

Original Research Article

ASSOCIATION OF GLYCEMIC CONTROL WITH LEFT ATRIAL REMODELLING IN NORMOTENSIVE PATIENTS WITH DIABETES MELLITUS WITHOUT SYMPTOMATIC CARDIOVASCULAR DISEASE: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Diabetes mellitus is associated with structural and functional myocardial abnormalities that may occur before the development of clinically apparent cardiovascular disease. Left atrial volume is considered an important marker of chronic left ventricular filling pressure and diastolic dysfunction. In patients with diabetes mellitus, metabolic abnormalities, microvascular disease, myocardial fibrosis and reduced left ventricular compliance may contribute to left atrial remodelling. The present study evaluated left atrial volume and its association with glycemic status, treatment status, sex and body surface area among normotensive diabetic patients without symptomatic cardiovascular disease.

Materials and Methods: A prospective observational study was conducted among 60 consecutive patients with diabetes mellitus admitted to Government Rajaji Hospital and Madurai Medical College during a six-month study period from March 2020 to August 2020. Patients were aged 45–75 years and included both males and females. Patients with hypertension, heart failure, renal failure, chronic obstructive pulmonary disease, liver disease and type 1 diabetes mellitus were excluded. Clinical examination, laboratory investigations, electrocardiography, chest radiography and echocardiographic evaluation were performed. Left atrial volume was assessed using the biplane area-length method and indexed to body surface area. Statistical analysis included Student's t-test and Pearson's chi-square test, with $p < 0.05$ considered statistically significant.

Results: Among the 60 participants, 38 (63.3%) were males and 22 (36.7%) were females. The largest proportion of participants belonged to the 61–70-year age group (41.7%). Left atrial remodelling was observed in 49 (81.6%) participants, while 11 (18.3%) had normal left atrial measurements. Left atrial volume >28 was observed in 51 participants. The association between left atrial volume category and sex was not statistically significant (chi-square=0.811, $p=0.368$). Mean HbA1c was substantially higher in participants with left atrial volume >28 than in those with left atrial volume ≤ 28 (9.235 ± 1.544 vs. 5.667 ± 1.00 ; $p < 0.001$). Treatment status was also significantly associated with left atrial volume category (chi-square=36.29, $p < 0.001$). A moderate positive correlation was reported between HbA1c and left atrial volume (correlation coefficient=0.530).

Conclusion: The study demonstrates a significant association between poor glycemic control and increased left atrial volume among normotensive diabetic patients without symptomatic cardiovascular disease. Increased left atrial volume was also associated with treatment status and body surface area. Assessment of left atrial remodelling may therefore help identify diabetic patients at increased risk of subclinical cardiac involvement.

Keywords: Diabetes mellitus, Left atrial volume, Left atrial remodelling, HbA1c, Echocardiography.

INTRODUCTION

Diabetes mellitus is a major metabolic disorder associated with a wide range of microvascular and macrovascular complications.^[1] Cardiovascular involvement represents one of the major causes of morbidity and mortality among individuals with diabetes. Importantly, structural and functional abnormalities of the myocardium may develop before the appearance of clinically evident cardiovascular disease.^[2] The concept of diabetic cardiomyopathy describes myocardial structural and functional abnormalities occurring in patients with diabetes in the absence of other major causes of cardiac dysfunction.^[3] The left atrium plays an important role in maintaining normal cardiac filling and ventricular performance. Left atrial volume is influenced by left ventricular filling pressure, ventricular compliance and diastolic function.^[4] Consequently, enlargement of the left atrium may represent the cumulative effect of chronically elevated left ventricular filling pressures rather than merely the haemodynamic state at a single point in time. The uploaded study protocol specifically describes left atrial volume as a potential marker of early cardiovascular disease in normotensive, asymptomatic patients with type 2 diabetes mellitus.^[5] Several mechanisms may contribute to cardiac remodelling in diabetes mellitus. Persistent hyperglycaemia can result in accumulation of advanced glycation end products, altered collagen metabolism and myocardial interstitial fibrosis. These changes may reduce left ventricular compliance and contribute to left ventricular diastolic dysfunction. The resulting increase in left atrial afterload can lead to progressive enlargement of the left atrium. The proposed mechanism in the study document is: long-standing hyperglycaemia → advanced glycation end-product accumulation → collagen formation → myocardial interstitial fibrosis → decreased left ventricular compliance → diastolic dysfunction → increased left atrial afterload → increased left atrial volume index.^[6, 7] In addition to hyperglycaemia, altered myocardial metabolism may contribute to diabetic myocardial dysfunction.^[8] The study document discusses microvascular disease, altered myocardial metabolism, structural myocardial changes and increased fibrosis as potential mechanisms for reduced left ventricular compliance.^[9] Myocardial lipid accumulation and lipotoxic injury have also been proposed as possible contributors to myocardial dysfunction in diabetes. Left atrial volume can be assessed non-invasively by echocardiography. The biplane area-length method uses measurements obtained from apical four-chamber and two-chamber views. The left atrial volume is calculated from the planimetered areas and longitudinal length, and the resulting volume can be indexed to body surface area. The study protocol specifies that left atrial measurements should be obtained at ventricular end-systole while avoiding foreshortening.^[10] The present

study was therefore designed to evaluate left atrial volume and remodelling in normotensive diabetic patients without symptomatic cardiovascular disease. Particular attention was given to the relationship between left atrial volume and HbA1c, treatment status, sex and body surface area.

MATERIALS AND METHODS

Study Design and Setting: A prospective observational study was conducted at Government Rajaji Hospital and Madurai Medical College, in collaboration with the Department of Cardiology. The study was carried out over a period of six months, from March 2020 to August 2020.

Study Population: The study included 60 consecutive patients with diabetes mellitus admitted to Government Rajaji Hospital and Madurai Medical College during the study period. Both male and female patients between 45 and 75 years of age were considered for enrolment. The study specifically focused on diabetic patients without hypertension or symptomatic cardiovascular disease.

Inclusion Criteria

Patients were eligible for inclusion if they fulfilled the following criteria:

1. Age between 45 and 75 years.
2. Both male and female patients.
3. Patients with diabetes mellitus.
4. Patients receiving antidiabetic treatment as well as those not receiving treatment.
5. Diabetes mellitus of more than 5 years' duration.
6. Patients without symptomatic cardiovascular disease.
7. Patients without hypertension.
8. Patients satisfying the HbA1c criteria specified in the study protocol, namely HbA1c <7% among patients receiving treatment and HbA1c >7% among patients not receiving treatment.

Exclusion Criteria

Patients were excluded if they had any of the following:

- Hypertension
- Heart failure
- Renal failure
- Chronic obstructive pulmonary disease
- Liver disease
- Type 1 diabetes mellitus

Clinical Assessment: After enrolment, a detailed history was obtained using a structured study proforma. Information regarding demographic characteristics, presenting complaints, past medical history and personal history was recorded. Particular attention was given to the history of diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease and cerebrovascular disease. History of seizure disorders and previous pulmonary tuberculosis was also documented. A complete general and systemic examination was performed. General examination included assessment of

consciousness, pallor, cyanosis, jaundice, clubbing, lymphadenopathy and pedal oedema. Vital parameters including pulse rate, blood pressure and peripheral oxygen saturation were recorded. Cardiovascular, respiratory, abdominal and central nervous system examinations were performed.

Laboratory Investigations

The following investigations were performed as part of the study evaluation:

- Complete blood count
- Erythrocyte sedimentation rate
- Liver function tests
- Renal function tests
- Fasting blood glucose
- Postprandial blood glucose
- HbA1c
- Electrocardiography
- Chest radiography
- Echocardiography

These investigations were performed to assess the general clinical status of the participants and to evaluate associated cardiovascular and metabolic abnormalities.

Echocardiographic Assessment

Echocardiographic assessment was performed to evaluate left atrial size and volume. The study protocol describes assessment using real-time echocardiography and specifies measurement of left atrial volume using the biplane area-length method. The left atrial measurements were obtained from the apical four-chamber and apical two-chamber views. Measurements were obtained at ventricular end-systole, and care was taken to avoid foreshortening of the left atrium.

Measurement of Left Atrial Volume:

The maximum planimetered left atrial area was measured in:

- Apical four-chamber view (A1)
- Apical two-chamber view (A2)

The longitudinal length of the left atrium (L) was measured from the posterior wall to the line connecting the mitral valve hinge points.

Left atrial volume was calculated using the following formula:

$$LA \text{ volume} = 0.85 \times (A1 \times A2) / L$$

where A1 represents the maximum planimetered left atrial area in the apical four-chamber view, A2 represents the maximum planimetered left atrial area in the apical two-chamber view, and L represents the longitudinal left atrial length.

Left Atrial Volume Index: Left atrial volume was indexed to body surface area (BSA) to obtain the left atrial volume index (LAVI):

$$LAVI = \text{Left atrial volume} / \text{Body surface area}$$

Height and weight were recorded for calculation of body surface area.

Assessment of Glycemic Control: Glycemic control was assessed using HbA1c. HbA1c values were compared between participants with lower and higher left atrial volume. The relationship between HbA1c

and left atrial volume was additionally assessed using correlation analysis.

Assessment According to Treatment Status: Participants were categorised according to whether they were receiving antidiabetic treatment or were not receiving treatment. Left atrial volume categories were then compared between the two groups to determine whether treatment status was associated with left atrial remodelling.

Assessment of Body Surface Area: Body surface area was calculated using recorded height and weight measurements. Mean BSA was compared between participants with LAV ≤ 28 and those with LAV > 28 to assess the relationship between body size and left atrial volume.

Outcome Measures: The principal study outcome was the presence of increased left atrial volume/left atrial remodelling among diabetic patients without hypertension or symptomatic cardiovascular disease. The study also evaluated the association of left atrial volume with:

- Age
- Sex
- HbA1c
- Antidiabetic treatment status
- Body surface area

Statistical Analysis: Categorical variables were expressed as frequencies and percentages, while continuous variables were summarised using mean and standard deviation. Between-group comparisons for continuous variables were performed using the Student's t-test, while categorical variables were compared using the Pearson chi-square test. Correlation analysis was performed to assess the relationship between HbA1c and left atrial volume. A p value of < 0.05 was considered statistically significant. The study document also describes Kaplan-Meier analysis, log-rank testing and Cox proportional-hazards modelling; however, corresponding follow-up outcome data are not presented in the reported results. Therefore, these analyses should only be retained in the final manuscript if the original dataset contains the relevant longitudinal outcome information.

Ethical Considerations: The study received ethical clearance/Institutional Ethics Committee approval. Individual written informed consent was obtained from all participants before inclusion in the study.

RESULTS

A total of 60 patients with diabetes mellitus were included in the present study. The demographic characteristics and echocardiographic findings were analysed with respect to age, sex, left atrial volume, HbA1c, treatment status and body surface area.

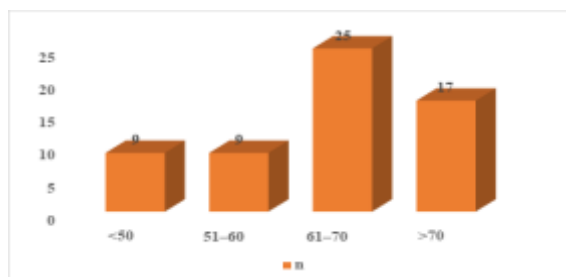


Figure 1: Age distribution of study participants

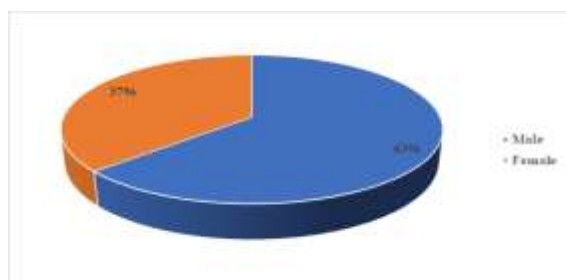


Figure 2: Sex distribution of study participants

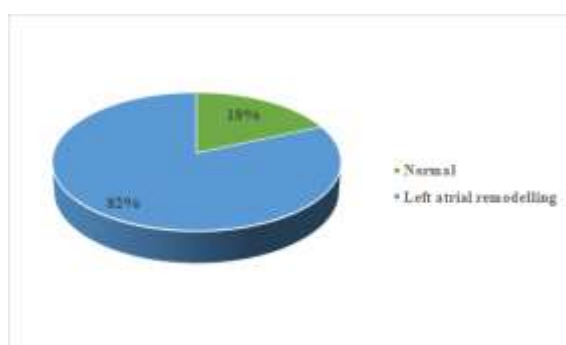


Figure 3: Distribution of left atrial remodelling

Age and Sex Distribution: The age distribution of the study population is presented in [Table 1]. The

majority of participants were in the 61–70-year age group (41.7%), followed by those aged >70 years (28.3%). Participants aged <50 years and 51–60 years each accounted for 15.0% of the study population [Figure 1]. Of the 60 participants, 38 (63%) were males and 22 (37%) were females, demonstrating a male predominance in the study population [Figure 2].

Left Atrial Remodelling: Left atrial remodelling was observed in 49 (82%) participants, whereas 11 (18%) had normal left atrial measurements [Figure 3]. Thus, left atrial remodelling was frequently observed among the diabetic patients included in the study.

Association Between Left Atrial Volume and Sex: The association between left atrial volume (LAV) and sex is shown in [Table 4]. Among the 38 male participants, 34 had LAV >28, whereas 17 of the 22 female participants had LAV >28. Although increased LAV was more frequently observed among males, the association between sex and LAV category was not statistically significant ($\chi^2=0.811$, $p=0.368$) [Table 1].

Association Between Left Atrial Volume and HbA1c: A significant difference in HbA1c was observed between the two LAV categories. The mean HbA1c was 5.667 ± 1.00 among participants with LAV ≤ 28 compared with 9.235 ± 1.544 among those with LAV >28. The difference was statistically significant ($t=-6.66$, $p<0.001$; 95% CI, -4.640 to -2.497) [Table 2]. Correlation analysis demonstrated a moderate positive correlation between HbA1c and LAV ($r=0.530$), which was reported to be statistically significant. This finding indicates that higher HbA1c levels were associated with greater left atrial volume.

Table 1: Association between left atrial volume and sex

Sex	LAV ≤ 28 , n	LAV >28, n	Total
Male	4	34	38
Female	5	17	22
Total	9	51	60
χ^2		0.811	
p value		0.368	

Table 2: Comparison of HbA1c according to left atrial volume

Parameter	LAV ≤ 28 (n=9)	LAV >28 (n=51)
Mean HbA1c	5.667	9.235
SD	1	1.544
t value	-6.66	
95% CI	-4.640 to -2.497	
p value	<0.001	

Association Between Left Atrial Volume and Treatment Status: A statistically significant association was observed between antidiabetic treatment status and LAV category ($\chi^2=36.29$,

$p<0.001$). Among patients receiving treatment, 9 had LAV ≤ 28 and 1 had LAV >28, whereas among untreated patients, 2 had LAV ≤ 28 and 49 had LAV >28 [Table 3].

Table 3: Association between left atrial volume and treatment status

Treatment status	LAV ≤ 28 , n	LAV >28, n
On treatment	9	1
Not on treatment	2	49
χ^2		36.29
p value		<0.001

Association Between Left Atrial Volume and Body Surface Area: Participants with LAV >28 had a higher mean body surface area than those with LAV ≤28. The mean BSA was $1.744 \pm 0.201 \text{ m}^2$ in the

LAV ≤28 group and $2.037 \pm 0.199 \text{ m}^2$ in the LAV >28 group. This difference was statistically significant ($t=-4.066$, $p<0.001$; 95% CI, -0.437 to -0.149) [Table 4].

Table 4: Comparison of body surface area according to left atrial volume

Parameter	LAV ≤28 (n=9)	LAV >28 (n=51)
Mean BSA (m ²)	1.744	2.037
SD	0.201	0.199
t value	-4.066	
95% CI	-0.437 to -0.149	
p value	<0.001	

DISCUSSION

The present study evaluated left atrial remodelling among 60 patients with diabetes mellitus without hypertension or symptomatic cardiovascular disease. Left atrial remodelling was observed in 81.6% of the study population, suggesting that structural cardiac abnormalities may occur in diabetic patients even before the development of clinically overt cardiovascular disease. Diabetes mellitus is known to cause myocardial structural and functional abnormalities through several mechanisms, including chronic hyperglycaemia, advanced glycation end-product accumulation, myocardial fibrosis, altered myocardial metabolism and impaired ventricular compliance.^[11,12] In the present study, a significant association was observed between HbA1c and left atrial volume. Patients with LAV >28 had a considerably higher mean HbA1c than those with LAV ≤28 (9.235 ± 1.544 vs. 5.667 ± 1.00 ; $p<0.001$). Furthermore, a moderate positive correlation was observed between HbA1c and LAV ($r=0.530$). These findings suggest that poor glycemic control may be associated with progressive left atrial remodelling. Similar findings were reported by Zapolski et al., who demonstrated an association between glycemic control and left atrial volume index in patients with type 2 diabetes mellitus.^[12] Tadic et al. also reported increased left atrial volume and impaired left atrial function among diabetic patients, supporting the presence of early atrial remodelling in diabetes.^[2] The high prevalence of left atrial remodelling in the present study is also consistent with previous observations. Chillo et al. reported increased left atrial volume index in asymptomatic diabetic patients and demonstrated an association between left atrial enlargement and left ventricular diastolic dysfunction.^[13] Similarly, Zoppini et al. demonstrated left atrial remodelling and left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus despite preserved left ventricular systolic function.^[7] These findings support the concept that left atrial enlargement may represent an early manifestation of diabetic cardiac involvement.

A statistically significant association was observed between antidiabetic treatment status and left atrial volume in the present study ($\chi^2=36.29$, $p<0.001$). Increased LAV was substantially more frequent among participants who were not receiving

treatment. However, this finding should be interpreted cautiously because the observational design does not establish a causal relationship between treatment and left atrial remodelling. Differences in HbA1c, duration of diabetes, disease severity and other metabolic factors may have contributed to this association. The present study also demonstrated a significant association between body surface area and left atrial volume. Participants with LAV >28 had a higher mean BSA than those with LAV ≤28 (2.037 ± 0.199 vs. $1.744 \pm 0.201 \text{ m}^2$; $p<0.001$). This finding is clinically relevant because cardiac chamber dimensions are influenced by body size, which supports the importance of indexing left atrial volume to body surface area when assessing atrial enlargement.^[14] Although increased LAV was numerically more frequent among males, the association between sex and left atrial volume was not statistically significant ($p=0.368$). This suggests that sex alone may not be an important determinant of left atrial remodelling in this population. Previous studies have similarly emphasised metabolic and haemodynamic factors, particularly glycemic control and ventricular diastolic abnormalities, in the development of diabetic cardiac remodelling.^[2,7] The prognostic importance of increased left atrial volume has been demonstrated in previous studies. Poulsen et al. reported that increased LAVI was associated with adverse long-term cardiovascular outcomes in patients with type 2 diabetes mellitus without previous cardiovascular disease.^[10] Therefore, the increased frequency of left atrial remodelling observed in the present study may have potential clinical significance. However, because the current study did not include long-term cardiovascular follow-up, it cannot establish whether increased LAV independently predicts future heart failure or cardiovascular mortality. Overall, the findings of the present study support the presence of subclinical left atrial remodelling in diabetes mellitus, particularly among patients with poor glycemic control. Echocardiographic assessment of left atrial volume may therefore provide useful information for the early identification of diabetic patients at increased cardiovascular risk. Larger prospective studies incorporating left ventricular diastolic parameters, left atrial strain and long-term cardiovascular outcomes are required to determine the independent prognostic value of LAVI in diabetes mellitus.

Limitations: This study has several limitations. First, it was a single-centre study with a relatively small sample size of 60 patients, which may limit the generalizability of the findings to the broader diabetic population. Second, the cross-sectional/observational nature of the analysis limits the ability to establish a causal relationship between diabetes, glycemic control and left atrial remodelling. Third, the study specifically excluded patients with hypertension, heart failure, renal failure, chronic obstructive pulmonary disease, liver disease and type 1 diabetes mellitus; therefore, the findings may not be applicable to diabetic patients with these common comorbidities. In addition, the study did not provide longitudinal follow-up to determine whether increased left atrial volume subsequently translated into clinical cardiovascular events, heart failure or mortality. Other potential determinants of left atrial remodelling, including duration of diabetes, obesity, lipid abnormalities, medication use and detailed assessment of left ventricular diastolic function, may also have influenced the observed associations. Finally, the use of left atrial volume as the principal marker of remodelling may not fully reflect the functional changes occurring in the left atrium. Larger, multicentre prospective studies with long-term follow-up and comprehensive echocardiographic assessment are warranted to validate these findings.

CONCLUSION

Diabetes mellitus is associated with left atrial remodelling in normotensive patients without symptomatic cardiovascular disease. In the present study, increased left atrial volume was observed in a substantial proportion of diabetic patients, suggesting that atrial structural changes may occur even in the absence of clinically apparent cardiovascular disease. Higher HbA1c levels were significantly associated with increased left atrial volume, highlighting the potential importance of poor glycemic control in the development of early cardiac remodelling. The association between treatment status and left atrial volume further emphasizes the importance of adequate diabetes management. Early echocardiographic assessment of left atrial volume may therefore help identify diabetic patients with subclinical cardiac involvement before the development of overt cardiovascular disease. Larger prospective studies with long-term follow-up are required to confirm these findings and determine whether left atrial remodelling can serve as an early predictor of future cardiovascular outcomes.

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