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Research Article

An Observational Study to Assess the Predictors of Cardiac Dysfunction in Type 2 Diabetes Patients

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A B S T R A C T

Introduction: Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from either insufficient insulin production or ineffective insulin utilisation by the body. Cardiac dysfunction refers to abnormalities in the structure or function of the heart, leading to impaired pumping ability and compromised circulation. The relationship between diabetes mellitus and cardiac dysfunction is complex and involves multiple factors, including metabolic, molecular, and cellular mechanisms.

Aim: The aim of this study was to identify the predictors of cardiac dysfunction in patients with type 2 diabetes mellitus (T2DM).

Material and Methods: The study employed an observational design and included a sample size of 284 participants with type 2 diabetes. It included T2DM patients (> 10 years of duration of the disease) who were more than 40 years of age.

Result: The results showed a significant positive association between the age group of 61-80 years and abnormal/ elevated levels of B-type natriuretic peptide (BNP) [odds ratio (OR): 2.32; confidence interval (CI): 1.013 ± 3.301; p value: 0.039]. Furthermore, an increase in the duration of T2DM (21-30 years) was significantly associated with abnormal/ elevated BNP levels (> 100) [OR: 3.283; CI: 1.704 ± 3.827; p value: 0.003].

Conclusion: This study links BNP to ejection fraction (EF) in T2DM patients without heart failure symptoms. It also shows that elevated BNP is associated with reduced EF, and normal BNP is linked to preserved EF. It was seen that age, T2DM duration, and HbA1c impact BNP levels. Longer T2DM duration was found to be associated with lower EF.

Keywords: Cardiac Failure, Heart Failure, Diabetes Mellitus, Diabetes Mellitus Type 2

Introduction

Type 2 diabetes mellitus (T2DM) encompasses a diverse range of disorders marked by varying levels of insulin resistance, compromised insulin secretion, and heightened hepatic glucose production. Diabetes mellitus (DM) and cardiac dysfunction often occur concomitantly, and each disease independently increases the risk for the other.

Patients hospitalised with overt heart failure have a higher prevalence of diabetes mellitus (DM), with certain reports indicating rates exceeding 40%. Among individuals with DM, the prevalence of heart failure ranges from 9% to 22%, which is approximately four times higher than that observed in the general population.[1]

Scope of the Problem

Although MI and hypertension are the most common risk factors associated with cardiac dysfunction, diabetes also independently predicts heart failure risk, with an associated twofold to fivefold increased risk.[2]

When cardiac dysfunction is already present, the presence of diabetes signifies a particularly unfavourable prognosis concerning subsequent morbidity and mortality.[2] In patients with diabetes and prevalent Atherosclerotic Cardiovascular Disease (ASCVD) observed in a registry over 4 years, overt heart failure at baseline was independently associated with increased CV death (HR adjusted, 2.5; 95% CI: 2.2 to 2.8).[3]

Epidemiology of DM and Cardiac Dysfunction

Among patients with diabetes mellitus (DM), the prevalence of heart failure (HF) is high. Furthermore, the prevalence of HF is even higher in DM patients who are aged 60 years or above.

Mechanisms of Cardiac Dysfunction in Diabetes Mellitus

Figure 1 shows that alterations in cardiac functions can be experienced by diabetics through varying mechanisms. These include decreased glucose transport and carbohydrate oxidation, increased utilisation of free fatty acids (FFAs), reduced sarcolemmal calcium transport, and modifications in myofibrillar regulatory contractile proteins. These changes contribute to the impaired cardiac function observed in individuals with diabetes.[4] The potential mechanism behind the effect of diabetes on cardiac dysfunction has been explained in Table 1.

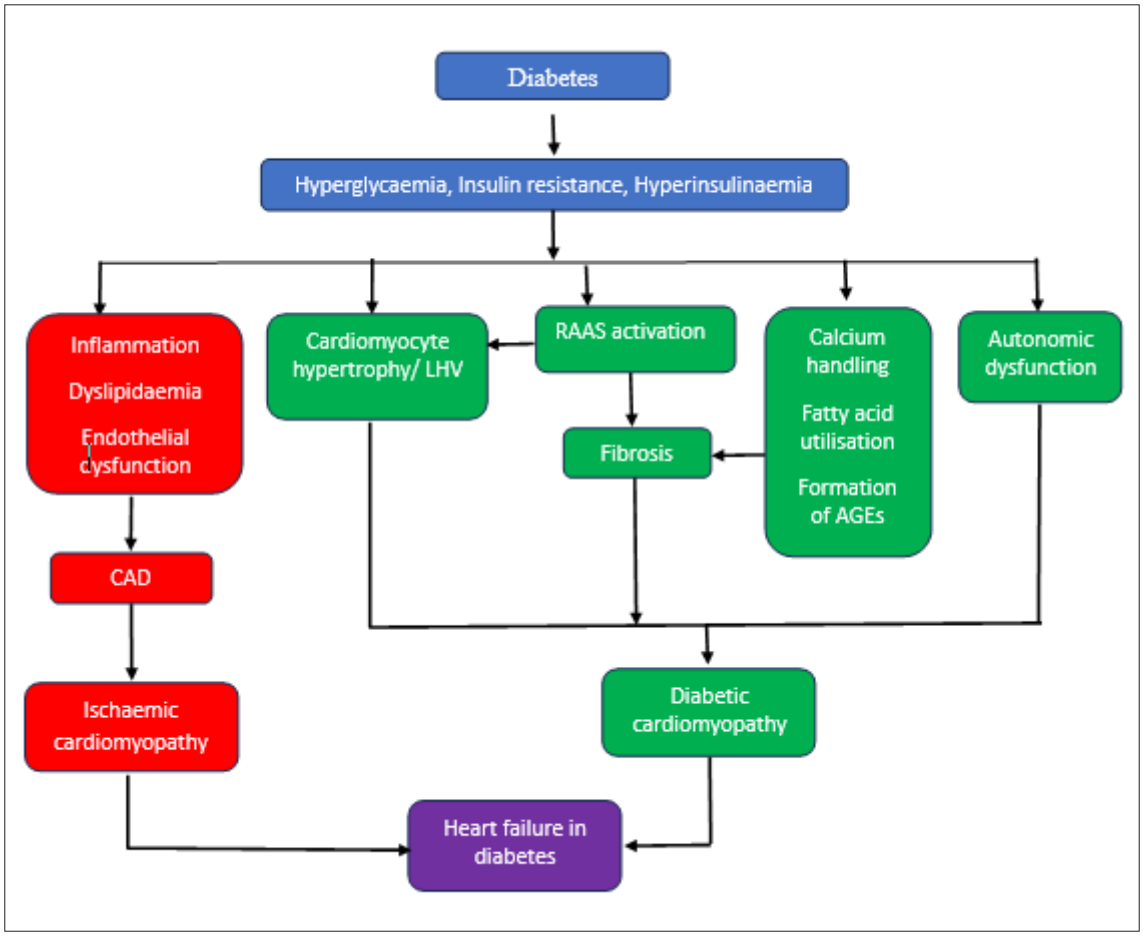

Figure 1.Various Mechanisms that can Cause Alterations in Cardiac Function in Diabetics[4]

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Table 1.Potential Mechanisms Underlying Diabetic Cardiomyopathy and Their Consequences on Cardiac Function[5]

Level	Manifestation	Mechanism	Consequence
Systemic	Hyperglycaemia	Protein modification (AGE, N-acetyl glucosamine) Epigenetic changes, mitochondrial damage	Myocardial dysfunction
	Oxidative stress	Impaired cardiomyocyte calcium handling	Reduced cardiac contractility and relaxation
	Inflammation	Up-regulated inflammatory signalling	Macrophage infiltration
Innervations	Autonomic dysfunction	Systemic and coronary vascular function, myocardial performance	Myocardial hypertrophy, fibrosis myocardial dysfunction
Cardiac	Disturbed insulin signalling	Myocardial energetics, substrate utilisation	Myocardial dysfunction
	Disturbed renin-angiotensin-aldosterone system	Cardiac remodelling	Cardiac stiffness, fibrosis
	Small and large vessel disease	Impaired perfusion	Myocardial dysfunction, fibrosis
Cardiomyocyte	Cytosolic calcium trafficking	Excitation-contraction coupling	Cardiomyocyte contraction, relaxation
	Gene expression, signalling		

AGE: Advance Glycation End-product

Diagnosis of Cardiac Dysfunction

Common symptoms of cardiac dysfunction include but are not limited to, dyspnoea, reduced exercise capacity, and peripheral oedema. When patients present with signs or symptoms suggestive of cardiac dysfunction, it is recommended to perform an echocardiogram to confirm the diagnosis. However, in current guidelines, natriuretic peptides are also recommended as an alternative initial screening tool, which can potentially help rule out the presence of cardiac dysfunction.

Both B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have a questionable positive predictive value, but they exhibit a very high negative predictive value in terms of ruling out cardiac dysfunction with reduced ejection fraction (rEF). According to current guidelines, patients suspected of having cardiac dysfunction and displaying BNP levels above 100 pg/mL or NT-proBNP levels above 125 pg/mL should undergo echocardiography to confirm the diagnosis. On the other hand, patients with BNP and NT-proBNP levels below these cut-offs are considered very unlikely to have cardiac dysfunction.[6]

The normal left ventricular ejection fraction (LVEF) ranges from 50% to 70%, and an LVEF below 50% indicates reduced systolic function. In current medical practice, LVEF is typically calculated using two-dimensional measurements by Simpson's Biplane method. This involves tracing the endocardial border at end diastole and end systole to estimate left ventricular (LV) volumes and LVEF.

In a normal scenario, the E wave (early diastolic filling wave) is larger than the A wave (atrial contraction wave), resulting in an E/A ratio greater than 1.0. An impaired relaxation pattern is a mild form of diastolic dysfunction. It indicates an abnormality in active, energy-dependent LV relaxation and is characterised by a decreased E/A wave ratio (less than 1.0). This pattern is observed in the presence of significantly reduced LV compliance and markedly elevated left atrial (LA) pressure. Importantly, this pattern is associated with an adverse prognosis that is largely independent of the underlying LVEF.

Aim & Objectives

1. Estimation of BNP in patients with type 2 diabetes without overt heart failure
2. Estimation of ejection fraction in patients with type 2 diabetes without overt heart failure
3. Correlation of BNP and ejection fraction in patients with type 2 diabetes without overt heart failure

Material and Methods

This is a cross-sectional study, which was conducted in

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the OPD, Department of Medicine, BRD Medical College, Gorakhpur from August 2021 to July 2022. It included T2DM patients (> 10 years of duration of the disease) who were more than 40 years of age. The total sample size was 284, as calculated by the following formula, $N = 4pq/L^2$, with a 95% confidence interval and error taken at 5%. Here "N" is sample size, "p" is prevalence (23%)[7], "q" is (1-p) and "L" is absolute error.

Patients with evidence of valvular disease or a history of symptoms of peripheral artery disease, or chronic obstructive pulmonary disease, or arrhythmias, or those diagnosed with stage III/ IV chronic kidney disease (CKD) were excluded from the study.

During the study period, a total of 710 diabetic patients attending the OPD were screened, out of which 284 patients satisfying the inclusion and exclusion criteria were enrolled as the study subjects. The study was carried out according to good clinical practice and was approved by the College Research Council and Institutional Ethics Committee. Written informed consent in the local language was taken from all the study subjects. Each study subject underwent evaluation for history, examination, and investigations (HbA1C, haemoglobin, serum creatinine, TSH, lipid profile, brain natriuretic peptide (BNP) level, and echocardiography for ejection fraction (EF)) as a routine part of their standard evidence-based treatment protocol.

The study's data were recorded in a Microsoft Excel spreadsheet, and subsequently, the analysis was conducted using the trial version 24.0 of SPSS and Epi-Info online. The statistical methods employed in the study encompassed the utilisation of frequency tables, chi-square tests, and regression analysis.

Results and Observations

The majority of the study subjects (142, 50.00%) belonged to the age group of 61-80 years, followed by 136 (47.89%) who belonged to the age group of 40-60 years. Most of the study subjects (174, 61.27%) were male and the rest (110, 38.73%) were female. The majority of the study subjects (224, 78.87%) belonged to the 10-20 years T2DM duration group followed by those who belonged to the duration of 21-30 years (56, 19.72%). The HbA1c levels for most subjects (210, 73.95%) were between 6.5% and 9.5%, followed by 59 (20.77%) subjects for whom it was more than 9.5%. 215 (75.40%) study subjects had normal BNP levels (< 100 pg/dl), followed by 69 (24.60%) who had abnormal/ elevated BNP levels (> 100 pg/dl). Out of all the study subjects, 231 (81.35%) belonged to Preserved Ejection Fraction (pEF), followed by 29 (10.21%) who belonged to Moderate Ejection fraction (mEF), and the rest (24, 8.44%) belonged to Reduced Ejection Fraction (rEF) (Table 2). The occurrence of increased BNP (> 100 pg/dl)) was more common in the age group of 61-80 years among T2DM patients and the association was found to be statistically significant ($p < 0.002$). The associations of T2DM duration and HbA1c levels with BNP levels were found to be statistically significant ($p < 0.001$ for both). Out of all the study subjects with abnormal/ elevated BNP (69, 24.29%), the majority (29, 42.03%) had moderate ejection fraction (mEF), followed by 24 (34.78%) who had reduced ejection fraction (rRF) and rest (16, 23.19%) had preserved ejection fraction (pEF). The association between EF and BNP was statistically highly significant (Table 3).

In terms of age distribution among subjects with pEF, 126 individuals (54.54%) fell within the age group of 40-60 years, and 105 individuals (45.45%) were in the age group of 61-80 years. No subjects with pEF were over 80 years old. Among those with mEF, 16 subjects (55.17%) were aged between 40 and 60 years, 11 subjects (37.93%) were in the age group of 61-80 years, and 2 subjects (6.89%) were over 80 years old. Regarding subjects with rEF, 13 individuals (54.2%) were in the age group of 61-80 years, 11 subjects (45.8%) were aged 40-60 years, and none were over 80 years old. The statistical analysis indicated that the association between age groups and ejection fraction was not significant ($p < 0.107$). Regarding the duration of T2DM, the majority of subjects with pEF (212 subjects; 91.77%) had a T2DM duration of 10-20 years, followed by 18 subjects (7.79%) with a duration of 21-30 years, and only 1 subject (0.43%) with a duration of over 30 years. Among subjects with mEF, 19 subjects (65.51%) had a T2DM duration of 21-30 years, 8 subjects (27.58%) had a duration of 10-20 years, and 2 subjects (6.89%) had a duration of over 30 years. For subjects with rEF, 19 subjects (79.2%) had a T2DM duration of 21-30 years, 4 subjects (16.7%) had a duration of 10-20 years, and 1 subject (4.2%) had a duration of over 30 years. The statistical analysis revealed a significant association between T2DM duration and ejection fraction ($p < 0.001$). Regarding HbA1c levels, among subjects with pEF, 171 individuals (74.2%) had HbA1c levels between 6.5% and 9.5%, 45 subjects (19.48%) had HbA1c levels greater than 9.5%, and 15 subjects (6.49%) had HbA1c levels less than 6.5%. Among subjects with mEF, 18 subjects (62.07%) had HbA1c levels between 6.5% and 9.5%, 11 subjects (37.9%) had HbA1c levels greater than 9.5%, and none had HbA1c levels less than 6.5%. Among subjects with rEF, 21 individuals (87.5%) had HbA1c levels between 6.5% and 9.5%, 3 subjects (12.5%) had HbA1c levels greater than 9.5%, and none had HbA1c levels less than 6.5%. The statistical analysis revealed a significant association between HbA1c levels and abnormal ejection fraction ($p = 0.044$) (Table 4).

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Table 2.Distribution of Demographic and Predictors of Cardiac Disorders among Study Subjects (N = 284)

S. No.	Variables		Frequency (n)	%
1.	Age (years)	40-60	136	47.89
		61-80	142	50.00
		> 80	6	2.11
2.	Gender	Male	174	61.27
		Female	110	38.73
3.	T2DM duration (years)	10-20	224	78.87
		21-30	56	19.72
		> 30	04	1.41
4.	HbA1c (%)	< 6.5	15	5.28
		6.5-9.5	210	73.95
		> 9.5	59	20.77
5.	BNP range (pg/dl)	Normal (< 100)	215	75.40
		Abnormal (> 100)	69	24.60
6.	EF range (%)	pEF (≥ 50)	231	81.35
		mEF (41-49)	29	10.21
		rEF (≤ 40)	24	8.44

Table 3.Association between BNP Status and Evaluating Predictors

Variables		BNP Status		p Value
		Normal (N = 215) (< 100 pg/dl) n (%)	Abnormal (N = 69) (> 100 pg/dl) n (%)	
Age (years)	40-60	116 (53.95)	20 (29)	0.002
	61-80	95 (44.18)	47 (68.1)	
	> 80	4 (1.86)	2 (2.9)	
T2DM duration (years)	10-20	213 (99.07)	11 (15.94)	< 0.001
	21-30	2 (0.93)	54 (78.26)	
	> 30	0 (0.0)	4 (5.79)	
HbA1c (%)	< 6.5	15 (7)	0 (0.0)	< 0.001
	6.5-9.5	165 (76.74)	45 (65.22)	
	> 9.5	35 (16.28)	34 (34.78)	
EF Range (%)	pEF (≥ 50)	215 (100)	16 (23.19)	< 0.001
	mEF (41-49)	0 (0.0)	29 (42.03)	
	rEF (≤ 40)	0 (0.0)	24 (34.78)	

Test of significance: Chi-square test

p value < 0.05: Significant

p value < 0.001: Highly significant

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Table 4.Association between Ejection Fraction Status and Evaluating Predictors

Variables		Ejection Fraction %			p Value
		pEF n (%)	mEF n (%)	rEF n (%)	
Age (years)	40-60	126 (54.5)	16 (55.17)	11 (45.8)	0.107
	61-80	105 (45.45)	11 (37.93)	13 (54.2)	
	> 80	0 (0.0)	2 (6.89)	0 (0.0)	
T2DM duration (years)	10-20	212 (91.77)	8 (27.58)	4 (16.7)	< 0.001
	21-30	18 (7.79)	19 (65.51)	19 (79.2)	
	> 30	1 (0.43)	2 (6.89)	1 (4.2)	
HbA1c (%)	< 6.5	15 (6.49)	0 (0.0)	0 (0.0)	0.044
	6.5-9.5	171 (74.2)	18 (62.07)	21 (87.5)	
	> 9.5	45 (19.48)	11 (37.93)	3 (12.5)	

Test of significance: Chi-square test
p value < 0.05: Significant
p value < 0.001: Highly significant

Table 5.Multinomial Regression between the Elevated BNP Level and Independent Variables (Age, T2DM Duration, and HbA1C Levels)

BNP Levels > 100 (Elevated)		p Value	Odds Ratio (OR)	95% Confidence Interval for OR	
				Lower bound	Upper bound
Age (years)	40-60	0.754	0.697	0.073	6.636
	61-80	**0.039**	2.320	1.031	3.301
	> 80 (R)	-	-	-	-
T2DM duration (years)	10-20	0.163	0.946	0.046	3.046
	21-30	**0.003**	3.283	1.704	3.827
	> 30 (R)	-	-	-	-
HbA1c level (%)	< 6.5	0.997	1.857	0.000	2.901
	6.5-9.5	**0.013**	1.576	1.241	1.972
	> 9.5 (R)	-	-	-	-

R: Reference
p value < 0.05: Significant
p value < 0.001: Highly significant

The increase in age (61-80 years) of the study subjects had a significant positive association with abnormal/ elevated BNP levels [OR: 2.32 (1.013 ± 3.301), p value = 0.039]. The increase in the duration of T2DM (21-30 years) had a significant positive association with abnormal/ elevated BNP (> 100) [OR: 3.283 (1.704 ± 3.827); p value = 0.003]. Similarly, the increase in HbA1c levels had a positive association with abnormal/ elevated BNP levels [OR: 1.576 (1.241 ± 1.972); p value = 0.013] (Table 5). The result revealed that the T2DM duration had a significant negative impact on the ejection fraction (B = -1.474, t = -14.869, p < 0.001), i.e., an increase in T2DM duration will cause a decrease in ejection fraction. The rest of the independent variables were found to be statistically insignificant (Table 6).

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Table 6.Multiple linear regression analysis between Ejection fraction and independent variables (Age, T2DM Duration, HbA1C Levels)

Ejection Fraction (a)	Unstandardised Coefficients		Standardised Coefficients	t	p Value
	B	Std. error	Beta		
Constant	76.910	4.125	-	18.645	0.000
Age (years)	0.015	0.052	0.013	0.284	0.777
T2DM duration (years)	-1.474	0.099	-0.673	-14.869	**0.000**
HbA1C (%)	0.355	0.280	0.056	1.270	0.205

a: Dependent Variable: EF%

p value < 0.05: Significant

p value < 0.001: Highly significant

Discussion

The study aimed to estimate BNP (B-type natriuretic peptide) and ejection fraction in the enrolled study subjects and to correlate these two parameters in T2DM patients without overt heart failure. Studies conducted earlier have reported a high prevalence of cardiovascular complications in patients with type 2 diabetes mellitus.

The findings in the study show that the mean T2DM duration observed in this study was 15.46 ± 4.8 years. This is in line with a study conducted by Venkataraman et al.[8] in India, which reported a mean T2DM duration of 15.5 years. The prolonged T2DM duration has been associated with a higher risk of developing CVD in patients with T2DM.[9]

BNP is a sensitive biomarker of cardiac function and elevated BNP levels have been associated with an increased risk of cardiovascular disease in patients with T2DM.[10] The study found that the majority of the study subjects (75.40%) had normal BNP levels, whereas 24.60% had abnormal/ elevated BNP levels. Among the study subjects with normal BNP levels, the majority had HbA1c levels between 6.5% and 9.5%, and among those with abnormal/ elevated BNP levels, the majority had HbA1c levels between 6.5% and 9.5% followed by HbA1c levels > 9.5%. The results suggested that patients with HbA1c levels > 9.5% are at a higher risk of developing elevated BNP levels, which is consistent with previous studies.[11,12]

Ejection fraction is an important measure of heart function, and a reduced ejection fraction is a marker of systolic dysfunction, which can increase the risk of heart failure and cardiovascular events. Finding low (moderate or reduced) ejection fraction in T2DM subjects without clinical features of heart failure is consistent with the findings of Rosano et al.[13] Previous studies have reported that age is an independent predictor of heart failure and that it has a significant impact on the pathophysiology of heart failure.[14]

The findings of this study suggest a strong association between BNP and ejection fraction (EF). Specifically, all subjects with normal BNP belonged to the preserved ejection fraction group, while the majority of those with abnormal/ elevated BNP had moderate or reduced ejection fraction. This is consistent with previous research indicating that BNP levels are associated with cardiac dysfunction, particularly in patients with heart failure.[15] Our findings are in line with a previous study that has reported a positive association between age and elevated BNP levels in patients with T2DM.[16]

Conclusion

In conclusion, this study highlights a significant association between B-type natriuretic peptide (BNP) and ejection fraction (EF) in patients with type 2 diabetes mellitus (T2DM), particularly in those without overt heart failure symptoms. The results demonstrate that abnormal or elevated BNP levels are linked to moderate or reduced EF, while normal BNP levels are associated with preserved EF. Furthermore, increasing age, longer T2DM duration, and higher HbA1c levels were found to be associated with abnormal or elevated BNP levels, while longer T2DM duration was linked to lower EF.

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Conflict of Interest: None

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