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Association Of Aortic Stiffness And Microvascular Complications In Type 2 Diabetes Mellitus

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ABSTRACT

Background: Arterial stiffness (AS) is considered to be an age-related progressive and continuous process which is a shared consequence of various different diseases inclusive of diabetes mellitus (DM), hypertension, the metabolic syndrome and chronic kidney disease (CKD).The present study was carried out with an aim to assess AS in patients with type 2 diabetes mellitus patients.

Material and methods: This cross sectional observational study was carried out from January 2022 to December 2022. A total of 250 samples were collected from all the patients attending General Medicine Department. All the patient microvascular complication was assessed by fundoscopy, presence of microalbumunuria and monofilament test. Statistical analysis was carried out using SPSS version 22.0.

Results: The mean age of the participants was 51.2 ± 8.5 years, with the majority (58.4%) ranging between the age group of 46–60 years. With an increasing duration of DM, the number of patients with aortic stiffness increased significantly. ($p<0.001$) Additionally, aortic stiffness was identified in the majority of individuals with microvascular complications.

Conclusion: Regular screening for AS is recommended for patients with DM and higher frequency of screening may be required in patients who are diabetic for a longer duration, old age and patients with micro vascular complications of DM.

Keywords: *Diabetes Mellitus, Insulin Resistance, Arterial stiffness, Microvascular complications, Cardiovascular Disease.*

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic illness that results from either insufficient insulin synthesis by the pancreas or inadequate insulin utilization by the body. This occurrence results in hyperglycemia, or an elevated blood glucose levels. The risk of ischemic heart disease and stroke is 2-3 times higher in those with DM.[1] Number of people living with diabetes all over the world was 108 million in 1980 and it has steeply risen to 422 million in 2014. From 4.7% in 1980 to 8.5% in 2014, the overall prevalence of DM among those aged 18 years of age and above. A total of 1.5 million deaths in 2012 were directly associated with DM. Nearly half of all deaths linked to high blood sugar levels occurs in those under the age of 70.[2] The World Health Organization (WHO) predicted that in 2030, diabetes will rank as the seventh most common cause of death.[3]

The second largest population of diabetics worldwide is in India. In India, there were 74.9 million people with diabetes in 2021; by 2045, it is expected to rise to 124.9 million people in the age group of 20–79 years. As per the international diabetes federation (IDF), one in every seven adults with diabetes worldwide lives in India, and one in every third households has an individual with diabetes.[4] Diabetes raises the risk of cardiovascular disease (CVD) and all-cause mortality when it is

combined with arterial stiffness (AS). It has been suggested that arterial stiffness is a common, age-related, progressive, and an ongoing process that results from a number of different conditions, including DM, hypertension, the metabolic syndrome, and chronic kidney disease (CKD).

Recent studies suggested that arterial stiffness plays a significant role in the pathophysiology of DM. Endothelial dysfunction may even arise prior to the development of overt DM along with early insulin resistance (IR) and impaired fasting glucose.[5] As the DM increases the risk of vascular disease and since many of its sequelae include microvascular (diabetic retinopathy, nephropathy, and neuropathy) as well as macrovascular (cardiovascular disease, cerebrovascular disease, and peripheral artery disease), the present study was carried out with an aim to assess AS and microvascular complications in patients with type 2 DM (T2DM) patients.

2. MATERIAL AND METHODS

This cross sectional observational study was approved by the Institutional Ethics Committee and each patient provided written informed consent prior to participating in this study. This study consisted of patients with history of T2DM were recruited from tertiary care hospital in South India during the period from January 2022 to December 2022. By using convenient sampling technique, the required sample size was calculated to be 250.

2.1. Inclusion and Exclusion Criteria:

All patients presenting with T2DM irrespective of sex, age attending both outpatient and inpatient departments were included. Patients with CKD – end stage renal disease (ESRD), chronic inflammatory disorders, rheumatoid arthritis, systemic lupus erythematous, systemic vasculitis, congestive heart failure and age >70 years were excluded from the study. The following information was obtained from the patients using an interviewer-administered questionnaire: age, gender, body weight (kg), systolic (SBP) and diastolic blood pressure (DBP), and fasting plasma glucose (FPG). BMI is calculated as weight divided by squared height (kg/m2). Using a sphygmomanometer, SBP and DBP were assessed following a 5-minute rest.

2.2. Microvascular Complications

The Patients were examined for the presence of any these microvascular problems i.e. retinopathy, neuropathy and nephropathy, preferably alone or in combination. An ophthalmologist used fundoscopy to do the ophthalmoscopic examination. A microaneurysm, blot or flame-shaped hemorrhage, hard exudates, cotton wool patches, or macula oedema are examples of abnormalities that can indicate retinopathy.[6] The presence of proteinuria or microalbuminuria, an estimated glomerular filtration rate (eGFR) of less than 60 milliliters per minute, and serum creatinine levels greater than 150 micrograms per deciliter were used to diagnose nephropathy.[7] In order to identify neuropathy, a 10-gram monofilament was used to record any history of numbness, parasthesia, tingling, loss of ankle reflex, or loss of light touch feeling.[8]

2.3. Echocardiography Assessment:

A two-dimensional (2D) echocardiogram was done to assess the AS by using the formula (SBP/DBP) X (AoS - AoD) /AoD where AoS and AoD are the systolic and diastolic diameter of the ascending aorta (**Figure 1**). Standard parasternal and apical windows were used to obtain echocardiographic images. Three consecutive beats were recorded, and the offline data was analyzed at the end of the study. A cardiologist evaluated all the studies.

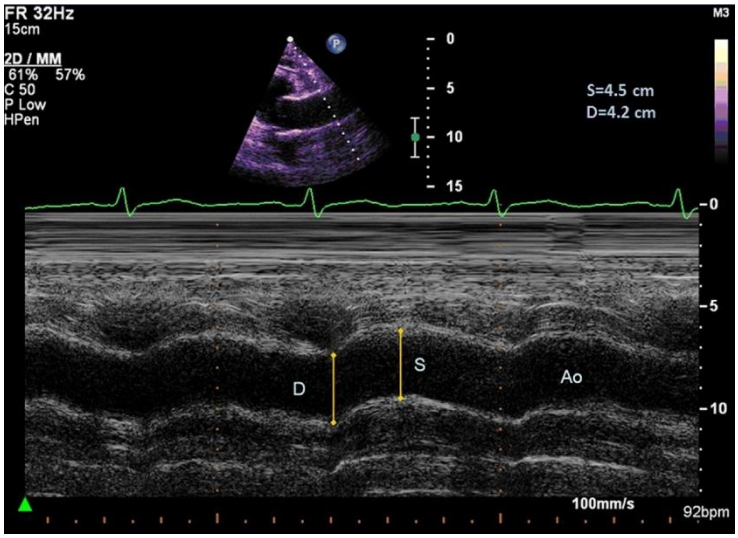

Figure 1: Measurements of aortic diameters shown on the M-mode tracing

2.4 Statistical Analysis:

For both continuous and categorical variables, means and proportions were calculated. Categorical variables were expressed as numbers with proportions (%) and significance was identified by using Chi-square test. Continuous variables are presented as mean ± SD and significance was identified using independent sample t test. For all statistical analyses, SPSS software version 25.0 was used and a p-value of less than 0.05 was taken as statistical significance.

3. RESULTS

The demographic characteristics of the participants were illustrated in **Table 1.** Majority of the participants were in the age group of 46 - 60 years (58.4%) followed by 31 - 45 years (30%), > 60 years (13.6%) and the mean age was 51.2 ± 8.5 years. 57.2% were male and 42.8% were female. Based on BMI classification, 91.6% were under normal category, 7.2% were overweight and only 1.2% were underweight.

Table 1: Demographic characteristics of the participants

Variables	n, (%)
Age (years)	
31-45	70 (30%)
46-60	146 (58.4%)
>60	34 (13.6%)
Gender	
Male	143 (57.2%)
Female	107 (42.8%)
BMI Classification	
Underweight	3 (1.2%)
Normal	229 (91.6%)
Overweight	18 (7.2%)

Based on the comorbidities listed in **Table 2,** 58% of the participants were in Stage 2 CKD followed by 36.4% in Stage 3 CKD, 24.4% had systemic hypertension, 9.6% had elevated blood urea nitrogen, 8.8% had AS, 6% had retinopathy, 5.6% had nephropathy, 4.8% had albuminuria, 4.4% had elevated serum creatinine and stage 4 CKD, 2.8% had neuropathy and 1.2% had stage 0 CKD.

Table 2: Distribution of participants based on co-morbidities (N=250)

Co-morbidities	n, (%)
Systemic hypertension	61 (24.4)
Albuminuria	12 (4.8)
Raised Blood Urea Nitrogen	24 (9.6)
Raised serum creatinine	11 (4.4)
Stages of CKD	
0	3 (1.2)
1	0
2	145 (58.0)
3	91 (36.4)

4	11 (4.4)
Retinopathy	15 (6.0)
Neuropathy	7 (2.8)
Nephropathy	14 (5.6)
AS	22 (8.8)

Proportion of patients with AS found to raise with increasing age of the patient. **(p = 0.021)** No significant association was noted between BMI of the patient and presence of AS in our study because most of the participants were in normal BMI classification range (91.6%).The proportion of patients with AS increased significantly with increasing duration for DM in the patient and was to be found to be statistically significant. **(Table 3)**

Table 3: Association between demographic characteristics and AS (n = 250)

Variables	**AS**		**Total**	**p value***
	Present n, (%)	**Absent n, (%)**	**n, (%)**	
Age (years)				
31 - 45	3 (4.3)	67 (95.7)	68 (100.0)	**0.021**
46 - 60	12 (8.2)	134 (91.8)	146 (100.0)	
> 60	7 (20.6)	27 (79.4)	34 (100.0)	
Gender				
Male	14 (9.8)	129 (90.2)	143 (100.0)	0.523
Female	8 (7.5)	99 (92.5)	107 (100.0)	
BMI (kg/m^2)				
Underweight	1 (33.3)	2 (66.7)	3 (100.0)	0.143
Normal	18 (7.9)	211 (92.1)	229 (100.0)	
Overweight	3 (16.7)	15 (83.3)	18 (100.0)	
Duration of Diabetes (years)				
0.1 - 1	0 (0.0)	43 (100.0)	43 (100.0)	**<0.001**
1 - 5	9 (5.8)	146 (94.2)	155 (100.0)	
6 - 10	6 (17.1)	29 (82.9)	35 (100.0)	
> 10	7 (41.2)	10 (58.8)	17 (100.0)	

Note: *chi-square test

There was a statistical association between albuminuria and AS. Nearly 41.7% of the patients with albuminuria had AS. Higher proportion of patients with albuminuria had AS when compared to those who did not have albuminuria. Majority of the patients with microvascular complications had AS. **(Table 4)**

Table 4: Association between comorbidities and AS (n = 250)

Comorbidities	AS		Total	p value*
	Present n, (%)	Absent n, (%)	n, (%)	
Albuminuria	5 (41.7)	7 (58.3)	12 (100.0)	**<0.001**
Raised blood urea levels	6 (25.0)	18 (75.0)	24 (100.0)	**0.003**
Raised serum creatinine levels	3 (27.3)	8 (72.7)	11 (100.0)	**0.027**
CKD stage				
0	1 (33.3)	2 (66.7)	3 (100.0)	**<0.001**
2	4 (2.8)	141 (97.2)	145 (100.0)	
3	12 (13.2)	79 (86.8)	91 (100.0)	
4	5 (45.5)	6 (54.5)	11 (100.0)	
Retinopathy	12 (80.0)	3 (20.0)	15 (100.0)	**<0.001**
Neuropathy	5 (71.4)	2 (28.6)	7 (100.0)	**<0.001**
Nephropathy	7 (50.0)	7 (50.0)	14 (100.0)	**<0.001**

Note:*chi-square test

Followed by, to find the influence of blood pressures on microvascular complications, mean differences (MD) were calculated. Both systolic and diastolic BP shows statistical significance with all the microvascular complications (**Table 5**).

Table 5: Comparison of systolic and diastolic measurements with various comorbidities

		SBP		Difference in mean (95% CI)	p value	DBP		Difference in mean (95% CI)	p value*
		Mean	SD			Mean	SD		
Retinopathy	Present	21.2	2.8	4.7 (3.6-5.9)	**<0.001**	23.2	3.0	5.5 (4.4-6.7)	**<0.001**
	Absent	26.0	2.1			28.7	2.1		
Neuropathy	Present	21.9	3.2	4.5 (2.8-6.3)	**<0.001**	23.4	3.0	5.1 (3.3-6.9)	**<0.001**
	Absent	25.8	2.3			28.5	2.4		
Nephropathy	Present	23.3	4.1	2.5 (1.3-3.8)	**<0.001**	25.3	4.1	3.2 (1.9-4.5)	**<0.001**
	Absent	25.8	2.2			28.6	2.3		

Note: SBP – systolic blood pressure, DBP – diastolic blood pressure, * independent sample t-test

4. DISCUSSION

This study was aimed to assess AS in T2DM and to evaluate the association between microvascular complication and AS. No significant association was found between BMI and presence of AS in our study because majority of the overweight individuals did not have AS (83.3%). Similarly, in normal and underweight individuals, absence of AS was found in higher number of participants. However, in a study conducted by Niruba *et al*, it was found that there was increase in AS with increase in BMI.[9] Another study showed when compared to lean controls, AS is higher in those with obesity-related T2DM.

Majority of the participants had DM for duration of 1-5 years. The proportion of patients with AS increased significantly with increasing duration for DM in the patient and was to be found to be statistically significant. Similar results were seen in

a study conducted by Smulyan H *et al.,* in which increased duration of diabetes was identified to be an independent risk factor for AS.[10] Thus, DM duration is one independent determinant of AS in T2DM patients.

Microalbuminuria is a well-established risk factor for CVD and significantly predicts mortality.[11] In our study, there was a statistical association between albuminuria and AS. 41.7% of patients with albuminuria had AS whereas the study conducted by Yokoyama *et al.,* which included patients with T2DM, approximately one third of the patients had microalbuminuria.[12] Previous studies showed that patients with T2DM and elevated albumin to creatinine ratio (ACR) identified raised AS.[13] In a 6 year follow-up longitudinal study, AS was associated with albuminuria and the reduction in glomerular filtration rate (GFR) among patients with type 2 DM.[14] Our study was in concordance with the above mentioned studies indicating that higher proportion of study participants with elevated blood urea and creatinine levels was found to have AS. Majority of our study participants were in CKD stage 2 (58.0%). With the increasing stages of CKD, AS was found to be associated significantly. Nearly, 45.5% of the patients with stage 4 CKD were found to have AS. Nakagawa ***et al.,*** reported that AS associated with decreased eGFR and increased with increasing CKD stages.[15]

When assessing the microvascular complications, the vast majority of patients with diabetic retinopathy do not exhibit symptoms until the final stage of the condition (at which point, treatment may be ineffective). Diagnosing retinal disease in those with diabetes is essential since the disease can proceed quickly and treatment can help both with symptom relief and slowing down the progression of disease. Diabetic retinopathy appears to be associated with an increased risk of morbidity and mortality, primarily related to cardiovascular conditions.[16,17] Majority of the patients with retinopathy were found to have AS (80%). It has been found to be correlated with the emergence of diabetic retinopathy, an independent predictor of mortality in DM patients.[16,18]

This has been confirmed in several studies.[19,20] Similarly, 71.4% with neuropathy were found to have AS. Another common manifestation of DM is neural dysfunction, its prevalence increases with the duration of DM, with rates as raised as 70% in subjects with long term DM. Peripheral or autonomic (central) neuropathy are two possible manifestations of neural involvement. Similar to other microvascular consequences of DM, autonomic dysfunction is a reliable indicator of cardiovascular mortality.[21,22]

It has been suggested that central arteries are more susceptible to the effects of diabetes on arterial stiffness than peripheral arteries.[23] Meta-analyses of clinical studies showed reducing blood pressure (BP) can effectively minimize the risk of DM and its microvascular and macrovascular consequences.[24] Similarly, we found statistical significance between blood pressures and microvascular complications (retinopathy, neuropathy and nephropathy).

However, our study also has potential limitations. First, we did not detect the cases at an early stage and also we did not do the follow-up of cases. Second, since this study was restricted to the particular tertiary care facility, it is possible that our conclusions cannot be applied to other populations. Third, the sample sizes for BMI classification were relatively small. As we attempted to study only the association of AS (from echocardiographic measurement) with the microvascular complications, we did not use any other indices like carotid-femoral pulse wave velocity (PWV).

5. CONCLUSION

Aortic stiffness was found to be significantly prevalence among the patients with T2DM and this prevalence found to be increased significantly with increasing age. Also, a significant association was identified between the occurrence of microvascular complications and presence of AS. Regular screening for AS is recommended for patients with DM and higher frequency of screening may be required in patients who are diabetic for a longer duration, old age and patients with micro vascular complications of DM. For greater elucidation of the potential cardiovascular consequences in these individuals, longer follow-up periods and larger sample sizes should be taken into consideration in future studies.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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