM with hypertension. In addition, AIx showed a very strong correlation with vascular age ($\rho = 0.95$), and PWV ($\rho = 0.75$) and a moderate correlation with ASI (brachial and ankle, $\rho = 0.4$). A moderate correlation was observed between WHR and ASI (ankle as well as brachial, $\rho = 0.4$).

DISCUSSION

The salient finding of the present study was that the markers of regional arterial stiffness, mainly pulse wave velocity (PWV), arterial stiffness index (ASI), and augmentation index (AIx) were significantly elevated in patients with type 2 DM as compared to healthy controls. ASI and AIx were significantly increased in patients above 60 years of age, and those with systolic BP > 140 mmHg.

Increased arterial stiffness is an independent predictor of death from cardiovascular disease, and aortic stiffness is more predictive than stiffness of other arterial regions [8]. PWV is a conventionally adopted index of arterial stiffness. It is defined as the velocity of the pulse wave to travel a given distance between two sites of the arterial system. Studies have reported that PWV is as an early indicator of atherosclerotic cardiovascular risk [9-11]. In the present study, brachial-ankle PWV and carotid-femoral PWV were significantly increased in patients with T2DM (> 5 years) with hypertension than healthy controls. Similarly, a few studies have demonstrated that PWV is significantly higher in patients with diabetes and hypertension as compared to healthy controls [12-14]. Carotid-femoral PWV has been proposed as the gold standard for

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: 0.001e: 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^2)	26.69 ± 4.37	24.99 ± 4.1	26.5 ± 4.8	26.0 ± 6.0	0.41
Waist circumference in (cm)	90.7 ± 10.1	86.9 ± 10.9	88.3 ± 10.5	88.0 ± 9.4	0.5
Hip circumference in (cm)	101.2 ± 11.6	94.4 ± 9.2	100.7 ± 10.7	100.2 ± 9.4	0.17
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:< 0.001)
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)

[Table/Fig-1]: Demographics in the 4 study groups (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

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)
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)
PWV	Right brachial-ankle- cm/s	1505 (-1810,5562)	1332 (-1400,24145)	1387 (-1863, 2764)	1286 (950, 12479)	0.02 (a: 0.04, b: 0.03, c: 0.004)
	Left brachial-ankle -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)
ASI	Right brachial 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 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)
ABI	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)
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)

[Table/Fig-2]: Comparison of markers ofatherosclerosis measured by oscillometricmethods across four studygroups(expressed as median, minimum and maximum)
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

Parameters	Group A-I		p-value
	40 – 60 years (n= 31)	61 – 80 years (n= 24)	
Vascular age (years)	67.12 ± 15.7	74.9 ± 14.1	0.06
Pulse pressure (mmHg)	61.32 ± 13.0	80.5 ± 21.6	<0.001***
Brachial-ankle PWV (cm/s)	1506.7 ± 584.6	3028.6 ± 1367.5	0.2
Carotid-femoral PWV (cm/s)	1254.7 ± 847.7	3213.8 ± 1210.2	0.07
Brachial ASI (mmHg)	30.3 ± 8.7	37.0 ± 12.5	0.02*
Ankle ASI (mmHg)	41.9 ± 8.5	50.8 ± 14.1	0.005***
Ankle brachial index	1.11 ± 0.07	1.08 ± 0.09	0.184
Augmentation index (%)	26.6 ± 10.9	33.1 ± 12.07	0.04*

[Table/Fig-3]: Age wise distribution of oscillometric parameters in patients with T2DM with hypertension (Group A-I)
PWV- pulse wave velocity, ASI- arterial stiffness index

arterial stiffness measurement and is a well-recognised predictor of adverse cardiovascular outcome [15]. Thus, findings of the present study imply that arterial stiffness in diabetic patients is more severe than those of healthy individuals.

The augmentation index (AIx) reflects the degree to which central arterial pressure is enhanced by wave reflection of the pulse wave [16]. AIx is a validated estimate of arterial stiffness and hence, cardiovascular risk [17,18]. Our study demonstrated increased AIx in patients with DM (> 5 years) with hypertension as compared to healthy controls. In the present study, AIx also significantly correlated with vascular age, PWV, Brachial and Ankle ASI, and systolic blood pressure in patients with T2DM (> 5 years) and hypertension and hypertensive controls. However, diabetic patients in our study had no clinical evidence of atherosclerosis indicating that high AIx may be a potential marker of sub-clinical atherosclerosis.

Parameters	Group A-I T2DM with hypertension (n = 55)		Group B-I Hypertensive controls (n= 31)	
	Systolic BP < 140 mmHg	Systolic BP ≥ 140 mmHg	Systolic BP < 140 mmHg	Systolic BP ≥ 140 mmHg
Brachial-ankle PWV (cm/s)	1565.5 ± 291.8	2639 ± 875.6	1531.7 ± 472.9	1423.0 ± 657.3
Brachial ASI (mmHg)	26.7 ± 6.1	38.3 ± 11.2*	28.1 ± 7.4	36.8 ± 8.6*
Ankle ASI (mmHg)	37.7 ± 7.1	52.0 ± 11.4*	36.9 ± 6.1	46.9 ± 8.8*
ABI	1.14 ± 0.05	1.07 ± 0.08	1.11 ± 0.07	1.09 ± 0.1
Augmentation index %	23.9 ± 8.6	33.7 ± 12.2*	22.3 ± 10.3	29.7 ± 6.9*

[Table/Fig-4]: Comparison of non-invasive markers in patients with (group A-I), and patients with hypertension only (group B-I) according to systolic blood pressure
PWV- pulse wave velocity, ASI- arterial stiffness index, ABI- ankle brachial index
* p <0.05 for comparison between 'systolic BP <140 mmHg' and 'systolic BP ≥ 140 mmHg'

Another non-invasive, surrogate marker of arterial stiffness is the "Arterial Stiffness Index" (ASI). It is measure of loss of elasticity in the arteries that occurs with onset of vascular disease and advancing age. In short it is defined as a number that correlates with atheriosclerosis. We found ASI (brachial as well as ankle) was significantly higher in patients with T2DM and hypertension, and hypertensive controls than in healthy controls, which corroborates the findings by Hiramine et al., [19].

In the present study, aortic augmentation pressure was significantly elevated in patients with T2DM with hypertension, and hypertensive controls compared to healthy controls. This is in accordance with findings by Westerbacka et al., [20] which also showed that increased augmentation pressure correlated with duration of diabetes.

Arterial stiffness surges with age and hypertension and it is also enhanced in subjects with diabetes mellitus [21-23]. Both the PWV and ASI increase with aging [24]. Results of the present study showed that pulse pressure, ASI and AIx, but not PWV, increased significantly with advancing age. However, a study has shown that changes in AIx were more prominent in younger individuals (<50 years), whereas the changes in aortic PWV were more marked in those older than 50 years [25].

Central blood pressure (BP) is a key risk factor of cardiovascular diseases [26]. Elevated systolic blood pressure is mainly attributed to extent of arterial stiffness [27]. Persistently elevated blood pressure accelerates atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby increasing arterial stiffness [28]. We found significant correlation between systolic blood pressure and markers of arterial stiffness such as, vascular age, brachial and ankle ASI, and AIx in patients of T2DM with hypertension, and hypertensive controls. In the present study, patients with systolic blood pressure above 140 mm hg had significantly elevated ASI and AIx. This indicates that controlling systolic blood pressure would favourably improve the cardiac risk profile of patients with T2DM who are at high risk for atherosclerosis.

CONCLUSION

This study reveals that arterial stiffness increased significantly in DM patients with further increase in patients above 60 years of age, and with systolic BP more than 140 mmHg. Thus, oscillometric markers have potential utility in identifying subclinical atherosclerosis in patients with Type 2 DM and instituting treatment for the prevention of its cardiovascular complications.

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